Chapter 12: Blood, Bones & Teeth Micronutrients

This chapter is a collection of vitamins and minerals that are involved in the structure or function of blood, bones and teeth. The individual sections are:

- 12.1 Vitamin D
- 12.2 Calcium
- 12.3 Phosphorus
- 12.4 Fluoride
- 12.5 Vitamin K
- 12.6 Vitamin A
- 12.7 Iron
- 12.8 Zinc
- 12.9 Copper

12.1 Vitamin D

Vitamin D is unique among the vitamins in that it is part vitamin, part hormone. It is considered part hormone for two reasons: (1) we have the ability to synthesize it, and (2) it has hormone-like functions. The amount synthesized, however, is often not enough to meet our needs. Thus, we need to consume this vitamin under certain circumstances, meaning that vitamin D is a conditionally essential micronutrient.

There are two major dietary forms of vitamin D: the form produced by plants and yeast is vitamin D$_2$ (ergocalciferol), and the form made by animals is vitamin D$_3$ (cholecalciferol). The structures of these two forms are shown below. Notice that the only difference is the presence of a double bond in D$_2$ that is not in D$_3$.

Figure 12.11 Structure of vitamin D$_2$ (ergocalciferol) and vitamin D$_3$ (cholecalciferol)$^{1,2}$
We synthesize vitamin D₃ from cholesterol, as shown below. In the skin, cholesterol is converted to 7-dehydrocholesterol. In the presence of UV-B light, 7-dehydrocholesterol is converted to vitamin D₃. Synthesized vitamin D will combine with vitamin D-binding protein (DBP) to be transported to the liver. Dietary vitamin D₂ and D₃ is transported to the liver via chylomicrons. Once in the liver, vitamin D₃ is converted into calcitriol (shown by its chemical abbreviation, 1,25(OH)₂D, in Figure 12.12), which is the circulating form of vitamin D. The synthesis and activation of vitamin D is shown in the figures below.

Figure 12.12 Vitamin D synthesis and activation³

For more information on vitamin D, see the Required Web Link below.

**Required Web Link**

*Vitamin D Fact Sheet for Health Professionals*

Subsections:
- 12.11 Environmental Factors That Impact Vitamin D₃ Synthesis
- 12.12 Sources of Dietary Vitamin D
- 12.16 Vitamin D Deficiency, Toxicity, & Insufficiency

**References & Links**

**Links**
Vitamin D Fact Sheet for Health Professionals - [https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/](https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/)
12.11 Environmental Factors That Impact Vitamin D$_3$ Synthesis

There are a number of environmental factors that affect vitamin D$_3$ synthesis: Latitude, Season, Time of Day, Skin Color, Age, and Clothing.

**Latitude**

The latitude a person is at affects that person's ability to synthesize vitamin D$_3$. There is an inverse relationship between distance from the equator and UV light exposure. Thus, with increased distance from the equator (increased latitude), there is decreased UV light exposure and vitamin D$_3$ synthesis. The link below shows the latitude and longitude lines of the United States.

**Required Web Link**
United States Latitude and Longitude Lines

**Seasons**

Seasons also make a difference in vitamin D$_3$ synthesis. In Boston (42° N), vitamin D synthesis only occurs from March-October, because during late fall and winter not enough UV-B reaches the earth's surface to synthesize vitamin D$_3$. However, in Los Angeles (34° N), vitamin D$_3$ synthesis occurs year round$^2$. The difference is the angle of the sun relative to latitude and how many UV-B photons are absorbed before they reach the earth's surface$^1$.

**Time**

Time of day is also an important factor in affecting vitamin D$_3$ synthesis. Vitamin D$_3$ synthesis increases in the morning before peaking at noon, then declines the rest of the day$^1$.

**Skin pigmentation**

Another factor that plays an important role in vitamin D$_3$ synthesis is skin pigmentation. Skin pigmentation tends to be darker around the equator to help protect inhabitants from the harmful effects of sun exposure. Skin color is the result of increased production of the pigment melanin, which is the pigment responsible for all skin colors.

Very dark skin color can provide a sun protection factor (SPF) 8-30 for those individuals who never burn$^2$. These individuals will require approximately 5- to 10-times greater sunlight exposure than a light-skinned, white person to synthesize the same amount of vitamin D$_3$$^{2,3}$. 
Age
Age also plays a factor in vitamin D\textsubscript{3} synthesis. Aging results in decreased 7-dehydrocholesterol concentrations in the skin, resulting in an approximately 75\% reduction in the vitamin D\textsubscript{3} synthesis capability by age 70\textsuperscript{3}.

Clothing
Clothing is another factor that influences vitamin D\textsubscript{3} synthesis. More clothing means that less sun reaches your skin, and thus less vitamin D\textsubscript{3} synthesis.

References & Links

Links
US Latitude and Longitude Lines - [http://modernsurvivalblog.com/survival-skills/basic-map-reading-latitude-longitude/](http://modernsurvivalblog.com/survival-skills/basic-map-reading-latitude-longitude/)

12.12 Dietary Sources of Vitamin D
Because of the possible double-edged sword of sun exposure for synthesizing vitamin D\textsubscript{3}, consuming vitamin D from the diet or supplements is the alternative.

However, there are a limited number of food naturally rich in vitamin D. Good sources of vitamin D are fatty fish (salmon, tuna, etc.) and their oils (such as cod liver oil). The amount in fatty fish varies greatly with wild-caught salmon being the highest. One study showed that farmed salmon contained almost 75\% less vitamin D than wild-caught salmon\textsuperscript{1}. It is not known whether this disparity exists between other types of farmed and wild-caught fish varieties.

<table>
<thead>
<tr>
<th>Fish</th>
<th>Vitamin D (IU/oz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue Fish</td>
<td>280 ± 68</td>
</tr>
<tr>
<td>Cod</td>
<td>104 ± 24</td>
</tr>
<tr>
<td>Grey Sole</td>
<td>56 ± 36</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------</td>
</tr>
<tr>
<td>Farmed Salmon</td>
<td>240 ± 108</td>
</tr>
<tr>
<td>Wild Salmon</td>
<td>988 ± 524</td>
</tr>
<tr>
<td>Farmed Trout</td>
<td>388 ± 212</td>
</tr>
<tr>
<td>Tuna</td>
<td>404 ± 440</td>
</tr>
</tbody>
</table>

Thus, since not many foods contain vitamin D, many brands of milk have been fortified with vitamin D₂ or D₃ (100 IU/8 oz) since the 1930s². However, the actual measured amount of vitamin D in many brands of milk is far less than stated on their labels³⁴. Part of this problem stems from a lack of a standardized method for measuring vitamin D in the past. Without standardized analysis, there inevitably was a wide range of variation from lab to lab in the reported amount of vitamin D.

**References & Links**

**12.13 Vitamin D Deficiency, Toxicity & Insufficiency**

**Rickets** is a vitamin D deficiency in infants and children. A lack of vitamin D leads to decreased bone mineralization, causing the bones to become weak. The bones then bow under pressure, leading to the characteristic bowed legs, as seen in Figure 12.131.
Osteomalacia is a vitamin D deficiency in adults and results in poor bone mineralization. The bone becomes soft, resulting in bone pain and an increased risk of fractures. While rickets and osteomalacia are fairly rare in the United States, it is believed that vitamin D insufficiency might be much more widespread. Insufficiency means that the level of intake, or body status, is suboptimal (neither deficient nor optimal). Suboptimal/insufficient means intake, or status, is higher than deficient, but lower than optimal. Thus, higher intake levels will provide additional benefits. The functions of vitamin D are growing by the day due to increased research discoveries. These functions now include benefits beyond bone health, further supporting the importance of vitamin D. In late 2010, an RDA for vitamin D was established (was an Adequate Intake before). This made it, along with calcium, the first micronutrients to have their DRIs revised. The RDA for vitamin D is 3-times higher than the previous AI. Many believe these are more reasonable levels, while others think that the new RDA is still not high enough. This belief, that many people’s vitamin D intake/status is suboptimal, is challenged by a recent review described in the link below that found that vitamin D did not reduce osteoporosis risk. In addition, a recent meta-analysis (second link) concluded, “there is probably no benefit to expect from vitamin D supplementation in normally healthy people.”

**Required Web Links**

- [Vitamin D Ineffective for Preventing Osteoporosis](#)
- [Limits of Vitamin D Supplements](#)

Vitamin D from supplements can become toxic. You cannot develop vitamin D toxicity from sun exposure, because the sunlight degrades a precursor of vitamin D₃ in the skin. Vitamin D toxicity results in hypercalcemia or high blood calcium levels. These become problematic because it can lead to the calcification of soft tissues.
12.2 Calcium

Calcium is a macromineral and the most abundant mineral in the body. The reason for calcium’s abundance is its distribution in the skeleton, which contains 99% of the calcium in the body.

For more information on calcium, see the Required Web Link below.

**Required Web Link**

[Calcium Fact Sheet for Health Professionals](https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/)

**Links**

Calcium Fact Sheet for Health Professionals - [https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/](https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/)

Subsections:
- 12.21 Calcium Absorption
- 12.22 Calcium Bioavailability
- 12.23 Calcium Functions
- 12.24 Calcium Deficiency & Toxicity
12.21 Calcium Absorption

Calcium is taken up into the enterocyte through Transient Receptor Potential V6 (TRPV6), a calcium channel found on the brush border. Calbindin is the calcium binding protein that facilitates uptake through TRPV6 and transport across the enterocyte. $\text{Ca}^{2+}-\text{Mg}^{2+}$ ATPase functions to pump calcium out of the enterocyte and into circulation and to pump magnesium into the enterocyte, as shown below\(^1\).

As we have previously discussed, increased calcitriol synthesis in the kidney causes increased binding to the vitamin D receptor, which increases calbindin synthesis. Increased calbindin ultimately increases calcium uptake and absorption.

There are a couple of calcium-binding compounds that inhibit its absorption. Therefore, even though some foods are good sources of calcium, the calcium is not very bioavailable. Oxalate, found in high levels in spinach, rhubarb, sweet potatoes, and dried beans, is the most potent inhibitor of calcium absorption\(^2\). Recall that calcium oxalate is one of the compounds that makes up kidney stones. Based on this understanding, it should not be a surprise that formation of this compound inhibits calcium absorption. Another inhibitor of calcium absorption is
phytate. Phytate is found in whole grains and legumes. So, ironically, the whole grains in your breakfast cereal can actually reduce slightly the amount of calcium you absorb from the milk you put on that same cereal.

**References & Links**

### 12.22 Calcium Bioavailability

Calcium bioavailability varies greatly from food to food, as shown in the table below. This table gives the serving size, calcium content of that food, and percent absorbed. The calcium content is multiplied by the absorption percentage to calculate the estimated calcium absorbed. Finally, it shows the servings of each food needed to equal the estimated calcium absorbed from 1 serving of milk.

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving Size (g)</th>
<th>Calcium content (mg)</th>
<th>Absorption (%)</th>
<th>Estimated Calcium Absorbed</th>
<th>Servings needed to equal 240 mL milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s Milk</td>
<td>240</td>
<td>300</td>
<td>32.1</td>
<td>96.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Almonds, dry roasted</td>
<td>28</td>
<td>80</td>
<td>21.2</td>
<td>17.0</td>
<td>5.7</td>
</tr>
<tr>
<td>Beans, Pinto</td>
<td>86</td>
<td>44.7</td>
<td>26.7</td>
<td>11.9</td>
<td>8.1</td>
</tr>
<tr>
<td>Beans, Red</td>
<td>172</td>
<td>40.5</td>
<td>24.4</td>
<td>9.9</td>
<td>9.7</td>
</tr>
<tr>
<td>Beans, White</td>
<td>110</td>
<td>113</td>
<td>21.8</td>
<td>24.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Bok Choy</td>
<td>85</td>
<td>79</td>
<td>53.8</td>
<td>42.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Broccoli</td>
<td>71</td>
<td>35</td>
<td>61.3</td>
<td>21.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Brussel Sprouts</td>
<td>78</td>
<td>19</td>
<td>63.8</td>
<td>12.1</td>
<td>8.0</td>
</tr>
<tr>
<td>Cabbage, Chinese</td>
<td>85</td>
<td>79</td>
<td>53.8</td>
<td>42.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Cabbage, Green</td>
<td>75</td>
<td>25</td>
<td>64.9</td>
<td>16.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>62</td>
<td>17</td>
<td>68.6</td>
<td>11.7</td>
<td>8.2</td>
</tr>
<tr>
<td>Food</td>
<td>Calories</td>
<td>Calcium</td>
<td>Magnesium</td>
<td>Phosphorus</td>
<td>Oxalate</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------</td>
<td>---------</td>
<td>-----------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Cheddar Cheese</td>
<td>42</td>
<td>303</td>
<td>32.1</td>
<td>97.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Chinese mustard greens</td>
<td>85</td>
<td>212</td>
<td>40.2</td>
<td>85.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Chinese spinach</td>
<td>85</td>
<td>347</td>
<td>8.36</td>
<td>29</td>
<td>3.3</td>
</tr>
<tr>
<td>Fruit Punch (CCM)</td>
<td>240</td>
<td>300</td>
<td>52</td>
<td>156</td>
<td>0.6</td>
</tr>
<tr>
<td>Kale</td>
<td>85</td>
<td>61</td>
<td>49.3</td>
<td>30.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Kohlrabi</td>
<td>82</td>
<td>20</td>
<td>67.0</td>
<td>13.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Mustard Greens</td>
<td>72</td>
<td>64</td>
<td>57.8</td>
<td>37.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Orange juice (CCM)</td>
<td>240</td>
<td>300</td>
<td>36.3</td>
<td>109</td>
<td>0.8</td>
</tr>
<tr>
<td>Radish</td>
<td>50</td>
<td>14</td>
<td>74.4</td>
<td>10.4</td>
<td>9.2</td>
</tr>
<tr>
<td>Rhubarb</td>
<td>120</td>
<td>174</td>
<td>8.54</td>
<td>10.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Rutabaga</td>
<td>85</td>
<td>36</td>
<td>61.4</td>
<td>22.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Sesame seeds, no hulls</td>
<td>28</td>
<td>37</td>
<td>20.8</td>
<td>7.7</td>
<td>12.2</td>
</tr>
<tr>
<td>Soy milk (tricalcium phosphate)</td>
<td>240</td>
<td>300</td>
<td>24.0</td>
<td>72.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Soy milk (calcium carbonate)</td>
<td>240</td>
<td>300</td>
<td>21.1</td>
<td>66.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Spinach</td>
<td>85</td>
<td>115</td>
<td>5.1</td>
<td>5.9</td>
<td>16.3</td>
</tr>
<tr>
<td>Sweet Potatoes</td>
<td>164</td>
<td>44</td>
<td>22.2</td>
<td>9.8</td>
<td>9.8</td>
</tr>
<tr>
<td>Tofu with Ca</td>
<td>126</td>
<td>258</td>
<td>31.0</td>
<td>80.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Turnip Greens</td>
<td>72</td>
<td>99</td>
<td>51.6</td>
<td>51.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Watercress</td>
<td>17</td>
<td>20</td>
<td>67.0</td>
<td>13.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Yogurt</td>
<td>240</td>
<td>300</td>
<td>32.1</td>
<td>96.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Notice that the foods high in oxalate like spinach, rhubarb, sweet potatoes, and dried beans are poorly absorbed. But there are still a number of calcium sources outside of milk.

The 2 most common forms of calcium found in supplements are calcium carbonate and calcium citrate. As you can see in the figure below, they differ in the amount of elemental calcium they contain. This shows how much of the molecular weight of the compound is calcium.
Figure 12.221 Percent of calcium supplements that is elemental calcium

The higher the percent elemental calcium, the greater the amount of calcium you will receive per given weight of that compound, versus a compound that has a lower elemental calcium percentage. Both carbonate and citrate forms are well absorbed, but individuals with low stomach acid absorb citrate better. Also, carbonate is best absorbed when taken with food, while for citrate it is equally well absorbed when taken alone.

Older research suggested that calcium citrate malate was more bioavailable than other calcium sources. However, a more recent clinical study found no difference in the bioavailability of calcium from calcium citrate malate in orange juice, skim milk, or calcium carbonate supplements. There is some evidence that suggests that even though bioavailability is the same among these different forms, they might not be equally effective in improving bone measures.

References & Links
12.23 Calcium Functions

In terms of bone and teeth, calcium is found in bone and referred to as hydroxyapatite (a mineralized form of calcium). There are also a number of non-bone functions of calcium. Calcium is an intracellular signaling molecule. Because of this, intracellular calcium is tightly controlled, primarily stored within organelles.

Non-bone functions include:\1

**Neurotransmitter release** - Neurotransmitter release is stimulated by the opening of voltage-gated Ca\textsuperscript{2+} channels. This stimulates the synaptic vesicle to fuse with the axon membrane and release the neurotransmitter into the synapse.

**Muscle contraction** - Calcium is released in muscle cells, where it binds to the protein troponin, changes its shape, and removes the tropomyosin blockade of actin active sites so that contraction can occur\textsuperscript{2}. This can be seen in the following animation and figure (same link).

**Hormone release** - Calcium acts as an intracellular messenger for the release of hormones, such as insulin. The link below shows how in the beta cells of the pancreas, the opening of voltage-gated calcium channels stimulates the insulin granules to fuse with the beta cell membrane to release insulin.

**Blood Clotting** - As will be discussed more in the vitamin K section, calcium binding to activated Gla proteins is important in the blood clotting cascade.
**Enzyme regulation** - The binding of calcium to calcium-binding proteins also regulates the action of a number of enzymes³.

**References & Links**
2. [http://legacy.owensboro.kctcs.edu/GCaplan/anat/Notes/API%20Notes%20J%20%20Muscle%20Contraction.htm](http://legacy.owensboro.kctcs.edu/GCaplan/anat/Notes/API%20Notes%20J%20%20Muscle%20Contraction.htm)

**Links**
- Muscle contraction - [http://legacy.owensboro.kctcs.edu/GCaplan/anat/Notes/API%20Notes%20J%20%20Muscle%20Contraction.htm](http://legacy.owensboro.kctcs.edu/GCaplan/anat/Notes/API%20Notes%20J%20%20Muscle%20Contraction.htm)

**12.24 Calcium Deficiency & Toxicity**

Because of the large amount of calcium in bones, deficiency is rare¹. Hypocalcemia (low serum calcium levels in blood) can result in tetany (involuntary muscle contractions)². In addition, calcium deficiency in children can lead to rickets, which is a vitamin D deficiency. While not a deficiency, low calcium intake can lead to decreased bone mineral density and the conditions osteopenia and osteoporosis. How these differ from osteomalacia and normal bone is illustrated and described below. There are two different bone components that we will consider to understand what is happening in the bone. Matrix is the scaffolding onto which mineral is deposited. Mineral is at it sounds, the mineral that is deposited on the matrix.

**Osteomalacia** - Bone mass is normal, but the matrix to mineral ratio is increased, meaning there is less mineral in bone.

**Osteopenia** - Bone mass is decreased, but the matrix to mineral ratio is not altered from normal bone. This condition is intermediate in between normal and osteoporosis.

**Osteoporosis** - Bone mass is further decreased from osteopenia, but the matrix to mineral ratio is not altered from normal bone³.
To prevent osteoporosis it is important to build peak bone mass, 90% of which is built in females by age 18 and age 20 in males, but can continue to increase until age 30. After that time, bone mass starts to decrease. For women after menopause, bone mass decreases dramatically because of the decrease in estrogen production, as shown in the link below.

Required Web Link
Bone Mass

Calcium toxicity is rare, occurring in those with hyperparathyroidism or high calcium supplementation levels. Like vitamin D, toxicity can lead to calcification of soft tissues. In addition, a very high intake of calcium can lead to kidney stone formation.

References & Links
3. Sambrook, P. Bone structure and function in normal and disease states [link](http://v5.books.elsevier.com/bookscat/samples/9780443070150/9780443070150.pdf)

Link

12.3 Phosphorus

Animal products are rich sources of phosphate. Plant products contain phosphorus, but some is in the form of phytic acid (phytate). In grains, over 80% of the phosphorus is phytate. The bioavailability of phosphorus from phytate is poor (~50%) because we lack the enzyme phytase. Nevertheless, ~50-70% of phosphorus is estimated to be absorbed from our diet. Another source of phosphorus is phosphoric acid that is used to acidify colas. Colas are caramel-colored, carbonated soft drinks that contain caffeine, such as Coca-Cola, Pepsi, etc. Epidemiological studies have found that soft drink consumption is associated with decreased bone mineral densities, particularly in females. It has been hypothesized that phosphoric acid
plays some role in this effect, but there is limited evidence to support this belief.

Most phosphorus is excreted in the urine.

Phosphorus deficiency is rare, but can hinder bone and teeth development. Other symptoms include muscle weakness, rickets, and bone pain. Toxicity is also rare, but it causes low blood calcium concentrations and tetany.

http://lpi.oregonstate.edu/mic/minerals/phosphorus#reference10

Subsection:
- 12.31 Phosphorus Functions

References & Links

12.31 Phosphorus Functions

Phosphorus has a number of functions in the body. Phosphate is a component of hydroxyapatite in bones and teeth, and can have non-bone function.

Non-bone functions include:

**Phosphorylation** - Phosphates are used to activate and deactivate a number of proteins. In addition, compounds are also frequently phosphorylated, like the monosaccharides shown below.
**Phospholipids** - Phosphates are a component of phospholipids

**DNA/RNA** - DNA/RNA have a phosphate backbone as shown below.

**ATP** - The major energy currency, ATP, stores energy in its phosphate bonds.

**Secondary Messengers** - The intracellular secondary messengers cyclic AMP (cAMP) and inositol triphosphate (IP$_3$) both contain phosphate. The action of these secondary messengers can be seen in the links below.

**Required Web Links**
- [cAMP](#)
- [IP$_3$](#)
12.4 Fluoride

Fluoride is a nonessential mineral that is not required by the body and it is not widely found in the food supply. The majority of what we consume comes from fluoridated water. Other good non-dietary sources are fluoridated toothpaste and dental rinses. Absorption of fluoride is near 100% for both dietary and non-dietary forms and it is rapidly excreted in the urine.

Since it is a nonessential mineral, there is no fluoride deficiency. However, fluoride can be quite toxic. Acute toxicity symptoms from large intakes of fluoride include: Nausea, Vomiting, Diarrhea, and Convulsions. Chronic toxicity results in an irreversible condition known as fluorosis.

There is debate as to whether water should be fluoridated. The following links are examples of just how conflicted the U.S. is. The first is a New York Times article on this topic. There is also an article about Portland’s decision to begin fluoridating its water in 2014. The third article is about a bill introduced by a Kansas lawmaker concerned about the effects of water fluoridation.

**Required Web Links**

- Fluoridation Debate, Redux
- Portland Approves Fluoridation by ‘14
- Dentists speak out as fluoride bill nears hearing

**References & Links**

12.5 Vitamin K

There are 3 forms of vitamin K. **Phyloquinone (K1)**, the plant form of vitamin K, is the primary dietary form of vitamin K and found in green leafy vegetables, broccoli, Brussels sprouts, and asparagus are foods that are good sources of phyloquinone\(^1\). Another form of vitamin K, **menaquino (K2)**, is synthesized by bacteria in the colon. Menaquinone comprises \(~10\%\) of absorbed vitamin K every day and can also be found in small amounts in animal products. Its structure is shown below\(^2\). The third form, a synthetic form of vitamin K, is **menadione (K3)**.

Vitamin K is absorbed like other fat-soluble substances. Approximately 80\% of phyloquinone and menaquinone are incorporated into chylomicrons and stored primarily in the liver\(^1,3\). Once metabolized, vitamin K is primarily excreted via bile in the feces, with a lesser amount excreted in urine\(^3\).

For more information on vitamin K, see the Required Web Link below.

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**References & Links**

12.51 Vitamin K Functions

Vitamin K is a cofactor for carboxylation reactions that add a CO₂ to the amino acid, glutamic acid (glutamate), in certain proteins. The enzyme, gamma-glutamyl carboxylase, uses a vitamin K cofactor to convert glutamic acid to gamma-carboxyglutamic acid (Gla). Gla proteins are those that contain glutamic acid(s) that have been converted to gamma-carboxyglutamic acid(s). The formation of Gla proteins allows the 2 positive charges of calcium to bind between the 2 negative charges on the carboxylic acid groups (COO\(^{-}\)) in the Gla. The binding of calcium activates these proteins\(^{1-3}\).

![Figure 12.512 Gamma-glutamyl carboxylase converts glutamic acid to gamma-carboxyglutamic acid (Gla).](image)

Gla proteins are important in blood clotting. Blood clotting occurs through a cascade of events, as shown in the following 2 videos. The animation below gives an overview of blood clotting, the video is a fun depiction of the blood clotting cascade.

**Web Links**
- [Hemostasis Animation](Hemostasis Animation)
- [Video: The Clotting Cascade (1:20)](Video: The Clotting Cascade (1:20))

If these proteins within the blood clotting cascade are not activated to Gla, the cascade does not proceed as normal, leading to impaired blood clotting. After being used as a cofactor by gamma-glutamyl carboxylase to produce a Gla protein, vitamin K becomes vitamin K epoxide. Vitamin K epoxide needs to be converted back to vitamin K to serve as a cofactor again.

Warfarin (Coumadin) and dicumarol are a couple of blood thinning drugs that inhibit this regeneration of vitamin K. This reduces the amount of Gla in the blood clotting proteins, thus reducing the clotting response. The structure of warfarin and dicumarol are shown in Figure 12.514.
Vitamin K may also be important for bone health. There are 3 Gla proteins found in bone: osteocalcin, matrix Gla protein (MGP), and protein S\(^4\). Osteocalcin is a major bone protein, constituting 15-20% of all non-collagen proteins in bone. However, overall, the function of these 3 proteins in bone is not known\(^2,3\). Some research suggests that higher vitamin K status or intake decreases bone loss, but it is still not clear whether vitamin K truly is important for bone health\(^7\).

**References & Links**
12.52 Vitamin K Deficiency & Toxicity

Vitamin K deficiency is rare, but can occur in newborn infants. They are at higher risk, because there is poor transfer of vitamin K across the placental barrier, their gastrointestinal tracts do not contain vitamin K producing bacteria, and breast milk is generally low in vitamin K. As a result, it is recommended (and widely practiced) that all infants receive a vitamin K injection within 6 hours of birth.

Prolonged antibiotic treatment (which kills bacteria in the gastrointestinal tract) and lipid absorption problems can also lead to vitamin K deficiency. Vitamin K deficient individuals have an increased risk of bleeding or hemorrhage. Remember that high levels of vitamin E intake can also interfere with vitamin K's blood clotting function. It is believed that a vitamin E metabolite, with similar structure to the vitamin K quinones, antagonizes the action of vitamin K.

Phylloquinone and menaquinone have no reported toxicities. However, menadione can cause liver damage.

References & Links
12.6 Vitamin A

There are 3 forms of vitamin A (retinol, retinal, and retinoic acid) that collectively are known as retinoids. Retinol is the alcohol (OH) form, retinal is the aldehyde (COH) form, and retinoic acid is the carboxylic acid (COOH) form, as shown in the figure below (areas of difference are indicated by red).

For more information on vitamin K, see the Required Web Link below.

Required Web Link
Vitamin A Fact Sheet for Health Professionals

Subsections:
- 12.61 Carotenoids
- 12.62 Vitamin A Uptake, Absorption, Transport & Storage
- 12.63 Vitamin A Functions
- 12.64 Vitamin A Deficiency & Toxicity

References & Links

Links
Vitamin A Fact Sheet for Health Professionals - https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/
12.61 Carotenoids

Carotenoids are 40-carbon compounds that are found throughout nature. Animals do not produce carotenoids, thus any found in animals came from consumed plants or microorganisms. There are more than 600 natural carotenoids. However, the 6 main ones found in the diet and in the body are: Beta-carotene, Alpha-carotene, Beta-cryptoxanthin, Lutein, Zeaxanthin, and Lycopene.

Many carotenoids are pigments, meaning they are colored. The table below gives the color of some of these carotenoids, as well as some food sources.

Table 12.611 Carotenoids’ color and food sources

<table>
<thead>
<tr>
<th>Carotenoid</th>
<th>Color</th>
<th>Food Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-carotene</td>
<td>Orange</td>
<td>Carrots, Sweet Potatoes, Leafy Greens</td>
</tr>
<tr>
<td>Lycopene</td>
<td>Red</td>
<td>Tomatoes, Watermelon, Pink Grapefruit</td>
</tr>
<tr>
<td>Lutein/Zeaxanthin</td>
<td>Yellow</td>
<td>Kale, Corn, Egg Yolks, Spinach</td>
</tr>
</tbody>
</table>

Carotenoids can be further classified as provitamin A or non-provitamin A. Provitamin A carotenoids are those that can be cleaved to form retinal, while the non-provitamin A carotenoids cannot. After provitamin A carotenoids are taken up into the enterocyte, some are cleaved to form retinal. In the case of symmetrical beta-carotene, it is cleaved in the center to form 2 retinal molecules.

References & Links

12.62 Vitamin A Uptake, Absorption, Transport & Storage

The uptake, absorption, transport, and storage of vitamin A and carotenoids are summarized in the Figure 12.621.

Esters are removed by esterases so that free retinol can be taken up into the enterocyte. Preformed vitamin A is highly bioavailable (70-90%) if consumed with some fat. Carotenoids
have a much lower bioavailability, which varies based on the carotenoid and matrix it is in when consumed. Once provitamin A carotenoids are taken up into the enterocytes, they are: (1) cleaved to retinal and then converted to retinol or (2) absorbed intact and incorporated into chylomicrons.

Figure 12.621 Vitamin A uptake, absorption, transport, and storage. Adapted from reference 1

Retinol in the enterocyte is esterified, forming retinyl esters. The retinyl esters are packaged into chylomicrons (CM) and enter the lymph system. Once the chylomicrons reach circulation, triglycerides are cleaved off to form chylomicon remnants (CM Rem). These are taken up by hepatocytes, where the retinyl esters are de-esterified to form retinol.

The liver is the major storage site of vitamin A. For storage, the retinol will be transported from the hepatocytes to the stellate cells and converted back to retinyl esters, the storage form of vitamin A. If vitamin A is needed to be released into circulation, retinol will combine with retinol binding protein (RBP). Retinol + RBP are then bound to a large transport protein, transthyretin (TTR). It is believed that retinol + RBP would be filtered out by the kidney and excreted in urine if it was not bound to TTR

After it is further metabolized, 60% of vitamin A is excreted in the urine, 40% in feces².
12.63 Vitamin A Functions

Vitamin A has a number of important functions in the body.

Vision

The retina is the inner back lining of the eye that takes visual images and turns them into nerve signals that are sent to the brain to form the images that we "see", as shown in the following link¹.

References & Links

Links
Retina - http://webvision.umh.es/webvision/imageswv/Sagschem.jpeg

12.64 Vitamin A Deficiency & Toxicity

Vitamin A deficiency is rare in North America, but is a huge problem in developing countries. In many developing countries, they do not have a stable dietary source of retinoids or provitamin.

Often the earliest symptom of vitamin A deficiency is night blindness, due to the insufficient production of rhodopsin. The reason that this is the earliest symptom, is that circulating vitamin A levels are homeostatically-controlled, meaning that they do not change until after vitamin A
stores are exhausted. This means that blood, serum, plasma measurements are going to appear normal until all stores are exhausted. As a result, sensitively assessing someone as vitamin A deficient can be challenging. There are further changes to the eye that occur during vitamin A deficiency, collectively referred to as xerophthalmia, which are shown in the Required Web Link on the next page.

Ultimately the person can become blind. Vitamin A deficiency is the leading cause of blindness in some parts of the world\(^1\).

Another symptom of vitamin A deficiency is hyperkeratosis. In this condition, cells overproduce the protein keratin, causing the skin to become rough and irritated, as shown in the link below\(^1\).

One way to counter vitamin A deficiency in developing countries is for staple crops, like rice and corn, to contain beta-carotene. In the case of rice, Golden Rice was genetically modified to produce beta-carotene. A second generation of golden rice, known as Golden Rice 2, has now been developed. However, politics and regulations have prevented it from being used. This is described in the first link. The second link shows some of the opposition to Golden Rice. The third is a nice figure that details the progress towards Golden Rice being used.

Vitamin A can be very toxic and can cause serious symptoms, such as blurred vision, liver abnormalities, skin disorders, and joint pain\(^{1,2}\). In addition, research has suggested that people who consume high levels of vitamin A are more prone to bone fractures\(^2\). Toxic levels of vitamin A are also teratogenic, which means they could cause birth defects.
References & Links

Links
Hyperkeratosis - [http://api.ning.com/files/pKcbly8a8fSwvjlw-NqcoyW-h1U9xsjxM86*Pg7xe7WAS91frtrQFTbTH2oDWcMvbUJ9MuItd3B9tXk8hjbfrmXkeZyJs-7Mi/follicularhyperkeratosis1.jpg](http://api.ning.com/files/pKcbly8a8fSwvjlw-NqcoyW-h1U9xsjxM86*Pg7xe7WAS91frtrQFTbTH2oDWcMvbUJ9MuItd3B9tXk8hjbfrmXkeZyJs-7Mi/follicularhyperkeratosis1.jpg)

12.7 Iron

There are 2 major dietary forms of iron: **heme iron** and **non-heme iron**. Heme iron is only found in foods of animal origin, within hemoglobin and myoglobin. The structure of heme iron is shown below.

![Figure 12.71 Structure of heme iron](http://www.irri.org/images/golden_rice/GoldenRiceProjectTimelineAugust2013.jpg)

Approximately 40% of iron in meat, fish, and poultry is heme-iron, and the other 60% is non-heme iron.

Non-heme iron is the mineral alone, in either its oxidized or reduced form. The 2 forms of iron are:
- Ferric (Fe³⁺, oxidized)
- Ferrous (Fe²⁺, reduced)
It is estimated that 25% of heme iron and 17% of non-heme iron are absorbed\(^2\). Approximately 85-90% of the iron we consume is non-heme iron\(^2,3\).

In addition to getting iron from food sources, if food is cooked in cast iron cookware, a small amount of iron can be transferred to the food. On the next page you will find a link to a story about the iron fish that is being used in Cambodia to increase iron intake in an area with prevalent iron deficiency. However, they found that the iron fish was not effective in reducing anemia\(^4\).

**Web Link**

Canadian’s lucky iron fish saves lives in Cambodia

Many breakfast cereals are fortified with reduced iron, which looks like iron filings, as the following video shows.

**Web Link**

Video: Iron for breakfast (1:02)

While the iron bioavailability of this reduced iron is low, some is absorbed\(^5\).

**Supplements**

Most iron supplements use ferrous (Fe\(^{2+}\)) iron, because this form is better absorbed, as discussed in the next section. The figure below shows the percent of elemental iron in different supplements. This is the percentage of elemental iron that is in each compound.

![Elemental iron in different iron supplements](Figure 12.72 Elemental iron in different iron supplements\(^3\))
Vitamin C does not increase absorption of ferrous supplements because they are already in reduced form, as discussed in the following subsection. Iron chelates are marketed as being better absorbed than other forms of iron supplements, but this has not been proven. It is recommended that supplements are not taken with meals, because they are better absorbed when not consumed with food.

For more information on vitamin K, see the Required Web Link below.

**Required Web Link**
Iron Dietary Supplement Fact Sheet

Subsections:
- 12.71 Iron Uptake & Absorption
- 12.72 Iron Transport & Storage
- 12.73 Iron Functions
- 12.74 Iron Deficiency & Toxicity

**References & Links**
3. [http://foodfix.ca/health.php#en65](http://foodfix.ca/health.php#en65)

**Link**

**Video**
Iron for breakfast - [https://www.youtube.com/watch?v=pRK15XSqtAw](https://www.youtube.com/watch?v=pRK15XSqtAw)
12.71 Iron Uptake & Absorption

There are 2 transporters for iron, one for heme iron and one for non-heme iron. The non-heme transporter is the divalent mineral transporter 1 (DMT1), which transports Fe\(^{2+}\) into the enterocyte. Heme iron is taken up through heme carrier protein 1 (HCP-1), and then metabolized to Fe\(^{2+}\). Fe\(^{2+}\) may be used by enzymes and other proteins or stored in the enterocyte bound to ferritin, the iron storage protein. To reach circulation, iron is transported through ferroportin\(^{1,2}\). This process is summarized in Figure 12.711.

![Figure 12.711 Iron uptake into the enterocyte](image)

Since only the reduced form of non-heme iron (Fe\(^{2+}\)) is taken up, Fe\(^{3+}\) must be reduced. There is a reductase enzyme on the brush border, duodenal cytochrome b (Dcytb), that catalyzes the reduction of Fe\(^{3+}\) to Fe\(^{2+}\), as shown below. Vitamin C enhances non-heme iron absorption because it is required by Dcytb for this reaction. Thus, if dietary non-heme iron is consumed with vitamin C, more non-heme iron will be reduced to Fe\(^{2+}\) and taken up into the enterocyte through DMT1 as shown in Figure 12.712.
In addition to vitamin C, there is an unidentified factor in muscle that enhances non-heme iron absorption if consumed at the same meal\(^3\). This unidentified factor is referred to as meat protein factor (MPF).

Inhibitors of non-heme iron absorption typically chelate, or bind, the iron to prevent absorption. Phytates (phytic acid), which also inhibit calcium absorption, chelate non-heme iron decreasing its absorption.

Other compounds that inhibit absorption are:

Polyphenols (coffee, tea)\(^1\)

---

Figure 12.712 Reduction of non-heme iron by Dcytb

Figure 12.713 Structure of phytic acid\(^4\)

Figure 12.714 Structure of gallic acid, a polyphenol\(^5\)
Oxalate (spinach, rhubarb, sweet potatoes, and dried beans)\(^2\)

![Figure 12.715 Structure of calcium oxalate](http://en.wikipedia.org/wiki/File:Calcium_oxalate.png)

Calcium is also believed to inhibit iron uptake.

**References & Links**


### 12.72 Iron Transport & Storage

*Transferrin* is the major iron transport protein (transports iron through blood). \(\text{Fe}^{3+}\) is the form of iron that binds to transferrin, so the \(\text{Fe}^{2+}\) transported through ferroportin must be oxidized to \(\text{Fe}^{3+}\). There are 2 copper-containing proteins that catalyze this oxidation of \(\text{Fe}^{2+}\): hephaestin and ceruloplasmin. Hephæastin is found in the membrane of enterocytes, while ceruloplasmin is the major copper transport protein in blood. Hephæastin is the primary protein that performs this function in a coupled manner (need to occur together) with transport through ferroportin. This means that the \(\text{Fe}^{2+}\) needs to be oxidized to be transported through ferroportin. Evidence suggests that ceruloplasmin is involved in oxidizing \(\text{Fe}^{2+}\) when iron status is low\(^1\). Once oxidized, \(\text{Fe}^{3+}\) binds to transferrin and is transported to a tissue cell that contains a transferrin receptor. Transferrin binds to the transferrin receptor and is endocytosed, as shown in Figure 12.721\(^2\).
Once inside cells, the iron can be used for cellular purposes (cofactor for enzyme etc.) or it can be stored in the iron storage proteins ferritin or hemosiderin. Ferritin is the primary iron storage protein, but at higher concentrations, iron is also stored in hemosiderin\(^2\).

There are 3 major compartments of iron in the body\(^3\):
1. Functional Iron
2. Storage Iron
3. Transport Iron
Functional iron consists of iron performing some function. There are 3 functional iron subcompartments.

1. Hemoglobin
2. Myoglobin
3. Iron-containing enzymes

The functions of these sub-compartments are discussed in the next section.

Iron Stores consist of:
1. Ferritin
2. Hemosiderin

The liver is the primary storage site in the body, with the spleen and bone marrow being the other major storage sites.

Circulating iron is found in transferrin³.

The majority of iron is in the functional iron compartment. The figure below further reinforces this point, showing that most iron is found in red blood cells (hemoglobin) and tissues (myoglobin).

![Iron distribution in different compartments](image-url)

Figure 12.723 Iron distribution in different compartments⁴

Also notice how small oral intake and excretion are compared to the amount found in the different compartments in the body. As a result, iron recycling is really important, because red blood cells only live for 120 days. Red blood cells are broken down in the liver, spleen, and bone marrow and the iron can be used for the same purposes as described earlier: cellular use, storage, or transported to another tissue on transferrin². Most of this iron will be used for heme
and ultimately red blood cell synthesis. The figure below summarizes the potential uses of iron recycled from red blood cells.

![Figure 12.724 Iron recycling from red blood cells](image)

Iron is unique among minerals in that our body has limited excretion ability. Thus, absorption is controlled by the hormone hepcidin. The liver has an iron sensor so when iron levels get high, this sensor signals for the release of hepcidin. Hepcidin causes degradation of ferroportin. Thus, the iron is not able to be transported into circulation.

![Figure 12.725 Action of hepcidin](image)

The iron is now trapped in the enterocyte, which is eventually sloughed off and excreted in feces. Thus, iron absorption is decreased through the action of hepcidin.
Enterocytes are sloughed off the villus and unless digested and their components reabsorbed, they will be excreted in feces.

References & Links

12.73 Iron Functions

As we talked about in the previous subsection, there are 3 primary functional iron subcompartments:
1. Hemoglobin
2. Myoglobin
3. Iron-containing enzymes

Hemoglobin contains heme that is responsible for red blood cells’ red color. Hemoglobin carries oxygen to tissues. The function of hemoglobin can be seen in the Required Web Link below.

Required Web Link
Hemoglobin

Myoglobin is similar to hemoglobin in that it can bind oxygen. However, instead of being found in blood, it is found in muscle. The color of meat products is a result of the state that myoglobin is in, as shown in the Required Web Link on the next page.
There are a number of enzymes that use iron as a cofactor. We've already talked about two in this class.

Iron is a cofactor for the antioxidant enzyme, catalase that converts hydrogen peroxide to water, as shown below.

Figure 12.731 Catalase uses iron as a cofactor

Iron is also a cofactor for proline and lysyl hydroxylases that are important in collagen cross-linking. This will be discussed further in the vitamin C section. The function of these enzymes is shown below.

Figure 12.732 Importance of ascorbic acid and iron to proline and lysyl hydroxylases.
Heme iron is also found in cytochromes, like cytochrome c in the electron transport chain as shown below\(^1\).

![Electron Transport Chain](ETC.png)

Figure 12.733 Cytochrome c in the electron transport chain contains iron\(^2\)

**References & Links**

**Links**

### 12.74 Iron Deficiency & Toxicity

The levels of iron in the different compartments is illustrated by the figure below. The red above the table is meant to represent the amount of iron in the different compartments. In early negative iron balance stage, iron stores are slightly depleted. Once the stores are almost completely exhausted, this state is referred to as iron depletion. In iron deficiency, stores are completely exhausted and the circulating and functional iron levels are also depleted. In iron anemia, the circulating and functional iron levels are further depleted from iron-deficiency.
Great measure, but invasive

Small amount are released from liver, bone, and spleen – proportional to body stores

Also referred to as total iron-binding capacity

Figure 12.741 Measures of iron status¹⁻³

The most common measures of iron status are hemoglobin concentrations and hematocrit (described below) levels. A decreased amount of either measure indicates iron deficiency, but these two measures are among the last to indicate that iron status is depressed. This is because, as you can see in the figure above, circulating iron (plasma iron) levels are not altered until you reach iron deficiency. Thus, other measures are likely better choices.

The hematocrit, as illustrated in the figure below, is a measure of the proportion of red blood cells (erythrocytes) as compared to all other components of blood. The components are separated by a centrifuge. The red blood cells remain at the bottom of the tube. They can be quantified by measuring the packed cell volume (PCV) relative to the total whole blood volume.
One of the best measures of iron status is bone marrow iron, but this is an invasive measure, and is therefore not commonly used. Plasma ferritin, the iron storage protein, is also found in lower amounts in the blood (plasma) and is a good indicator of iron stores. Thus, it is a sensitive measure to determine if someone is in negative iron balance or iron depleted. It is not as useful of a measure beyond this stage because the iron stores have been exhausted for the most part. Transferrin iron binding capacity (aka total iron binding capacity), as it sounds, is a measure of how much iron transferrin can bind. An increase in transferrin iron binding capacity indicates deficiency (>400 indicates deficiency). But the best measure for deficiency or anemia is either percent serum transferrin saturation or plasma iron. A lower % saturation means that less of the transferrin are saturated or carrying the maximum amount of iron that they can handle. Plasma iron is easily understood as the amount of iron within the plasma.

Iron deficiency is the most common deficiency worldwide, estimated to affect 1.6 billion people. In the US, it is less common, but an estimated 10% of toddlers and women of childbearing age are deficient. Iron deficiency often results in a microcytic (small cell), hypochromic (low color) anemia, that is a result of decreased hemoglobin production. With decreased hemoglobin, the red blood cells cannot carry as much oxygen. Decreased oxygen leads to slower metabolism. Thus, a person with this anemia feels fatigued, weak, apathetic, and can experience headaches. Other side effects include decreased immune function and delayed cognitive development in children.

Those who are particularly at risk are:

- Women of childbearing age - because of losses due to menstruation
- Pregnant women - because of increased blood volume
- Vegetarians - because they do not consume heme iron sources
- Infants - because they have low iron stores that can quickly be depleted

To give you a better understanding of these risks, it is helpful to look at how much higher the RDAs are for women of reproductive age and pregnant women compared to men.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Women of reproductive age</td>
<td>18 mg/day</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>27 mg/day</td>
</tr>
<tr>
<td>Men</td>
<td>8 mg/day</td>
</tr>
</tbody>
</table>

To put this in perspective, 3 oz of beef contains ~3 mg of iron. Thus, it can be a challenge for some women to meet the requirement. The RDA committee estimates the iron requirements to be 80% and 70% higher for vegans and endurance athletes, respectively. The increased requirement for endurance athletes is based on loss due to "foot strike hemolysis", or the
increased rupture of red blood cells due to the striking of the foot on hard surfaces\textsuperscript{3}.

Iron toxicity is rare in adults, but can occur in children who consume too many supplements containing iron. Symptoms of this acute toxicity include nausea, vomiting, and diarrhea\textsuperscript{7}.

50 out of 10,000 newborns in the United States are born with the genetic condition, hemochromatosis. In this condition, there is a mutation in a protein in the enterocyte that prevents the normal decrease of intestinal iron absorption. Without this protein these individuals cannot decrease iron absorption. Since the body cannot excrete iron, it accumulates in tissues, and ultimately can result in organ failure\textsuperscript{1}.

**References & Links**


**12.8 Zinc**

Many animal products are good sources of zinc and are estimated to account for 70% of the zinc North Americans’ consume\textsuperscript{1}. An estimated 15-40% of consumed zinc is absorbed\textsuperscript{2}. Zinc is taken up into the enterocyte through the Zir-and Irt-like protein 4 (ZIP4). Once inside the enterocyte, zinc can:

1. Bind to the zinc storage protein thionein. Once thionein has bound a mineral (or a metal) it is known as metallothionein.

2. Be used for functional purposes.
3. Bind to the cysteine-rich intestinal protein (CRIP) where it is shuttled to a zinc transporter (ZnT). After moving through the basolateral membrane, zinc primarily binds to the circulating protein albumin.

These functions are represented in the figure below.

The zinc attached to albumin is transported to the liver through the portal vein. There is not a major storage site of zinc, but there are pools of zinc in the liver, bone, pancreas, and kidney.

Zinc is primarily excreted in feces.

There are some similarities between zinc and iron absorption. Increased zinc consumption results in increased thionein synthesis in the enterocyte. As a result, more zinc is bound to thionein (forming metallothionein) and not used for functional uses or transported into circulation, as represented by the thick and thin arrows in the figure below.
The enterocytes are then sloughed off preventing the bound zinc from being absorbed.

Figure 12.83 Enterocytes are sloughed off and excreted in feces.

There are a number of inhibitors of zinc absorption:

1. Phytate (phytic acid), which inhibits calcium and iron absorption, also binds to and inhibits zinc absorption\(^3\)
2. Polyphenols (coffee, tea)\(^3\)
3. Oxalate (spinach, rhubarb, sweet potatoes, and dried beans)\(^3\)

Non-heme iron also inhibits zinc absorption.

In supplements, zinc is found as\(^3,4\):
- Zinc oxide - 80% zinc
- Zinc chloride - 23% zinc
- Zinc sulfate - 23% zinc
- Zinc gluconate - 14.3% zinc

Zinc oxide is the least bioavailable form, but since it is 80% zinc, it is commonly used in supplements\(^7\).

For more information on vitamin K, see the Required Web Link below.

**Required Web Link**

[Zinc Fact Sheet for Health Professionals](#)

Subsections:
- 12.81 Zinc Functions
- 12.82 Zinc Deficiency & Toxicity

**References & Links**
12.81 Zinc Functions

Zinc is a cofactor for up to 300 enzymes in the body. Enzymes that use zinc as a cofactor are known as metalloenzymes.

Zinc is a cofactor for the antioxidant enzyme superoxide dismutase that converts superoxide to hydrogen peroxide, as shown below.

![Superoxide dismutase uses zinc as a cofactor](image)

Alcohol dehydrogenase uses 4 zins per enzyme. Its role in ethanol metabolism is shown in Figure 12.812.
Figure 12.812 Ethanol metabolism\textsuperscript{3,4}

Zinc is also important for the formation of zinc fingers in proteins. Zinc fingers help proteins bind to DNA\textsuperscript{2}.

Figure 12.815 Structure of a zinc finger, zinc is the green atom bound in the center\textsuperscript{5}

Zinc is also important for growth, immune function, and reproduction\textsuperscript{2,6}.

**References & Links**
12.82 Zinc Deficiency & Toxicity

As can be seen on the bottom map in the link below, the risk of zinc deficiency is low in North America, but there are other places in the world where it is much more common.

![Worldwide prevalence of zinc deficiency](image)

At particular risk are children, pregnant women, elderly and the poor. Symptoms of zinc deficiency include:
- Growth inhibition
- Delayed sexual maturation
- Dermatitis
- Hair loss
- Impaired immune function
- Skeletal abnormalities

In the link below you can see a picture of an infant with dermatitis caused by zinc deficiency.

[Web Link](Zinc Deficiency Dermatitis)

Zinc toxicity is not common, but an acute toxicity results in:
- Nausea
- Vomiting
- Intestinal cramps
- Diarrhea

Chronic toxicity can result in copper deficiency, as will be discussed in the copper section.

References & Links

Links

12.9 Copper

Like iron, copper is found in 2 forms:
1. Cupric (Cu$^{2+}$), oxidized
2. Cuprous (Cu$^{1+}$), reduced

Cu$^{1+}$ is the form that is primarily absorbed, thus Cu$^{2+}$ is reduced to Cu$^{1+}$ in the lumen. Like zinc, copper is transported through the portal vein to the liver bound to albumin, as shown below. Albumin has a high affinity for Cu$^{2+}$, so Cu$^{1+}$ is oxidized before transported to albumin through ATP7A, as illustrated below.

Figure 12.91 Copper absorption

Like zinc, there is not much storage of copper in the body. The liver is the primary site of storage, where copper is taken up through an unknown transporter. If it is going to be stored, it will bind with thionein to form metallothionein. Copper to be sent out to the body is transferred to the copper transport protein ceruloplasmin, which can bind 6 coppers/protein as shown below.
Legumes, whole grains, nuts, shellfish, and seeds are good sources of copper. It is estimated that over 50% of copper consumed is absorbed. Copper is primarily excreted in the feces.

There are number of different forms of copper used in supplements:

- Copper sulfate (25% copper)
- Cupric chloride (47% copper)
- Cupric acetate (35% copper)
- Copper carbonate (57% copper)
- Cupric oxide (80% copper)

All of these forms of copper are bioavailable, except cupric oxide. Assays have shown that it is not absorbed at all. Nevertheless, some supplements still use this form of copper.

Subsections:

12.91 Copper Functions
12.92 Copper Deficiency & Toxicity
12.93 How High Zinc Intake Can Lead to Iron & Copper Deficiencies

References & Links
3. Baker DH. (1999) Cupric oxide should not be used as a copper supplement for either animals or humans. J Nutr
12.91 Copper Functions

Copper has a number of functions that are described and shown below.

Two copper-containing proteins, ceruloplasmin and hephaestin, oxidize Fe$^{2+}$ to Fe$^{3+}$. Fe$^{3+}$ is the form that binds to transferrin, as shown below.²

Because copper is needed for this function, it is important for iron absorption.

Copper is also a cofactor for superoxide dismutase, which converts superoxide to hydrogen peroxide, as shown below.
Copper is also needed for hormone synthesis. For example, it is a cofactor for dopamine beta-hydroxylase, which converts dopamine to norepinephrine.

Hopefully the following example looks vaguely familiar because we talked about this pathway in the vitamin C functions subsection. Ascorbic acid reduces Cu$^{2+}$ back to Cu$^{1+}$ so that this enzyme can continue to function, as shown below. This is analogous to how ascorbic acid reduces Fe$^{3+}$ back to Fe$^{2+}$ so proline and lysyl hydroxylases can continue to function.

![Figure 12.914 Dopamine beta-hydroxylase](image)

Cytochrome c oxidase (complex IV) in the electron transport chain is a copper-containing enzyme that reduces oxygen to form water, as shown below.

![Figure 12.915 Cytochrome c oxidase (complex IV)](image)

Lysyl oxidase, an enzyme that is important for cross-linking between structural proteins (collagen and elastin), requires copper as a cofactor. 
12.92 Copper Deficiency & Toxicity

Copper deficiency is rare in humans, but results in the following symptoms\(^1,2\):

- Hypochromic anemia
- Decreased white blood cell counts leading to decreased immune function
- Bone abnormalities.

Copper deficiency can result in a secondary iron deficiency, since Fe\(^{2+}\) cannot be oxidized to Fe\(^{3+}\) to bind to transferrin. This can cause the hypochromic anemia that occurs in iron deficiency.

Copper toxicity is also rare in humans, but acute toxicity results in the following symptoms\(^1,2\):

- Nausea, vomiting, diarrhea, and abdominal pain.

Chronic symptoms include\(^1,2\): Brain, liver, and kidney damage as well as neurological damage.

Wilson's disease is a genetic disorder where a mutation in ATP7B prevents copper excretion, resulting in copper toxicity. One notable symptom is that individuals with this disease have golden to greenish-brown Kayser-Fleischer rings around the edges of the cornea, as shown in the link below\(^1,2\).

**Web Link**
[Kayser-Fleischer ring](http://www.nejm.org/doi/full/10.1056/NEJMicm1101534#t=article)

**References & Links**

12.93 How High Zinc Intake Can Lead to Copper & Iron Deficiencies

As you learned previously, thionein is the storage protein for zinc, but it more avidly binds copper. When it binds a mineral, it becomes metallothionein. High zinc intake results in increased thionein synthesis in the enterocyte. Thus, when an individual is consuming high zinc levels, the enterocyte will have high levels of thionein as shown below.

Figure 12.931 Zinc increases thionein production

The high levels of thionein will bind any copper that is taken up into the enterocyte (as metallothionein), "trapping" the copper in the enterocyte and preventing it from being absorbed into circulation, as shown below.

Figure 12.932 Copper taken up into the enterocyte is bound to thionein forming metallothionein.
The enterocytes containing the "trapped" copper move up the crypt and are sloughed off and excreted in feces. The copper consumed essentially is lost from the body through this process.

Figure 12.933 Enterocytes are sloughed off and excreted in feces

Without adequate copper being transported to the liver, no ceruloplasmin is produced and released into circulation. The lack of copper further influences iron transport by decreasing ceruloplasmin in circulation and hephaestin (another copper-containing protein) on the membrane of the enterocyte. These 2 proteins normally convert Fe$^{2+}$ to Fe$^{3+}$ so that iron can bind to transferrin.

Figure 12.934 Lack of copper means that hephaestin and ceruloplasmin aren't available to oxidize Fe$^{2+}$ to Fe$^{3+}$

Without hephaestin and ceruloplasmin, Fe$^{3+}$ is not formed from Fe$^{2+}$. As a result Fe$^{2+}$ is "trapped" in the enterocyte because it can't bind to transferrin as shown in Figure 12.935.
The enterocytes containing the "trapped" iron move up the crypt and are also sloughed off and excreted in feces. The iron consumed essentially is lost from the body through this process.

In summary, high zinc intake increases thionein production, which traps all copper; the lack of copper decreases circulating ceruloplasmin and hephaestin, which causes all iron to be trapped as well. This example illustrates the interconnectedness of zinc, copper, and iron.

No References