Chapter 5. Vitamins

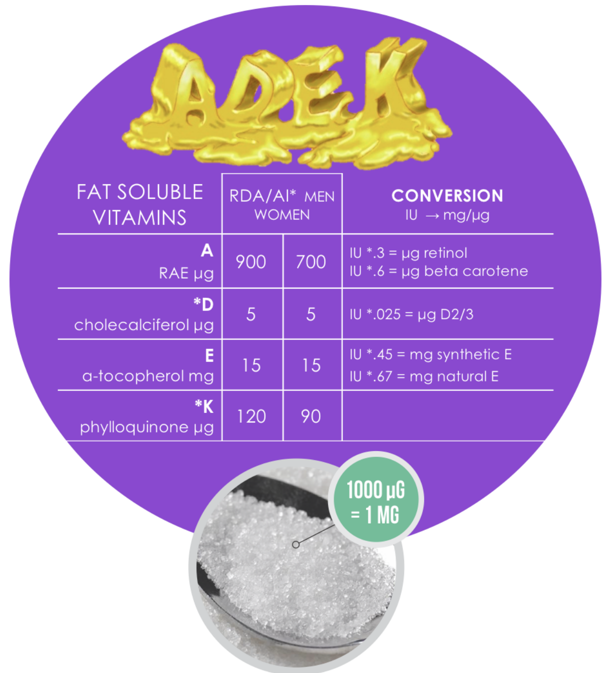
5.1 Vitamin Needs

Vitamins and their many chemical 'vitamers' are essential in small quantities in the daily human diet. Nutrition research has established a recommended daily allowance (RDA) for thirteen vitamins and continues to progresses in characterizing newly discovered biologically active vitamers.

Large-scale studies evaluating the average daily intake of vitamins indicate that adults in the US, on average, consume an adequate level of vitamins from a variety of single foods, mixed meals, and supplemental vitamin enriched products. The data also indicate that additional vitamin supplementation is not necessary for the average diet and that intakes at the higher end of each range do not confer any beneficial health outcomes related to overall morbidity or mortality. More work is needed to determine valid upper intake levels for certain vitamins as the number of fortified food products and market for functional vitamins and supplements continues to grow.

Smaller, more controlled trials have evaluated vitamin absorption, transport, retention and bodily excretion across a wide range of doses and a large number of experimental conditions. These experiments have uncovered some of the mechanisms of how the body maintains vitamin homeostasis and some of the acute and longer-term effects of inadequate or excessive intake.

These studies also laid the groundwork for current molecular phytochemical research, which continues to progress and concentrate with increasing technology. As scientists learn more about the non-essential, but beneficial, role of these thousands of vitamin like-compounds in the diet, our current understating of vitamins will evolve. For now, of the seemingly countless number of natural vitamers and newly developed synthetic ones, the current scientific consensus regarding essential daily vitamin intake includes thirteen vitamins that are typically sub-classified into two groups by solubility.



The **fat-soluble vitamin** class includes vitamins **A, D, E and K**. The chemical configurations of the fat-soluble class, like dietary lipids, are immiscible in food systems and in the human body. This feature, while requiring more laborious bodily processing, lends to a number of critical biological roles – most notably, a protein binding factor required for vision, a hormone precursor needed for blood calcium homeostasis, a free radical scavenger for cell membrane and serum lipoprotein preservation, and a biosynthetic pathway needed for blood clotting proteins. Since fat-soluble vitamins are stored in relatively high concentrations in the body, the ones that are abundant in foods pose a risk of toxicity when taken in supplemental formats. To help people monitor their intake of fat-soluble vitamins, dietary supplements are labeled with International Units rather than by weight. The IU is a standardized vitamin dose that reflects the biologically active ingredients in a supplement formulation. These formulations may include blends of natural and synthetic vitamers with one or more chemical configurations, each with varying biological potencies. The fat-soluble vitamins that are less abundant in foods are synthesized in the body to meet a significant portion of the daily requirements. However, in instances where body synthesis may be compromised, more careful attention to dietary intake must be devoted. This is especially true for fat-soluble vitamin D, which is the only of the thirteen vitamins that is currently required on the Nutrition Facts Panel.

Vitamin A was the first vitamin ever discovered. The vitamin A family includes several members that are all referred to collectively in the DRI as **retinol.** Retinol is the biologically active form of vitamin A that is consumed directly from foods of animal origin. Humans also convert dietary provitamin A carotenoids, which are naturally concentrated in darkly pigmented plants, to biologically active retinol in a manner that is two- to three-fold less efficient than that of pre-formed dietary retinol. To compensate for the biological inefficiency of the pro-A vitamers, the daily allowance and food composition data for vitamin A are expressed in retinol activity equivalents (RAE), rather than total mcg vitamin A. The daily allowance for vitamin A has been established for men and women based on the amount needed to maintain normal vision adaptations from light to dark. Dietary and supplemental retinol intake should not exceed upper levels; however, supplemental doses of pre-formed vitamin A in the form of beta-carotene are not similarly restricted. Other non-retinol forming members in the vitamin A family, including lycopene, lutein, and zeaxanthin, are phytochemicals under study but are not included in the current DRI. They are, however, increasingly recognized on food packages, and are included in food compositional databases.

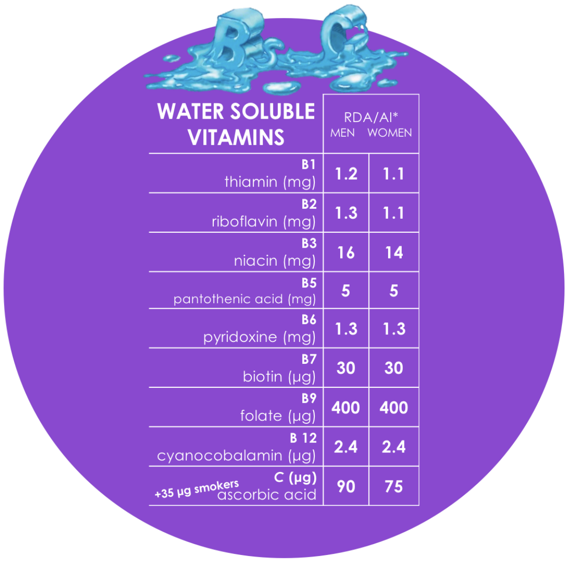
The **vitamin D** family includes two secosterols. **Cholecalciferol**, or **vitamin D3**, is synthesized in the skin of humans from 7-dehydrocholesterol and exposure to UV light. **Ergocalciferol**, or vitamin D2, exists naturally in low concentrations in a small number of plant foods and, along with D3, a large number of fortified foods and supplements. Vitamins D2 and D3 in natural or synthetic dietary forms are 25 times less biologically active than kidney-activated 25(OH)D. The daily intake for men and women is estimated based on minimal sunlight exposure and is most often expressed in International Units (IU). Supplemental vitamin D is said to be unnecessary unless cutaneous production of vitamin D from the sun's UV rays is compromised or impaired, such as that seen in populations with higher levels of UV blocking melanin (i.e., those with darker skin pigments) and those indigenous to regions beneath the latitude of the sun. Sun-produced vitamin D is not proportional to dietary intake and plateaus after just a short time in the sun. Therefore, it is not recommended to skip or skimp on using UV protectant sunscreens for the sake of effective vitamin D production. If and when supplementation is warranted, the dosing of vitamin D should not exceed the daily allowance.

There are eight naturally occurring vitamers in the **vitamin E** family. **Alpha-tocopherol** is the only isomer in the family that is biologically active. The other forms of the vitamin (i.e., β-, γ-, and δ-tocopherols and the β-, γ-, and δ tocotrienols) that are in foods are unrecognizable to the human liver, and therefore, biologically inactive. Natural alpha-tocopherol abundant in foods is characterized by a 3R stereo-isomeric configuration that is approximately thirty times more biologically potent than synthetic alpha-tocopherol, which features a 2R stereoisometric configuration. The amount of natural and synthetic alpha tocopherols that are listed in fortified foods and dietary supplements is typically expressed in IU to account for the differences in biological potency between the two forms. The other three non-biologically active tocopherols, and all four tocotrienols in the E family, are left out of food composition databases, the recommended daily allowance and upper limits.

Vitamin K includes a family of K1 and K2 vitamers that were named from a German word for "koagulation." Daily vitamin K needs are amply met by dietary **phylloquinone (K1)** and intestinally produced **menaquinone (K2)**. The body also recycles vitamin K in a process called the vitamin K-epoxide cycle that reduces the daily intake requirement. The adequate intake (AI) value for phylloquinon was determined based on representative dietary intake data from healthy individuals who maintain normal blood clotting responses. Individuals consuming higher amounts of dietary vitamin K have not reported adverse effects, so a UL for K has not been established.

Water-soluble B vitamins followed the discovery of vitamin A but preceded the discovery of vitamin C. Named in largely consecutive order, the B series of vitamins includes 9 vitamins: B1-B6, B7, B9, and B12. The phantom numbers (B4 and B8), and re-naming of some vitamins like B9 to folate, are products of scientific progress that invalidated previous, now outdated classifications.

Daily requirements for pre-formed **vitamins B1-B6 and 12,** as well as their related biological metabolites, have been determined using a number of methods to assess plasma, serum and urinary responses to controlled B vitamin intake. For most water-soluble B vitamins, toxicity is unlikely because urinary excretion is



WATER SOLUBLE VITAMINS	RDA/AI* MEN	WOMEN
B1 thiamin (mg)	1.2	1.1
B2 riboflavin (mg)	1.3	1.1
B3 niacin (mg)	16	14
B5 pantothenic acid (mg)	5	5
B6 pyridoxine (mg)	1.3	1.3
B7 biotin (μg)	30	30
B9 folate (μg)	400	400
B 12 cyanocobalamin (μg)	2.4	2.4
C (μg) ascorbic acid +35 μg smokers	90	75

Figure 5.2. Recommended Daily Water Soluble Vitamin Intake.

proportional to dietary intake, and plasma disappearance is relatively rapid when consumed in doses in excess of biological need. On the contrary, when dietary intake of water-soluble B vitamins is lower, excretion is reduced, suggesting there are conservation and recycling mechanisms maintaining body-vitamin homeostasis.

One WSV, B3, is also synthesized in human tissues from the amino acid tryptophan, therefore the daily allowance for niacin includes 1 NE for every 60mg dietary tryptophan. For pantothenic acid, the daily allowance is based on average intake of healthy adult populations, therefore only an AI was established.

Due to the Grain Fortification Act, the average adult consuming the typical American diet sufficiently meets daily vitamins B1-6 requirements. The daily requirement for vitamins B1-6 and 12 is around 25 mg/day, excluding the largest of the group, B3 niacin, which is closer to just 10 mg/day. When dietary supplements are included in the vitamin intake estimates, the upper ranges exceed anywhere from 2-10 times the recommended daily allowance. Data concerning adverse effects of excess levels of dietary vitamins are not sufficient to set a Tolerable Upper Intake Level (UL) for most of the water-soluble vitamins (i.e., B1, 2, 5 and12) but there is sufficient evidence, however, for vitamins B3 and B6 which have both been associated with adverse clinical symptoms in doses above the DRI. For B3, intakes of only two times the UL causes issues.

Dietary **Folate** comprises natural food folate (i.e., folacin) and synthetic folic acid. Both folate chemicals include a key amino peptide glutamate but synthetic folic acid is fully oxidized, more chemically stable, and about twice as biologically active as natural food folate. To adjust for variances in biological activity and the absorption enhancing effects of food, daily folate allowances are expressed as folate equivalents, whereby 1 μg of dietary folate equivalent = 0.6 μg folic acid from foods or supplements taken with meals, and 0.5 μg folic acid on an empty stomach. Due to the Grain Enrichment Act, folate intake in the US for healthy adult men and non-pregnant women is adequate from natural and fortified foods sources alone. The Tolerable Upper Intake Level (UL) excludes natural food folate since adverse effects of toxicity only occur with excessive intake of synthetic folic acid from dietary supplements.

Ascorbic acid contains two enolic hydrogen atoms that give the compound its acidic character and electrons to participate in cellular redox reactions. The molecular structure of ascorbic acid contains an asymmetric carbon atom that allows two enantiomeric forms: one of which, the L form, is naturally occurring in foods; and the other, D form chemicals, provide antioxidant activity but little or no anti-scorbutic activity. The daily allowance for vitamin C includes both forms at a level required to maintain near-maximal neutrophil concentration (i.e., storage) with minimal urinary ascorbate excretion. Because smoking increases oxidative stress and metabolic turnover of vitamin C, the daily requirement for smokers is increased by about 30%. While intake of vitamin C from foods is adequate in adult men and women, vitamin C supplement intake is high in the US. There is a Tolerable Upper Intake Level (UL) established for adults, as excessive doses of vitamin C can elicit adverse effects.

5.1 Homework 1

Homework • Answered

Which vitamin is water soluble?

- ○ **A** A
- ◉ **B** C
- ○ **C** D
- ○ **D** E

Explanation

Yes, Vitamin C

Answered - Correct!

1 attempt left Retry

5.1 Homework 2

Homework • Answered

Match each vitamin to its vitamer family member or more formal chemical name (each answer only used once)

Premise		Response
1 A	→	A retinol
2 D	→	B cholecalciferol
3 E	→	E tocopherol
4 B 12	→	C cobalamin
5 B 2	→	D riboflavin

Answered - Correct!

1 attempt left Retry

5.1 Homework 3

Homework • Answered

Smokers have a higher estimated daily requirement for what vitamin?

- ○ A D
- ○ B E
- ○ C B 3
- ◉ D C

Answered - Correct!

No attempts left

5.1 Homework 4

Homework • Answered

The RAE for Vitamin A includes which two vitamers?

- ◉ A Beta-carotene and retinol
- ○ B Lycopene and lutein
- ○ C Lutein and retinol
- ○ D Beta-carotene and lycopene

Answered - Correct!

1 attempt left Retry

5.1 Homework 5

Homework • Answered

Of the 8 vitamers in the vitamin E family, only ______________ -tocopherol is included in the DRI and food analysis data

- ○ **A** gamma
- ◉ **B** alpha
- ○ **C** omega
- ○ **D** beta

Answered - Correct!

No attempts left

5.1 Homework 6

Homework • Answered

A portion of the daily requirements for these two fat-soluble vitamins is synthesized in the body.

Multiple answers: You can select more than one option

- (selected) **A** K and D
- **B** C and A
- **C** B 2 and E
- **D** Folate and C

Explanation

The daily need for vitamin K and D is partially satisfied by endogenous production by the gastrointestinal track and skin, respectively.

Answered - Correct!

1 attempt left Retry

5.2 Vitamin Sources

Vitamins are consumed in the diet from whole natural plant and animal food sources and from fortified food products and dietary supplements. The vitamin content of foods is measured in laboratories using high-performance liquid chromatography techniques. While methods and protocols for determining the vitamin content of foods are highly standardized, the natural vitamin content of whole foods is highly variable and affected by a countless number of temporal and environmental interactions such as soil, climate, and maturation. The vitamin contents presented in this section are for standard reference foods and branded foods.

As the volume of vitamins in the daily diet is such a small proportion of total food intake (less than 2%) vitamins are ideal nutrients to use to fortify staple foods and to develop daily supplemental nutrition products. The primary source of added vitamins in the diet are from fortified food (e.g., milk and grains). A number of techniques are employed to add vitamins to these foods, and which technique is used depends on the chemical behavior of the vitamin and the processing treatments of the fortified foods, including their transit and cooking times, as well as the food matrix being fortified. The most commonly used techniques are spray drying and drum mixing. Some vitamin delivery concepts allow consumers to add vitamins to whole food systems, like drink products, themselves. Despite the fact that whole, natural and fortified foods are sufficient for meeting the daily allowance for most vitamins, vitamin supplements are also a major source of synthetic vitamin intake. The supplement market was originated by and still is dominated by vitamins because they are readily developed into palatable or tasteless, potent, small, convenient doses, and in a number of varieties including, but not limited to, tablets, candies, gummies, sprays, and gums. Vitamins are manufactured using a number of chemical forms that include one or more vitamins by themselves or grouped with other functional nutrient complexes like minerals or proteins.

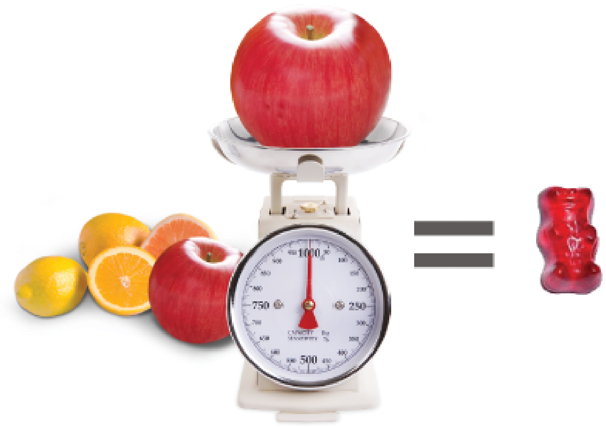
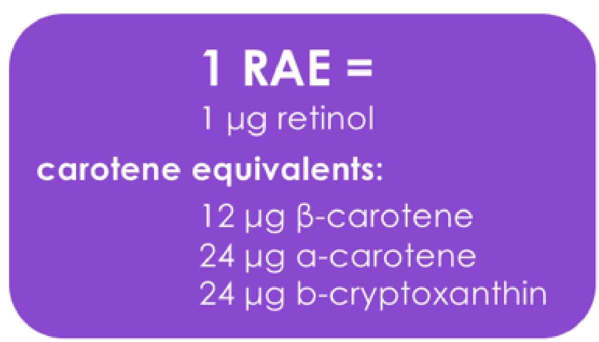


Figure 5.3. Micronutrients and Small Volume Supplements.

Vitamins in foods and supplements are generally classified by solubility. Fat-soluble vitamins in foods are generally less susceptible to cooking losses and are more biologically efficient in a food matrix that includes dietary fat. Since animals store fat-soluble vitamins in hepatic tissues, the most concentrated natural source of fat-soluble vitamins in the diet are liver and liver oil.

There are a wide variety of foods rich in **vitamin A retinoids**. The most abundant natural dietary source of preformed retinol is animal (e.g., beef, lamb or chicken) liver which, on average, provides 8-10 times the RDA per 3oz portion. Cod liver oil is the most concentrated animal sources of pre-formed retinol, providing more than four times the daily allowance in just one liquid tablespoon. Fish liver oil is often the leading ingredient in “all-natural” vitamin A supplements where it may be listed on the facts panel with palmitate, its natural esterification companion. The majority of vitamin A found in the US diet comes from dairy products, mainly fortified cow’s milk, which provides around 20% more vitamin A as retinol than non-fortified whole milk.

The majority of vitamin A consumed in the US is pre-formed retinol, with an estimated one-third from pre-formed beta-carotene. Provitamin A carotenoids (i.e., α-carotene, β-carotene, and β-cryptoxanthin) are abundant in darkly colored fruits and vegetables and oily fruits (e.g., red palm oil). Ripe, colored fruits and cooked yellow tubers are more bio-efficient than equal amounts of uncooked dark green, leafy vegetables. In the US, carrots are the major contributor of β-carotene, with significant, but lesser contributions from cantaloupe, broccoli, squash, and spinach. Vegan vitamin A supplements, or lines designed to market pre-formed vitamin A, feature beta-carotene as their primary vitamin A contributing ingredient. The major contributors of retinal family phytonutrients are also carrots followed by orange juice and its blends, tomatoes, and



tomato products, and spinach or collard greens. These chemicals have gained popularity as products like ketchup market their value for healthy vision. On average, one-half cup serving of carrots satisfies around 75% of the RAE allowance.

	RETINOL (PRE-FORMED)				BETA-CAROTENE PRO-VITAMIN				SUPPLEMENTAL	
VITAMIN A RDA: 700-900 µg/day	**Beef liver** 3 oz.	**Cod liver oil** 1 TBSP	**Fortified milk** 8 oz.	**Non-fat milk** 8 oz.	**Cooked carrot** 1/2 C (64g)	**Raw carrot** 1/2 C (64g)	**Raw kale** 4 C (64g)	**Cooked red tom.** 1/4 C (64g)	**Ready eat cereals** 30 g	**Juice drink** 8 oz.
RAE µg retinol + carotene equivalent	**8026**	**4080**	140	112	**545**	**534**	**320**	15	**162**	**1290**
Retinol µg	8014	4080	134	110	0	0	0	0	162	0
Carotene µg	138	0	10	17	7749	7527	3850	188	162	15,600
Lutein + zeaxanthin *µg*	*9*	*0*	*0*	*0*	*440*	*164*	*5247*	*60*	*60*	*2391*
Lycopene *µg*	*9*	*0*	*0*	*0*	*0*	*1*	*0*	*1946*	*0*	*2083*

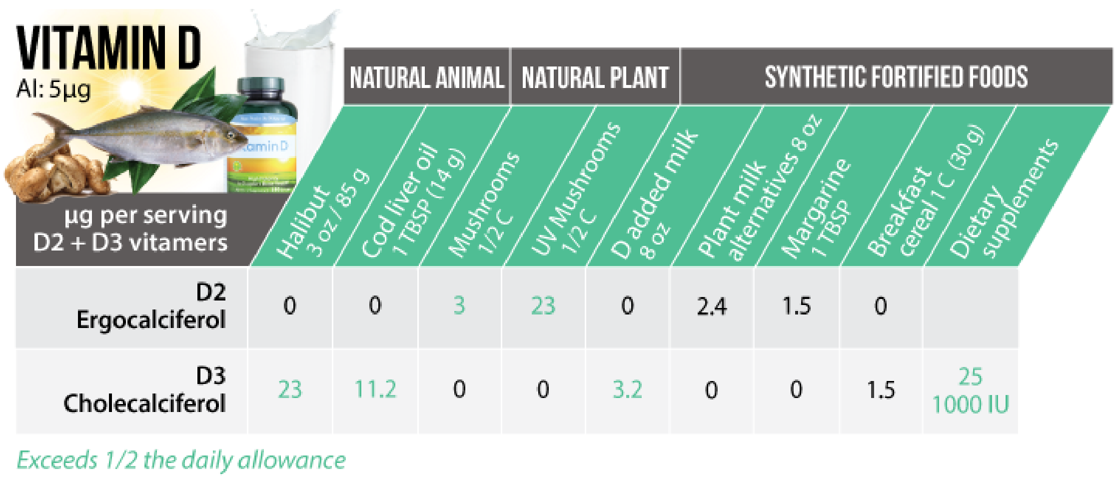
Dietary Sources of Vitamin A

The food matrix affects the bioavailability of carotenoids. Cooked and more comminuted food sources cause a greater increase in serum carotene compared to raw and whole counterparts. For example, cooked carrots, kale and spinach provide more than three times the amount of lutein and lycopene than raw versions with equivocal amounts of total vitamin A. The most concentrated green is kale, which per serving provides much more vitamin A than broccoli, but because broccoli is more popular in the US diet overall, it is a more significant source of pro-vitamin A in US diets.

In nature, very few foods contain **vitamin D**. The few animal food sources that provide natural dietary cholecalciferol (i.e., vitamin D3) include fish and shellfish and liver . The liver oil and flesh of fatty fish and aquatic mammals, and eggs from hens that have been fed vitamin D contain approximately 5-10 µg vitamin D3 per 3 ounces, with certain meat varieties (i.e., halibut) providing up to 23 µg per 3 ounces. The most concentrated source of D3 is fish liver oil, which provides more than half the vitamin D3 in only 1 TBSP. Another natural source of vitamin D is mushrooms. Mushrooms are one of the few plant foods that provide dietary ergocalciferol (i.e., vitamin D2). One-half cup of high vitamin D mushrooms, like morels and chanterelles, provide around 20% of the DV (1 µg). UV-treated mushrooms are now entering some retail markets as they increase the D2 content by 200-fold from 1 gram to 20 µg D2.

Foods infused with synthetic vitamin D account for most of our dietary intake of vitamin D in the US. Vitamins D2 and D3 are added to different foods in varying forms and quantities from different manufacturers in distinct regions under unique brand names in multiple product categories. In the United States, drinking milk is fortified with 10 µg (400 IU) of vitamin D2 or vitamin D3 per quart. This level of fortification increases the vitamin D content of natural cow's milk from .2 to 3.4 µg per cup, a level that satisfies 2/3 of the RDA per serving. In recent years, milk manufacturers have increasingly switched from vitamin D2 to the more stable, long-lasting vitamin D3. As a result, vitamin D testing is less variable and well within the 20% variance regulatory requirements, and, on average, yield consistently 2.4 µg D3 per cup. Alongside milk, many ready-to-eat breakfast cereals (75%), non-dairy milk substitutes (55%), yogurts (25%), and 10% of cheeses, juices, and spreads are also fortified with vitamin D. Breakfast can be one of the most efficient vessels of vitamin D fortification, as a combined bowl of cereal and milk satisfies 75% of RDA. High vitamin D-infused brands contain around 2.5 µg per cup (30 gram) serving but more popular brands, like General Mills, Post and Kellogg's, are fortified with 1-2 µg per cup. Other products like margarine and dairy milk alternatives still use the less expensive and less bioavailable, vitamin D2; however, differentiating between D forms can be hard difficult since food labels only list the combined D2+D3.

Dietary supplements of vitamin D typically provide a daily dose of 400 IU (10 mcg D3), but levels in supplements have been steadily increasing. In the United States, vitamin D can now be found in multi-vitamin/multi-mineral formulations as well as a single supplement in a range of dosage levels, ranging from 1,000 to 5,000 IU of vitamin D3 per dose which, is 20 times the RDA and 10% of the100 mcg UL. Most experts recommend that vitamin D supplements are taken in the D3 or cholecalciferol form because it is more bioavailable and less likely to cause toxic effects when high levels are supplemented to the diet.



VITAMIN D
AI: 5µg

µg per serving D2 + D3 vitamers	NATURAL ANIMAL		NATURAL PLANT		SYNTHETIC FORTIFIED FOODS				
	Halibut 3 oz / 85 g	Cod liver oil 1 TBSP (14 g)	Mushrooms 1/2 C	UV Mushrooms 1/2 C	D added milk 8 oz	Plant milk alternatives 8 oz	Margarine 1 TBSP	Breakfast cereal 1 C (30 g)	Dietary supplements
D2 Ergocalciferol	0	0	3	23	0	2.4	1.5	0	
D3 Cholecalciferol	23	11.2	0	0	3.2	0	0	1.5	25 1000 IU

Exceeds 1/2 the daily allowance

Figure 5.5. Dietary Sources of Vitamin D.

Vitamin E and all eight of its natural stereoisomers are available in many foods in varying amounts in the average diet. The primary source of natural alpha-tocopherol in the US diet is from **vegetable-cooking oils** and foods containing cooking oils such as dressings, dessert cakes and spreads. One tablespoon of vegetable oil made from sunflowers, safflowers, rapeseeds or almonds provides around 5.5 mg of vitamin E per tablespoon as 50% α-tocopherol. Whereas, vegetable-oils made from grains and legumes like soybean and corn oils contain, on average, nearly 10 times as much biologically inactive gamma (γ)-tocopherol. Other foods providing natural alpha-tocopherol include **vegetable greens** such as seaweed raw spinach, chard, turnip, mustard and dandelion greens, and the fatty portion of **meat**, **nuts** and **grain seed derivatives** like wheat germ. Natural vitamin E is the most sensitive of the fat-soluble vitamins to **processing losses** with as much as 25% lost in cooking and refining.

Synthetic alpha-tocopherol is also a significant source of dietary vitamin E. Synthetic vitamin E, while less biologically potent, is concentrated to **fortify** and **preserve** many types of products including, but not limited to, breakfast cereals, baked desserts and breads, and nutritionally formulated meal bars, juices and shakes which provide anywhere from 10 to 20 mg of vitamin E per serving. Synthetic vitamin E is listed in nutrient databases as “added” alpha tocopherol.

Both natural and synthetic vitamin E are isolated for **dietary supplement products** and usually delivered in a dose of 40 IU in a 1-2-gram glycerin-based capsule. Synthetic vitamin E is most often listed in the ingredients list with the words acetate and succinate, which means that the alpha-tocopherol supplement is in ester form. Esters are more resistant to oxidation than un-esterfied tocopherols which extend supplement shelf lives. Esterfied tocopherols are equally as bioavailable as free alpha-tocopherols. Synthetic vitamin E is listed as *all-rac*-α-tocopherol usually including all 8 vitamers in the E family, even though only the alpha is biologically active.

Only a small number of food items contribute substantially to our daily **vitamin K** requirements. A few green vegetables – kale, collard greens and spinach – provide 1000 µg of phylloquinone per cup serving. Other popular salad lettuces (e.g., bib and romaine lettuce, Swiss chard, and cabbage) and dinner vegetables (e.g., broccoli and Brussel sprouts) contain far less, closer to 200 and300 µg of phylloquinone per cup. While green vegetables are the predominant source of vitamin K/phylloquinone in the North American diet, there is plenty of room for less popular salad greens like amaranth leaves, Swiss chard and mustard greens which can satisfy more than half of the daily allowance per serving. Vitamin K is preserved by freezing and cooking. Some cooking treatments in certain plants can increase their total phylloquinone by more than ten times more than their raw counterparts.

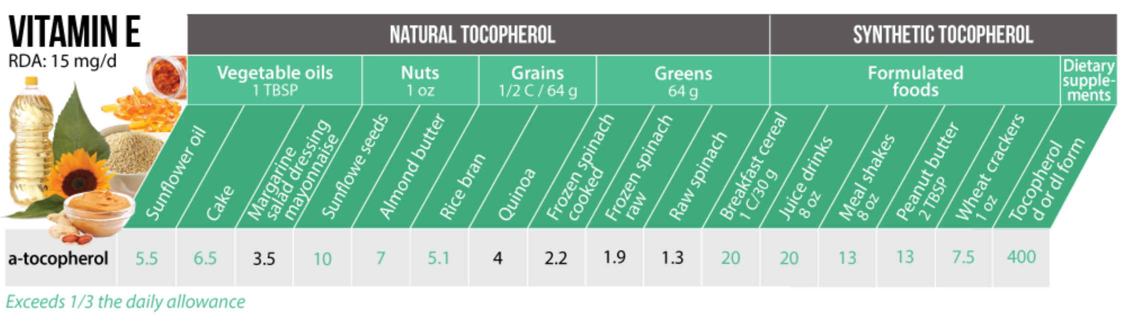


Figure 5.6. Dietary Sources of Vitamin E.

Plant oils are the second major source of phylloquinone in the diet at roughly 34%. The phylloquinone content of plant oils is variable, with soybean and canola oils containing greater than 100 µg of phylloquinone/100 g, cottonseed oil and olive oil containing nearly half of that, and corn oil including less than 5 µg/100 g. Margarines, dressings and condiments produced with plant oils and emulsifying plant lecithin contribute 15-25 µg per standard 1 TBSP serving. In hydrogenated oils (e.g., shortening and margarine), a large portion of phylloquinone is converted to 2',3'-dihydrophylloquinone during processing. Dietary intake of dihydrophylloquinone in the United States accounts for about 20 percent of total phylloquinone intake, with most sourced from prepared foods like French fries, pie crusts, crackers and cookies.

VITAMIN K

AI: 90-120 µg/d

µg per serving quinone vitamer	Greens 1 C/130 g: Kale	Greens 1 C/130 g: Brussel sprouts	Legume 0.5 C/64 g: Soybeans (raw)	Oils 1 TBSP: Soy lecithin	Oils 1 TBSP: dressing/ mayonnaise	Oils 1 TBSP: Shortening	Meat 3 oz: Pepperoni	Supplement µg dose: Natto
Phylloquinone (K1)	1000	300	40	25	20	8	5	100 Phytonadione
Dihydrophylloquinone	0	0	0	0	0	24	0	
Menaquinone (K2)	0	0	0	0	0	0	5	100 MK-7

Exceeds 1/4 the daily allowance

Figure 5.7. Dietary Sources of Vitamin K.

Water-soluble vitamins are readily available in a number of foods in the typical diet. Vitamins B1-B12 were first added to ready-to-eat breakfast cereals and enriched grain flours at a level intended to satisfy the RDA in 1998. Leading breakfast cereal brands in nearly every category from high- end health brands, to sugary cereals for kids, are designed to satisfy 100% or more of the major water-soluble vitamins. Bread and pasta products that are made with fortified flours also contribute significantly to the intake of water soluble vitamins. Water soluble vitamins are generally more susceptible to cooking losses than are those in the fat-soluble class, especially when the cooking method involves heat transfer via water.

VITAMIN B 1-6

DRI : 1-5 mg/d

	NATURAL									SYNTHETIC						
	Microbes	Nuts, seeds, legumes			Animal meat & dairy				Formulated drinks		Formulated food			Dietary supplements	
	Bakers yeast TBSP	Hemp seeds 1 oz	Almonds 1 oz	Garbanzo 0.5 c/100 g)	Yellowfin tuna 3 oz	Chicken liver 3 oz	Beef sirloin 3 oz	Milk 8 oz	Energy drink 8 oz	Designer fruit juice 8 oz	Energy meal bars 42 g	Cereal 1 C/30 g	Meat alternative 3 oz	Ingredient	B-complex doses
Thiamin 1.2	1.3	0.4	0	0.2	0.1	0.2	0	0	0.1	0	5.4	1.5	4	thiamin mononitrate	20
Riboflavin 1.3	0.4	0.1	0.4	0.4	0.1	1.5	0.1	0.6	0.5	0	1.3	1.7	0.2	Riboflavin	20
Niacin 16	4.8	2.7	1.4	1.5	16.1	8.2	6.5	0.3	48	20	22	20	0.9	Niacinamide inositol niacinate	25
Pantothenic acid 5	1.6	7	0.1	1.5	0.2	5.2	0.5	1	1.5	10	10	6	0	Calcium pantothenate	5.5
Pyridoxine 1.3	0.1	0.1	0	0.5	0.8	0.7	0.5	0.1	10	1.9	1.5	2.5	0.6	Pyridoxine hydrochloride	2

Exceeds 1/3 the daily allowance

Figure 5.8. Natural Dietary Sources of B Vitamins.

The most concentrated source of natural **thiamin** is baker's yeast, a bacterial leavening agent used to make breads. Seeds, especially those from hemp, sesame and sunflower, as well as their respective flours, are also naturally rich in thiamin. A one-ounce serving of whole seeds provides close to one-third of the daily allowance. Formulated meat analogs, mainly those featuring fermented soy, are also a significant source of thiamin with most commercial brands averaging around 4 mg per 3 oz., and some, like Morning Star, containing nearly twice as much. Less well-known but concentrated sources of dietary thiamin, like energy drinks and powdered meal mixes (e.g., cheeses and taco seasonings), are eclipsed in US markets by enriched grain flours used to make breads, pastas, tortillas, and cereals.

Riboflavin is a water-soluble, heat-stable, yellow, fluorescent compound that is found in small amounts in most plant and animal tissues. The most concentrated sources of riboflavin are **organ meats** but, in the U.S., the greatest contribution to the riboflavin intake adults is dairy milk. **Milk** is consumed in high volumes and high concentrations, supplying about half of our daily allowance for riboflavin in just one 8 oz. glass. Sheep's milk is less popular than cow's milk but considerably higher in riboflavin. Concentrated cheese and whey products provide more riboflavin than liquid milk per weighted amount but are not consumed to the same in extent in the typical diet. Following milk, the most significant source of riboflavin in the US diet is enriched bread products and fortified cereals. Other product categories that feature added riboflavin include meal bars (e.g., Clif Bars®), energy beverages (e.g., Rockstar®), and premier juices (e.g., Naked Blue Machine®), which are marketed as a way to increase energy.

Nicotinamide is found in highest concentrations naturally in **fish meat** and **legumes**. One serving of yellowfin tuna can satisfy the entire daily requirement for niacin; most other tunas provide just half that, or 7 mg per 3 ounces, on average. Liver and meat from beef and chicken also contain natural niacin in concentrations two- to three-times higher than hemp and sesame seed flours, the two most concentrated natural plant sources of nicotinamide. The greatest contribution to nicotinamide intake in the US comes from mixed dishes proportionally high in meat, fish, or poultry, which consumed singularly provide 2 mg per serving. Enriched bread products and ready-to-eat breakfast cereals satisfy anywhere from 25% to 100% of the daily niacin allowance. Breads and pastas contain significantly less niacin than breakfast cereals as they are targeted to satisfy in the range of 20-25% of the daily niacin allowance per serving. Like other B vitamins, niacin is used in supplemental energy products including dried coffee, energy drinks, energy candy lines, protein bars and high-end fruit and vegetable juices.

Pantothenic acid (i.e., vitamin B5) is found in both free and conjugated forms in virtually all plant and animal foods. To estimate the dietary intake of pantothenic acid in foods, it is necessary to convert bound pantothenic acid (for example, in coenzyme A (CoA) and fatty acid synthetase) to the free form. The most concentrated natural sources of pantothenic acid are chicken liver and hemp seeds, which both meet the daily need for B6 in just one serving. Significant dietary sources of pantothenic acid in the US include ready-to-eat cereals like oats, which provide about 6 mcg per 30 g serving, and formulated meal bars, juice smoothies, and shakes, which include around one- to two-times the daily allowance per standard serving. Less significant, but well-known sources of B6 are royal bee jelly and ovaries of tuna and cod. Freezing and canning of vegetables, fish, meat, and dairy products has been shown to decrease the pantothenic acid content of those foods, with loss spanning 37 to 74 percent.

Vitamin B6 (B6) comprises a group of six related compounds: pyridoxal (PL), pyridoxine (PN), pyridoxamine (PM), and their respective 5'-phosphates (PLP, PNP, and PMP). The major natural forms in animal meat are PLP and PMP, and in plant-derived foods, primarily PN and PNP, sometimes in the form of a glucoside. Especially rich sources of natural dietary PNP - pyridoxine are beef liver and other organ meats. Since these foods are consumed in small amounts in typical US diets, the greatest contributors to our vitamin B6 intakes are fortified foods: for example, ready-to-eat breakfast cereals, along with mixed meals including meat, fish, poultry or soy-meat alternative as the main ingredient. Cereal provides on average 2.5 mg per serving, with some brands reaching up to double that at 4mg per serving. Garbanzo beans are amongst the richest plant sources of B6, with around a ½ cup serving providing 1/3 of the daily vitamin B6 requirement.

	NATURAL				SYNTHETIC			
	Clams 3 oz	Beef liver 3 oz	Swiss cheese 1 oz	Whole milk 8 oz	Energy drink 8 oz	Energy bar 40 g	Cereal 1C/30 g	Dietary supplement dose
Total cyanocobalamin	84	70	0.75	1.7	7.2	3.8	6	500 methyl cyanocobalamin
Added (hydroxy) cyanocobalamin	0	0	0	0	7.2	3.8	6	

Figure 5.10. Dietary Sources of Vitamin B 12.

Dietary **cobalamin**, or natural vitamin B12, is the largest of all known vitamins and is exclusively consumed in foods of animal origin. Unlike the other B vitamins in the diet, vitamin B12 is not rich in plant foods (except certain algae). Plant sources of B12 are limited to foods that are rich in bacteria that produce the vitamin, as well as from plants that have been contaminated with soil, insects, or other substances that contain B12. The richest natural sources of B12 are certain crustaceans, like mollusks, crabs, sardines, caviar, and clams which provide up to 100 mcg per 3 oz. Animal organs like the liver provide around half as much, or 50 mcg. The brain, kidney and heart are also rich sources, whereas animal meat cuts are not, providing less than 1 mcg per standard serving. Ground meats, because they include organ tissues, are also significant sources of B12, but less so than milk and certain cheeses (e.g., Swiss), which contain around ½ and 1/3 of the RDA per standard serving, respectively. Second to mixed dishes that contain meat and dairy combined, milk is the leading singular source of natural dietary B12. Crystalline, or synthetic B12, appears in the diet only in fortified foods, such as breakfast cereals, dairy alternatives (e.g., enriched soy or rice milk), liquid meal replacements, energy drinks, smoothies, and sports nutrition products. Synthetic B12 has a higher bioavailability than natural protein-bound B12. Thus, for certain populations like the, elderly and vegans, synthetic B12 may be a preferable dietary intake form. In dietary supplement markets, B12 is listed on the ingredients list as un-methylated cyanocobalamin, or as biologically active methyl-cobalamin. Cyanocobalamin is the commercial preparation for B12 supplements and pharmaceuticals.

Most naturally occurring **folates**, called food folates, are pteroylpolyglutamates, which contain one to six additional glutamate molecules joined in a peptide linkage to the γ-carboxyl of glutamate. Many of the vegetables that contribute most to our folate intake in the US (e.g., green beans and broccoli) are actually lower in folate content than dark green vegetables like spinach and beans, which provide on average 300 mcg per half cup. On January 1, 1998, all enriched cereal grains (e.g., enriched bread, pasta, flour, breakfast cereal, and rice) were required by law to be fortified with folate at 1.4 mg synthetic folic acid/kg of grain. Ready-to-eat cereals and other retail cooked cereals provide up to 3% folic acid by weight, which is equivalent to approximately 800 mg per standard 30 gram serving size. Fortified cereals and formulated foods, provide anywhere from 200-700 µg folic acid, which is a more biologically potent form than is natural food folate. Supplemental folic acid is listed on supplement and food ingredient labels as methylfolate, which is the biologically active metabolite of folate. The natural methylated form is more popular in supplement markets than folic acid and is dosed anywhere from 400-800 mcg depending on the supplement category.

FOLATE
RDA: 400 µg

	NATURAL		COMBO		SYNTHETIC				
	Bakers yeast 1 TBSP 2 g	Soy beans 50 g	Garbanzo 54 g	Chicken liver 3 oz	Wheat germ 1 TBSP 2 g	Nutrition bar 43 g	Ready to east cereal 30 g	Enriched pasta 30 g	Dietary supplements
Folate, DFE 1 µg food folate = 0.6 µg folic acid	281	202	301	557	125	851	789	111	
Total folate µg Food folate + folic acid	281	349	301	528	94	507	466	68	
Food folate µg	281	349	301	528	49	16	6	7	
Folic folate µg	0	0	0	0	44	491	461	61	400 methylfolate

Exceeds 1/2 the daily allowance

Figure 5.11. Dietary Sources of Folate.

Almost 90 percent of **vitamin C** in the typical diet comes from fruits and vegetables, with citrus fruits, tomatoes and tomato juice, and potatoes contributing most in typical US diets. Other popular sources include Brussels sprouts, cauliflower, broccoli, strawberries, cabbage and spinach. The most concentrated sources of vitamin C are freeze dried sweet peppers of yellow, red and green varieties, and herbs, such as rose hips, coriander, thyme, and parsley. In other regions, guava, kiwifruit, zespri sungold, raw and litchis are abundant dietary sources. Values for the vitamin C content of foods can vary depending on the growing conditions, the season of the year, stage of maturity, location, cooking practices, and storage time prior to consumption. For instance, steaming and boiling causes a 22 percent to 34 percent loss of vitamin C, whereas microwaved and pressure-cooked vegetables retain closer to 90 percent of their vitamin C. Interestingly, vitamin C levels often are higher in frozen produce compared with fresh produce, likely because vitamin C levels in fresh produce degrade during storage and transport. Vitamin C is also added to some processed foods as a preservative as the acidity functions as an antioxidant, an anti-microbiant and to denature protein-bound enzymes that accelerate browning and spoilage. Ascorbic acid in foods and supplements is listed in the ingredients often as sodium ascorbate or ascorbic acid. Vitamin C supplements typically deliver around 1000 mcg of vitamin C, which is sometimes expressed in IU, or even labeled as the asymmetric or natural L-enantiomeric form.

VITAMIN C
RDA: µg

	NATURAL								NATURAL-SYNTHETIC COMBO					SYNTHETIC
	Fruits (54 g)				Vegetables (54 g)				Formulated drinks (8 oz)				Snacks (28 g)	
	Guava	Kiwi	Strawberries	Oranges	Sweet pepper	Kale	Broccoli	Green peas	Orange juice /drink	Tomato juice /drink	Fruit punch	Green tea	Fruit snacks	Supplements
Ascorbic acid	125	51	32	32	69	65	50	26	379	170	487	60	38	1000

Exceeds 1/2 the daily allowance

Figure 5.12. Dietary Sources of Vitamin C.

5.2 Homework 1
Homework • Answered

Put these Vitamin A rich foods in order from highest to lowest based on amount of pre-formed retinol

1	A	Beef Liver
2	B	Vitamin A Added Milk
3	C	Carrots

Answered - Correct!

1 attempt left Retry

5.2 Homework 2

Homework • Answered

What food contains **ergo**calciferol?

- ○ **A** halibut
- ○ **B** Vitamin D fortified milk
- ◉ **C** Mushrooms
- ○ **D** Fortified breakfast cereal

Answered - Correct! No attempts left

5.2 Homework 3

Homework • Answered

Natural vitamin E in foods is _____________ concentrated and _____________ biologically potent than synthetic vitamin E in fortified foods.

- ◉ **A** less, more
- ○ **B** more, more
- ○ **C** less, less
- ○ **D** more, less

Explanation

Natural food sources have less vitamin E than fortified sources, thus they are less concentrated. Natural vitamin E though is more biologically potent than the synthetic forms of tocopherol, commonly used for food additives

Answered - Correct! No attempts left

5.2 Homework 3

Homework • Answered

Match the following B vitamins with their most concentrated food source (each answer is used only once)

Premise		Response
1 riboflavin	→	C milk
2 thiamin	→	D meat alternatives
3 niacin	→	A energy drinks
4 folate	→	B breakfast cereals

Explanation

While breakfast cereals are fortified to meet the RDA for these listed minerals, Folate is nearly two times as high as the RDA for leading cereals. While the listed vitamins are all used to supplement energy products, the concentration of niacin in energy drinks compared to daily requirements is highest.

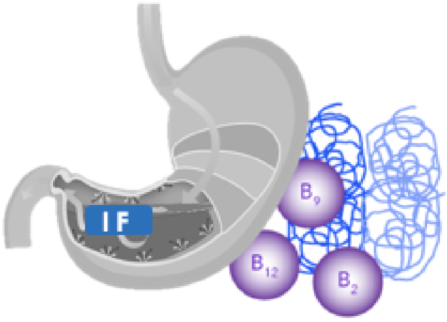
Answered - Correct!

1 attempt left Retry

5.3 Vitamin Processing

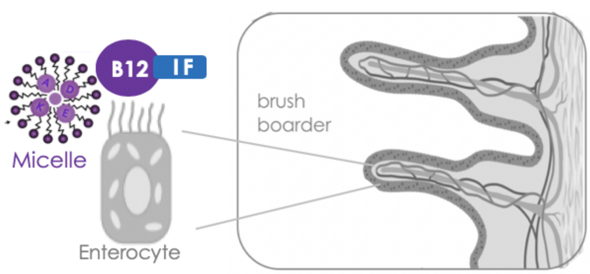
The solubility properties of vitamins and their proportional concentrations in food matrices affect their absorbability and route of entry from the small intestine to general circulation.

The mastication of foods by the teeth and tongue begin the vitamin digestion process. Swallowed foods head to the stomach down the esophagus and through the pyloric sphincter. Gastric sections containing hydrochloric acid and pepsin hydrolyze protein bound vitamins. Food folate (i.e., polyglutamate) is also hydrolyzed by enzyme folate conjugase to mono glutamate, and dietary Acetyl CoA to pantothiene, a pantothenic acid precursor. Parietal cells of the stomach also secrete **intrinsic factor**, a glycoprotein that facilitates the absorption of vitamin B12 more distally in the gastrointestinal tract.



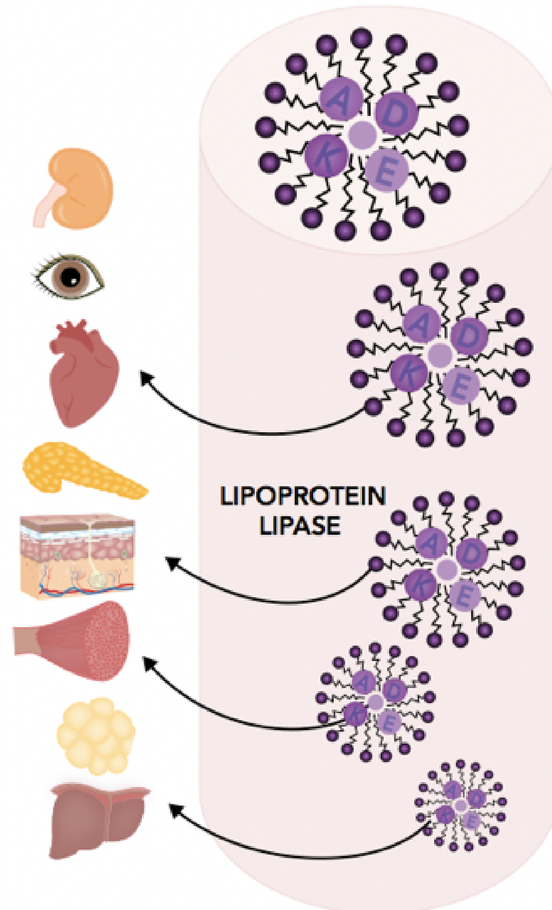
In the uppermost section of the small intestine, water-soluble vitamins are hydrolyzed and absorbed into the enterocyte and bloodstream by active or passive transport routes. At physiological doses, vitamin absorption is facilitated by saturable, active transport mechanisms that regulate the amount of each vitamin that is absorbed. When supra-physiological doses are administered, such as those eliciting more than 10-fold changes in natural body levels, water-soluble vitamins are absorbed passively and relatively limitlessly. The absorption mechanisms for water-soluble vitamins rely on protein-complexes and carriers, sodium-ion gradients, particular pH levels, and ATP dependent phosphorylation.

The majority of water-soluble vitamins are absorbed in proportionally increasing amounts with increasing intake, with the exception of B1 and B5, which are fractionally less absorbed as intake increases. Vitamin C and B12 are also absorbed in proportionally increasing amounts with increasing dietary intake until a physiological threshold is reached wherein absorption of both vitamins fractionally decreases with increasing dietary intake. Synthetic, crystalline forms of pantothenic acid and cyanocobalamin, like folic acid, are more efficiently absorbed than the natural food-provided counterparts, and in the case of crystalline B12, even without intrinsic factor. Along with small amounts of B1, folate and vitamin C, B12 is absorbed distally at the terminal ileum as part of an intrinsic factor-B12 complex.



Also in the upper small intestine, dietary **fat-soluble vitamins** are solubilized by bile salts to form **micelles**. Lipids and lipid-like vitamins packed in the soluble micelle diffuse passively across the brush boarder of the small intestine. Fat-soluble vitamins are much more efficiently absorbed into the enterocyte in the presence of dietary fat, either in mixed meals or isolated fats and oils that elicit the release of bile salts and micelle formation. In the enterocyte, fat-soluble vitamins along with dietary cholesterol and triglycerides are packaged as chylomicrons for diffusive passage to portal circulation. Distally, in the large intestine, menaquinone is synthesized by intestinal bacteria. A less significant amount of pantothenic acid and folate is also synthesized; some of which is excreted in the bile along with feces. A small amount of riboflavin is absorbed in the large intestine along with vitamin K.

Chylomicrons containing fat-soluble vitamins, fat and cholesterol circulate to peripheral tissues. Fat-soluble vitamins are released and taken into cells for processing during the hydrolysis of TAG inside the by **endothelial lipoprotein lipase.** Vitamin K is delivered particularly to tissues in the pancreas, blood vessels and testicles for conversion to menaquinone. Conversion to menaquinone precedes the carboxylation of glutamic acid residues by γ-glutamylcarboxylase, which together initiates the vitamin K dependent proteins that are needed for serum clotting function. Vitamin K is then reduced to **hydroquinone** in a two-step recycling process that is inhibited by **anti-coagulation drugs**, like Warfarin. Vitamin E (i.e., tocopherol) and vitamin D (i.e., calciferol) are sequestered by mainly adipose and skeletal muscles tissues to be stored for later use, and in the case of vitamin E, by integration into cell membranes. Some vitamin A (i.e., retinol) is also removed from chylomicrons in tissues of the eye, for delivery to photoreceptors located in the rods, where it is used in the synthesis of the vision protein, rhodopsin.



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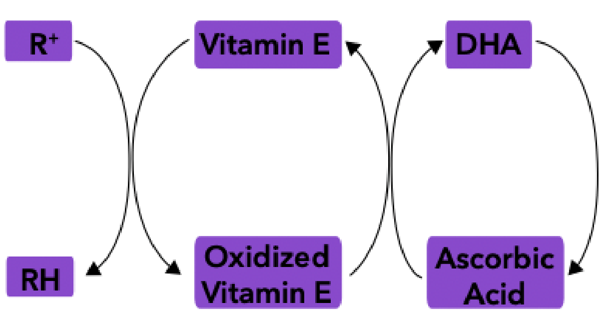
Elimination of *fat-soluble vitamins* from circulating chylomicron accounts for some postprandial plasma vitamin disappearance but, for the most part, fat-soluble vitamins travel to the liver to be bio-converted, stored, re-routed or any combination thereof. For instance, retinoids are esterified to long chain fatty acids for hepatocyte storage. When retinol is needed, the enzyme retinyl esterhydrolase catalyzes the release of esterified retinol so that it is free to attach to **retinol binding protein** for transport to the eyes. Vitamin K quinone returning to the liver in chylomicron remnant is reduced to quinol via NADPH dependent, **quinone reductase**. Returning vitamin D2/3 is activated in the liver and then sent back out to the kidneys packaged in lipoproteins, where there it will be converted to **calcitriol** and **ercalcitriol**. Vitamin E remaining in dietary remnant is also delivered to the liver for esterification and storage or integration into very low-density lipoproteins (VLDL). α-TTP catalyzes alpha tocopherol synthesis in the liver and facilitates the integration of tocopherol esters into VLDL. Interestingly, serum and cellular levels of natural RRR tocopherol is much higher than the rac isomer even with equivalent dietary doses of vitamin E, suggesting that liver hepatocytes preferentially synthesize tocopherol in the natural RRR isomer.



In liver hepatocytes, as well as in cells of the periphery, the phenolic hydroxyl group of α-tocopherol reacts with an organic peroxyl radical to form a tocopheroxyl radical . Tocopherols are single electron oxidation products that readily dismutate into ascorbate and DHA—two-electron oxidation products. These products react with other tocopheroxyl radicals to form non-reactive products such as tocopherol dimers. They can also undergo further oxidation to tocopheryl quinone but, in most instances, are simply reduced (i.e., recycled) back to tocopherol by cellular antioxidants like ascorbic acid and glutathione.

Water-soluble vitamins travel though the system bound to protein carriers like albumin, immunoglobulins and erythrocytes. Some, including cobalamin and ascorbic acid, have specific transport systems and vitamin specific binding cites for targeted destinations.

The majority of ascorbic acid in the body is found as free monoanion ascorbate in higher concentrations in pituitary adrenal glands, leukocytes, eye tissues, and the brain. Ascorbic acid contains two enolic hydrogen atoms that are reduced (i.e., donated) to yield a one-electron oxidation product that readily dismutates to ascorbate. **Ascorbate** is reduced by **glutathione** and nicotinamide adenine dinucleotide (NADH) reductases back to ascorbic acid in the same recycling process described above for vitamin E.

Riboflavin metabolism is a tightly controlled process in the cell cytoplasm that begins with the ATP-dependent phosphorylation of riboflavin to form FMN, a reaction that is catalyzed by hormonally controlled flavokinases. The majority of FMN in the cell cytosol is converted to FAD by **FAD synthetase**, with some FMN being complexed with specific apoenzymes to form a variety of lipoproteins. FAD is the predominant flavoco-enzyme in body tissues and the most predominant storage form for riboflavin which is found in most tissues with highest concentrations in the tissues of the small intestine, liver, heart, and kidney.

Erythrocyte-bound circulating nicotinamide, or nicotinic acid, enters cells of the periphery and the liver by simple diffusion. In the cell cytoplasm, the vitamin is converted to the co-enzymes, NAD and NADP by **gycohydrosylase**, to be stored or used in metabolic reactions. In the liver specifically, the hydrolysis of NAD releases niacin for transport to tissues that lack the ability to synthesize the co enzyme from tryptophan. Excess niacin is **methylated** in the liver to N^1-methyl-nicotinamide, which is excreted in the urine.

Three non-phosphorylated vitamin B6 vitamers are bound to erythrocytes and directed to the liver for uptake and phosphorylation to PLP by **PL kinase**. A small portion of PLP is oxidized to 4-PA, which is released and excreted, and a larger proportion forms PLP-albumin complex for release into circulation. Muscle, plasma, and erythrocytes (hemoglobin) have a high capacity for PLP-protein binding and tend to accumulate very high levels of PLP when other tissues are saturated. Cellular PLP storage is mainly concentrated in the mitochondria, bound to phosphorylase to protect from the action of phosphatases. When cellular concentrations of pyridoxine are high, free PLP is rapidly hydrolyzed and non-phosphorylated forms of B_6 are released into circulation. At target tissues, B6 may be integrated as a co-enzyme for **aminolevulinate synthase**, a critical enzyme for heme biosynthesis.

Folate monoglutamate is directed to the majority of cells in the body bound to albumin. Cellular uptake is proceeded by an anabolic conversion to polyglutamate by **polyglutamate synthetase**, as polyglutamate is the compound that functions in single-carbon transfer reactions. Polyglutamate is converted to 5-methyl-tetrahydrofolate, which is subsequently incorporated into **5,10-methylene-tetrahydrofolate**. This folate co-coenzyme (i.e., flavoenzyme) transfers methyl in several biochemical cycles, including those responsible for the production of heme and DNA. When needed elsewhere, folate polyglutamates are catabolized to mono- glutamate by γ-glutamylhydrolase for cellular release into circulation, and when in excess, are excreted in the urine and the bile.

Cyanocobalamin travels in circulation bound to vitamin-specific, plasma-binding proteins **transcobalamin** I, II, and III. Around half of the dietary cobalamin absorbed in meals is directed to the liver and used in the production of methionine. Crystalline cyanocobalamin binds less effectively to serum proteins; thus, they are excreted more rapidly. Inside the cell, both forms of the vitamin are methylated to methylcobalamin, which is subsequently incorporated into the enzyme **methionine synthase**. Like folate coenzymes, methionine synthase is involved in a methyl transfer cycle that is involved in the homocysteine to methionine conversion needed for heme production.

In the serum and whole blood, pantothenic acid is stored for CoA synthesis. The synthesis of CoA from pantothenate is catalyzed by **pantothenate kinase**, takes place in the cytosol, and is proceeded by acetyl CoA and succinyl CoA synthesis. CoA is not stored in the erythrocytes, but in most other tissues, is the primary form of pantothenic acid. CoA is hydrolyzed to pantothenate in a multiple-step reaction. The pantothenic acid is excreted intact in urine.

5.3 Homework 1

Homework • Answered

Which of the following groups of vitamins are protein-bound and at least partially hydrolyzed in the stomach?

- (●) **A** ribofalvin (B2) folate (B9) Cobalamin (B12)
- ( ) **B** Thiamin (B1) Niacin (B3) Pantothenate (B5)
- ( ) **C** Vitamin A Vitamin C Vitamin K

Answered - Correct!

1 attempt left Retry

5.3 Homework 2

Homework • Answered

Match each vitamin to the biological metabolite (i.e., compound) that it will be incorporated into.

Premise		Response
1 Vitamin A	→	E Rhodopsin
2 Vitamin D	→	A Calitriol
3 Riboflavin	→	G FAD Co-enzyme
4 Niacin	→	F NAD Co-enzyme
5 Pantothenic acid	→	D Co-enzyme A
6 Folate	→	B Polyglutamate
7 Cobalamin	→	C Methionine synthase

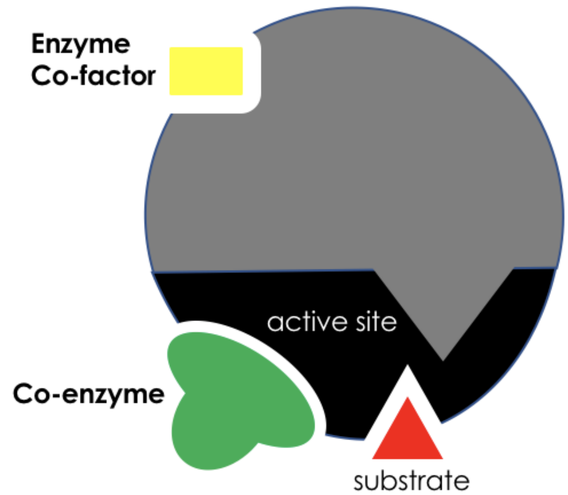
Explanation

Answered - Correct!

No attempts left

5.4 Vitamin Functions

Intake and processing of dietary vitamins provide our bodies with molecular compounds that are needed for regular bodily functioning. The primary role that vitamins play in the body are catalytic in nature. Catalytic vitamins are typically structural components of catalytic enzymes and are therefore known as **co-enzymes**. Some vitamins truly are catalytic in that they initiate enzymes to catalyze reactions. True catalytic vitamins are **enzyme co-factors**. Both complete apoenzyme to make a complete and activated halo-enzyme that is ready to initiate critical cellular actions.



Vitamins are Enzyme Co-Factors and Co-Enzymes

The functional role of some vitamins involved in enzymatic actions involve single-carbon, or transfer **methylation reactions**. For these vitamins, adequate intake is needed for normal cell division because transmethlylation reactions enable the synthesis of sulfur amino acids and other crucial protein intermediates, such as pyrimidine/purine (i.e., nucleotides), which are critical for DNA replication. The vitamins most directly involved in methylation reactions are dietary **folate and cobalamin,** which are both involved in the conversion of homocysteine to methionine, a critical step in normal erythropoiesis in the bone marrow. The role of folate is as a structural component of methylenetetrahydrofolate, a methylation enzyme. Cobalamin functions primarily as a co-enzyme for methyltransferase – another methylation catalyst needed to synthesize methionine synthase. Niacin is also a vitamin co-factor that is involved in DNA replication, but in a different capacity than methylation. Niacin is a co-enzyme for PARP enzyme (in nucleus) that is involved in non-redox reactions to transfer ADP-ribose units from NAD to proteins that repair and replicate DNA.

Vitamins are also critical co-factors for enzymes that are involved in **cell nutrient metabolism**. Catabolism of nutrients (i.e., cellular respiration) in the TCA cycle and subsequent oxidative phosphorylation in the ETC involves a series of redox reactions reliant on **riboflavin** (i.e., flavo) co-enzymes, FAD, FMN and **niacin**-dependent co-enzymes NAD and NADP that donate and accept hydrogen ions in a series of biochemical reactions that are needed to generate energy to re-synthesize ATP for muscle contraction. Cellular respiration is also reliant on coenzyme A, a pantothenic acid dependent cofactor that functions as an acyl group carrier and protein complex particularly critical for fatty acid metabolism. Thiamin is also a critical enzyme co-factor, only in amino acid interconversions converting dietary tryptophan to niacin.

Vitamin C is a co-factor for **hormone** enzyme dopamine-β-hydroxylase, which catalyzes the hydroxylation of the side chain of dopamine to form norepinephrine and monooxygenase enzymes, both of which are involved in the biosynthesis of the neuropeptides/catecholamines, norepinephrine and epinephrine. Vitamin

C is also needed for collagen and connective tissue syntheses, such as elastin and fibrinogen. Vitamin C serves as an enzyme co-factor needed for collagen cross-linking hydroxylases which can depending on cellular ascorbic acid, be recyclable. These metallo-enzymes reduce iron and copper in hydroxylation reactions involved in the production of hydroxyproline and hydroxylysine and are dependent on access of reducing power of vitamin C. **Vitamin K** is a cofactor for the enzyme γ-glutamylcarboxylase (GGCX) which catalyzes the carboxylation of the amino acid glutamic acid (Glu) to γ-carboxyglutamic acid (Gla).

Beyond the catalytic roles played by vitamins needed for cell division, vitamins also provide considerable **structural contributions**. For instance, Vitamin A is also a structural component of a protein-pigment rhodopsin that is needed for triggering the visual cortex of the brain. The mechanism that the eye adjusts in low lighting involves transduction of light into neural signals and isomerization of 11-cis-retinaldehyde. The result is effective transitioning between light and dark environments. Vitamin E is also a critical vitamin in the structure and integrity of cell membranes.

Vitamins, as **anti-oxidants**, protect cell integrity. Ascorbic acid also donates electrons in redox reactions that play a role in cellular protection. Alpha-tocopherol and ascorbic acid are the primary reducing agents for mixed-function oxidases that are "free" to interact and form "radicals" with functional lipids. Such intra and extracellular molecular oxygen/reactive oxidants (ROS) are neutralized by scavenging ascorbic acid antioxidants in activated leukocytes, lung, semen, and gastric mucosa, and by circulating alpha-tocopherol in the cell membrane and VLDL. Both radicals quench a variety of reactive oxygen species and reactive nitrogen species in aqueous environments, which protects membrane lipids from peroxidation. Both can also be reduced back to ascorbic acid or used to regenerate glutathione and α-tocopherol. Others reductants include vitamin A catotinoids lycopene and lutein, all which have antioxidant effects on macro degeneration comparable to that of vitamin C.

Regulatory roles played by enzymes outside of catalytic activities leading to hormones include gene expression, maintenance of nutrient homeostasis and bone turnover. Vitamin D, a hormone-like vitamin by classification, is critical to maintaining blood calcium levels through the action of 1,25-dihydroxyvitamin D (i.e., calcitriol). Activated vitamin D, as part of the endocrine system, acts to stimulate the release of PTH to initiate calcium conservation at the intestine and kidney, and the release of calcium from bone. This mechanism is crucial for regulating calcium and phosphate levels in the blood, and for the formation of osteoclasts, which, in turn, perform osteoclastogenesis and bone resorption.

Gene Expression for certain proteins requires adequate intracellular vitamins. **Retinoids** are not only a critical factor in the protein complex needed for transduction of light into neural signals but also for retinoic acid metabolite which is needed for normal differentiation of the cornea and conjunctival membranes. RA also interacts with receptors in cell nucleus to regulate the expression of various genes that encode for retinol binding proteins. The gene expressing role of vitamin A retinoids influences the synthesis of structural proteins, enzymes (e.g., alcohol dehydrogenase) and extracellular matrix proteins. Expression of various genes that encode for cell differentiation and proliferation in response to immune stimuli, such as increase phagocytic activity of macrophages and white blood cell production **Ascorbate,** both the oxidized mono and dianion promote gene expression for collagen, cellular procollagen secretion, and the biosynthesis of other connective tissue components besides collagen, including elastin, fibronectin, proteoglycans, bone matrix, and elastin-associated fibrillin/ fibrinogen. Gene expression for several nervous system components also apparently modulated by ascorbate concentrations include neurotransmitter receptors, the function of glutamatergic and dopaminergic neurons, and synthesis of glial cells and myelin. **Alpha tocopherol** plays a role in gene expression for proteins that modulate vascular and cellular tone. A cascade of up and down regulation for rate limiting enzymes for amino acid synthesis, results in the production of more prostacyclin, a potent vasodilator and inhibitor of platelet aggregation in humans.

5.4 Homework 1

Homework • Answered

What vitamin pair is involved in methylation reactions?

- (•) **A** Folate and Cobalamin
- ( ) **B** Vitamin K and Thiamin
- ( ) **C** Niacin and Pantothenic acid
- ( ) **D** Vitamin D and Riboflavin

Answered - Correct! 1 attempt left Retry

5.4 Homework 2
Homework • Answered

What vitamin pair are co-enzymes for energy metabolism?

- (selected) **A** Niacin and Riboflavin
- **B** Vitamin K and Thiamin
- **C** Vitamin K and Vitamin C

Answered - Correct! 1 attempt left Retry

5.4 Homework 3
Homework • Answered

Which vitamin set is most involved with cellular gene expression?

- (selected) **A** Vitamin A Vitamin C Vitamin E
- **B** Vitamin D Riboflavin Folate
- **C** Vitamin K Thiamin Pyridoxine
- **D** Vitamin C Niacin Cobalamin

Answered - Correct! 1 attempt left Retry

5.5 Vitamin Status Measures

When vitamins are restricted from the diet or fed in high experimental doses, biochemical changes manifest, and clinical symptoms occur. The scope and magnitude of symptoms created by vitamin imbalances are broad and highly variable. For instance, slightly disproportionate dietary intake of riboflavin, niacin and pyridoxine over time can lead to mild dermatitis-like symptoms, or a red-colored, perhaps sore tongue. When vitamins A and C are inadequate for an extended time, however, the body is at an increased risk of early mortality from susceptibility to infection.

Identifying predictable physiological outcomes for particular dietary vitamin levels has been difficult for several reasons: first, vitamin imbalances are usually accompanied by inadequate intake of other vitamins or nutrients; second, early stages of vitamin imbalances may be accompanied by non-specific symptoms that may be overlooked or easily misinterpreted; and third, there are a large number of confounding variables that contribute to chronic problems associated with vitamin imbalances including exercise, smoking, drugs and disease; and fourth, the variability in vitamin treatment responses in response to imbalances create wide parameters for defining status criteria. More specifically, some vitamins, like B12, are restored to homeostatic levels almost immediately after being re-introduced in the diet, whereas others, like B6, persist in eliciting symptoms even after typical dietary intake is restored.

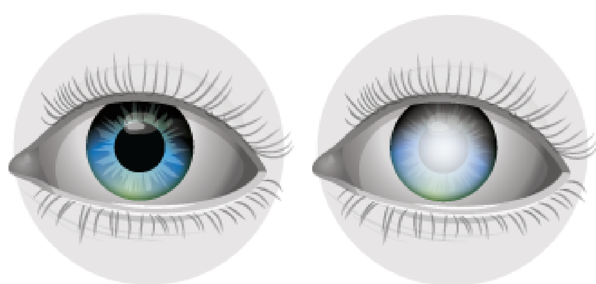


Figure 5.15. Vitamin A Deficiency and Vision Loss.

Generally, vitamin **deficiencies** in the US and other industrialized countries are relatively rare. In developing parts of the world, however, vitamin deficiencies are not uncommon because intake of certain vitamins is insufficient due to either a lack of quantity or quantity of the indigenous food supply, or because of underlying diseases that impair vitamin absorption and retention. Vitamin deficiency has been studied in animal models, experimental restrictive diets, and even with vitamin metabolism antagonists. The antagonistic method is used for vitamins that are difficult to limit from the diet as they are ubiquitous in foods, or for vitamins that have symptoms that do not elicit deficiency responses for a long period of time (e.g., B5 and B9). Deficiency for the water-soluble vitamins particularly has been reduced significantly through grain fortification, especially for populations consuming high corn and refined cereal diets. For healthy disease-free adults without impairments, the most common reason for water-soluble vitamin deficiency is alcoholism with reduced food intake. Deficiency for the fat-soluble vitamins is unlikely in the US due to the Milk Fortification Act and production of vegetable and grain seed oils.

The levels of vitamins provided in foods, both natural and fortified, are not sufficient to elicit clinical **vitamin toxicity**. However, under experimental conditions, intravenous feeding, excessive use of supplements, or restrictive fad diets can cause vitamin toxicity. This is especially for fat-soluble vitamins since their excess bio-metabolites can be stored in liver & fat tissues. A well-known fat-soluble vitamin toxicity is caused by a buildup of retinol in the dermis which causes a visibly orange coloring of the skin. For this reason, vitamin A has an established UL that is anywhere from 3 to 4 times RDA. Water-soluble vitamins are readily excreted in the urine with exceeding body levels, thus, naturally occurring accumulations to levels of toxicity are even less likely than for fat-soluble vitamins. There is a UL for six of the nine water-soluble vitamins with toxicity observed at levels anywhere from 2 times to 100 times the recommended daily allowance.

Imbalances in several vitamins, especially vitamins A and C, can lead to compromises in the integrity of epithelial cells. These changes manifest to affect the integrity of **connective tissue** so that dysfunction becomes clinically and visually apparent. Lack of ascorbate-related hydroxyproline and hydroxylysine formation needed for collagen cross-linking leads to defects in connective tissue, known clinically as **scurvy**. Scurvy usually occurs at a plasma concentration of less than 11 µmol/L (0.2 mg/dL), and is associated with poor clinical outcomes with respect to wound healing. Initial signs of scurvy are presented with bleeding gums and gingival inflammation, which are, interestingly, the same clinical symptoms that present with vitamin C doses exceeding 3 grams per day. Inadequate vitamin C intake also results in a clinical dermal condition called follicular hyperkeratosis, or dark coarse hair, which interestingly, has also been noted in case reports detailing symptom of clinical hypervitaminois A, or vitamin A toxicity.

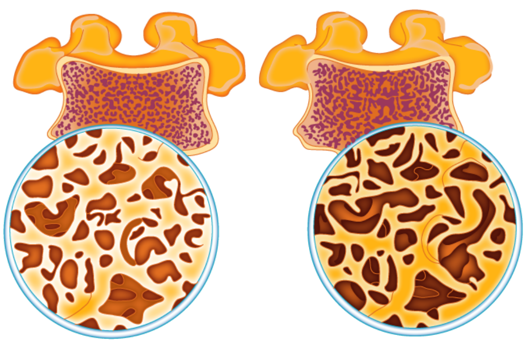


Figure 5.16. Bone Porosity with Vitamin D Deficiency.

The integrity and strength of the skeleton is dependent on vitamin D status. Any alteration in the cutaneous production of vitamin D3, the absorption of vitamin D in the intestine, or the metabolism of vitamin D to its active form can lead to **inadequate mineralization and demineralization of the skeleton.** In adults, vitamin D deficiency leads to a mineralization defect in the skeleton, causing osteomalacia. Inadequate vitamin D causes decreasing ionized calcium absorption, leading to secondary elevations in parathyroid hormone and subsequent mobilization of calcium and phosphorus away from the skeleton. Vitamin D deficiency is characterized biochemically by low-normal serum calcium, low-normal serum phosphorus, and an elevated serum parathyroid hormone. Serum alkaline phosphatase, which is also usually elevated in vitamin D-deficient states, is another measure of vitamin D status. Bone collagen byproducts, including hydroxyproline, pyridinoline, deoxypyridinoline, and N-telopeptide, can also be measured in the urine as elevated levels confirm bone breakdown. Conversely, excessive intake of vitamin D can result in calcium absorption that outpaces osteoclastic activity resulting in calcification of soft tissues, leading to a common condition otherwise known as kidney stones.

Vitamins play a major role in the integrity of the blood. Vitamin E, for instance, prevents hemolysis of blood cells, and vitamin C prevents oxidative degradation of blood coagulation factors which are, in part, dependent on vitamin K for activation. Many of the hemopoietic vitamins play a critical role in ensuring the blood is adequately saturated with oxygen. If dietary intake for these vitamins is inadequate, a series of changes related to the functionality of occurs that results in a condition called **megaloblastic anemia** . The underlying mechanism of this type of anemia is an interference with normal deoxyribonucleic acid (DNA) synthesis that results in megaloblastic changes in the cells of the blood. Leukocytes and erythrocytes are hyper-segmented and polymorphonuclic as a result of insufficiently supplied bone marrow tissues. The result is ultimately a depressed erythrocyte count, an elevated mean cell volume, and presence of any five-lobed, or any six-lobed cells per 100 granulocytes. Clinical symptoms include weakness, fatigue, difficulty concentrating, irritability, headache, palpitations and shortness of breath. Because the onset of macrocytic anemia is usually gradual, compensating cardiopulmonary and biochemical mechanisms provide adaptive adjustments to the diminished oxygen-carrying capacity of the blood until anemia is already moderate-to-severe. The most common three biochemical measures of anemia are hematocrit, hemoglobin concentration and erythrocyte concentration which are each influenced by restrictions. Within weeks of folate and/or cobalamin deficiency, and limited erythropoiesis in the bone marrow, the hyper-segmentation is apparent and larger-than-normal, oval-shaped red blood cells circulate in the blood. However, because of the 120-day lifespan of normal erythrocytes, macrocytosis is not evident in the early stages of folate-deficient megaloblastosis, and therefore, a secondary measure like elevated homocysteine is helpful in cases of suspected folate deficiency. The explanation for measuring homocysteine is based on the fact that cysteine accumulates when folate-mediated methylation of methionine is limited. Similarly, in cobalamin deficiency, folate may accumulate in the serum as a result of limited methyltransferase reactions from lack of cobalamin-dependent methyltransferase. Pernicious anemia is a type of megaloblastic anemia that is attributed specifically to limited cobalamin absorption, separate from folate status. Pyridoxine deficiency is directly associated with small red blood cells, or, most typically associated with iron-deficiency. The PLP form is a co-enzyme for aminolevulinate synthase which is the initiating enzyme catalyzing the synthesis of heme protein in the bone marrow.

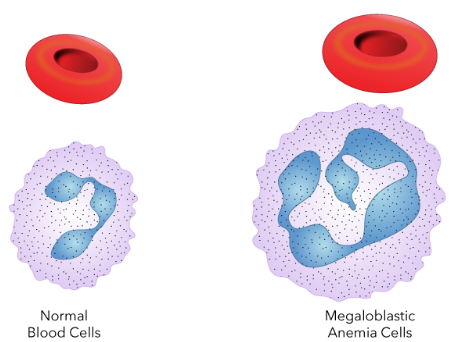


Figure 5.18. Macrocytic Anemia with folate, B12 and Pyridoxine Deficiency.

Hemopoietic vitamins play a major role in the integrity of the blood. Vitamin E, for instance, prevents hemolysis of blood cells, and vitamin C prevents oxidative degradation of blood coagulation factors which are, in part, dependent on vitamin K for activation. Many of the hemopoietic vitamins play a critical role in ensuring the blood is adequately saturated with oxygen. If dietary intake for these vitamins is inadequate, a series of changes related to the functionality of **red blood cells** occurs that results in a condition called **macrocytic anemia**. The underlying mechanism of this type of anemia is an interference with normal deoxyribonucleic acid (DNA) synthesis that results in megaloblastic changes in the cells of the blood. Leukocytes and erythrocytes are hyper-segmented and polymorphonuclic as a result of insufficiently supplied bone marrow tissues. The result is ultimately a depressed erythrocyte count, an elevated mean cell volume and presence of any five-lobed, or any six-lobed cells per 100 granulocytes. Clinical symptoms include weakness, fatigue, difficulty concentrating, irritability, headache, palpitations and shortness of breath. Because the onset of macrocytic anemia is usually gradual, compensating cardiopulmonary and biochemical mechanisms provide adaptive adjustments to the diminished oxygen-carrying capacity of the blood until anemia is already moderate-to-severe. The most common three biochemical measures of anemia are hematocrit, hemoglobin concentration and erythrocyte concentration which are each influenced by **folate, cobalamin and pyridoxine** restrictions. Within weeks of folate and/or cobalamin deficiency, and limited erythropoiesis in the bone marrow, the hyper-segmentation is apparent and larger-than-normal, oval-shaped red blood cells circulate in the blood. However, because of the 120-day lifespan of normal erythrocytes, macrocytosis is not evident in the early stages of folate-deficient megaloblastosis, and therefore, a secondary measure like elevated homocysteine is helpful in cases of suspected folate deficiency. The explanation for measuring homocysteine is based the fact that cysteine accumulates when folate-mediated methylation of methionine is limited. Similarly, in cobalamin deficiency, folate may accumulate in the serum as a result of limited methyltransferase reactions from lack of cobalamin-dependent methyltransferase. Pernicious anemia is a type of megaloblastic anemia that is attributed specifically to limited cobalamin absorption, separate from folate status. Pyridoxine deficiency is directly associated with small red blood cells, or **microcytic anemia**, most typically associated with iron-deficiency. The PLP form is a co-enzyme for aminolevulinate synthase which is the initiating enzyme catalyzing the synthesis of heme protein in the bone marrow.

In the immune cell production area of the bone marrow, vitamin A is hemopoietic. Retinol is needed in DNA replication processes involving humoral and cell-mediated immunity; thus, a deficiency in vitamin A can impair immune function by reducing lymphocyte numbers, natural killer T cells, and antigen-specific immunoglobulin responses. In developing societies that have chronic inadequate vitamin A intake, dietary supplementation with vitamin A can significantly reduce the risk of mortality associated with respiratory infection and diarrhea.

Many vitamins, when imbalanced in the diet, can cause **neurological symptoms**, including depression, changes in muscular coordination and control, apathy and dementia. For some of these vitamins, the neurological symptoms are the primary subjects of study; and for those, more is known about the effects of dietary intake and bodily status. A good example is classical pyridoxine deficiency, which is characterized by epileptiform convulsions, depression and confusion. Since PLP is a coenzyme of decarboxylase enzymes that are involved in neurotransmitter synthesis (dopamine, serotonin, and γ-aminobutyrate), defects in some of these enzymes could explain the onset of such convulsions in B6 deficiency. Cobalamin is also frequently associated with neurological manifestations including sensory disturbances in the extremities (e.g., tingling and numbness) that are worse in the lower limbs. Other motor disturbances and cognitive changes ranging from loss of concentration to memory loss, disorientation, and dementia, with or without mood changes, have been reported in cobalamin deficiency and may be dependent on the presence of anemia. Vitamin E deficiency symptoms observed in humans progress in a distinct pattern of spinocerebellar ataxia, skeletal myopathy and pigmented retinopathy. Pantothenic acid deficiency can elicit a neurological sensation, referred to as “burning feet syndrome,” that was reported by deficient soldiers. In classic niacin deficiency, Pellagra, neurological functions like gait are impaired. Gait changes often accompany impaired neuromuscular responses in other measures of hand-eye coordination and have also been seen in cases of inadequate cobalamin intake. Other classic vitamin deficiencies that have been noted to elicit neurological changes include Beri Beri, a clinical condition of thiamin deficiency, as well as ariboflavinosis, which develops from inadequate riboflavin intake.

5.5 Homework 1

Homework • Answered

Match each vitamin to the disease, symptom or condition that could exacerbate in periods of prolonged restricted intake and deficiency.
(answers will be used more than once)

Premise		Response
1 Night blindness	→	D Vitamin A
2 Scurvy	→	E Vitamin C
3 Rickets	→	C Vitamin D
4 Macrocytic anemia	→	A Folate
5 Microcytic anemia	→	B Pyridoxine

Answered - Correct!

No attempts left