INTRODUCTION TO NUTRIENTS

Food consists of nutrients, some of which are essential for the body to function on a daily basis. Digestion of food starts in our mouths, and food continues to break down as it travels from the mouth through the esophagus, stomach, and small intestine by a combination of mechanical forces and chemical reactions. Enzymes that are produced within the saliva, stomach, pancreas, liver, and small intestine target-specific chemical bonds holding complex nutrient structures together. Ultimately, those complex structures are broken down to simple nutrients that transporters along the stomach, small intestine, and large intestine can absorb into the body.

There are six main classes of nutrients existing in our dietary sources. They are categorized as (1) carbohydrates, (2) lipids, (3) proteins, (4) water, (5) vitamins, and (6) minerals. Carbohydrates, lipids, proteins, and water are all considered macronutrients while vitamins and minerals are micronutrients (see following sections for more detail). Food also contains other bioactive substances that may not be essential for the human body to function but over the past decades have been found to have beneficial effects on human health. Such substances include phytochemicals, pre- or probiotics, and polyphenols. For example, phytochemicals contained in plant-based food products have been found to have protective effects on chronic disease such as hypertension, cancer, and heart disease. This chapter will focus on the six main classes of nutrients by describing the different subclasses within each nutrient, defining their roles in the body, and relating their role to key health outcomes or development towards disease states.

MACRONUTRIENTS

Macronutrients encompass the nutrient classes of carbohydrates, lipids, proteins, and water. These nutrients are energy yielding, with the exception of water, and are needed in relatively large amounts (thus “macro-“). Macronutrients are essential for cells to function because of the energy they provide. The energy that macronutrients yield is measured in kilocalories, a unit representing the amount of heat required to raise the temperature of 1 kilogram of water by 1°C. Kilocalorie is commonly presented as Calorie on food labels and other dietary resources (note the capital “C” represents “kilo-” while a lowercase “c” technically represents 1/1000 of a kilocalorie). Although water is not energy yielding it is also categorized as a macronutrient because it is needed in larger amounts on a daily basis and is essential for the body to function. The recommended amount of macronutrients required for normal body functioning are typically expressed in grams or kilograms per day. The amount of energy one requires from macronutrients depends on factors such as age, gender, weight, level of physical activity, and height. All of these things can this can vary even in people within the same life stage. A dietary guideline called the Acceptable Macronutrient Distribution Range provides a range of percent of Calories that one should get from each macronutrient per day. The recommendations include obtaining 45–65% of Calories from carbohydrates, 20–35% of Calories from fat, and 10–35% of Calories from protein. By meeting this recommended combination of macronutrients, there is evidence that one will likely be taking in adequate micronutrient levels and reduce their risk to chronic disease.

Carbohydrates

Basic Definition and Dietary Sources

Carbohydrates are organic compounds containing hydrogen, carbon, and oxygen molecules. Carbohydrates contain 4 Calories per gram. There are some forms of carbohydrates that are readily digested and absorbed while other forms of carbohydrates, also referred to as fibers, are resistant to digestive enzymes and rather remain in the digestive tract and play a role in digestive health or other health outcomes. The carbohydrates that can be broken down in the digestive tract are readily available and preferred as an energy source for the majority of cell types within the human body. In the Westernized diet, carbohydrates make up an estimated 52% of Calories consumed on a daily basis. In regard to fiber intake, an adult eats about 16 g...
Carbohydrates are found in a variety of food products including breads, pasta, beans, vegetables, fruits, milk, yogurt, and juices.

**Carbohydrate Structure**

Carbohydrate is commonly abbreviated as CHO, giving us insight into its basic structural components. Carbohydrates are made of carbon chains with hydrogen and oxygen groups having the standard molecular formula of Cₙ(H₂O)ₘ. The carbohydrate structure contains two types of functional groups—(1) hydroxyl (-OH) and (2) carbonyl. A carbonyl group contains a carbon double bonded to oxygen. There are two types of carbonyl groups that a carbohydrate can contain—either an aldehyde or a ketone. The structure of an aldehyde carbohydrate includes a carbon double bonded to oxygen at the end of the carbon chain, while for a ketone, the double bond is in the middle of the carbon chain.

**Classes of Carbohydrates**

Carbohydrates fall into one of three classes: (1) monosaccharides, (2) oligosaccharides, or (3) polysaccharides. Of the three classes, monosaccharides have the simplest structure and are made up of a single sugar unit. Monosaccharides exist in the structural form available for absorption within the digestive tract. The two other classes are made up of monosaccharide unit chains. Glycosidic bonds link monosaccharides to form oligo- and polysaccharides. The glycosidic bond is named after the direction (alpha- or beta-) of the hydroxyl group attached to the anomeric carbon, the anomeric carbon number and the carbon number of the subsequent monosaccharide linking the units together. To form oligo- or polysaccharides through glycosidic bonding, the monosaccharides undergo condensation to eliminate a water group. Alternatively, the oligo- or polysaccharides can be broken down to their respective monosaccharide units through hydrolysis, or the addition of a water molecule. Hydrolysis is the key reaction that occurs during digestion that will break apart oligo- and polysaccharides contained in food into monosaccharide units that are readily available for absorption in the small intestine.

**First Class of Carbohydrates: Monosaccharides**

The first and simplest class is monosaccharides, often referred to as simple sugars. Monosaccharides include glucose, fructose, and galactose. They are found in food sources such as honey, fruits, and corn syrup. Typically, carbohydrates are not in this simple form in food sources but rather as di- or polysaccharides (see following sections), but during digestion humans break down these larger carbohydrates to simple sugars. Once in the form of glucose, fructose, or galactose, these simple sugars are capable of absorption at the small intestine via sugar transporters. Before discussing the larger carbohydrate classes, it is important to understand the glycosidic bond that links monosaccharides.

**Second Class of Carbohydrates: Oligosaccharides**

The next class of carbohydrates is oligosaccharides. They contain two to ten monosaccharides units with each unit linked by a glycosidic bond. Disaccharides are two monosaccharides linked by a glycosidic bond and are the most common type of oligosaccharides present in dietary sources. The three major disaccharides in dietary source are maltose, lactose, and sucrose. Maltose consists of two glucose units linked by a glycosidic bond. Sucrose consists of a glucose linked to fructose. Lactose contains a glucose linked to a galactose. Lactose is the main carbohydrate existing in dairy products and often associated with “lactose intolerance,” the overarching symptom of lactase nonpersistence that can develop in humans over the course of their lifetime and as early as in childhood.

**Lactase Nonpersistence**

Lactose intolerance is a common term used to describe the overarching symptom of the condition of lactase nonpersistence. This condition results from a deficiency of the digestive enzyme lactase. In mammals, the lactase gene is highly active during the lactation period when the sole dietary intake is from the mother’s lactose-containing breast milk. Following the introduction to other food products, in other words, exposure to foods containing carbohydrates other than lactose, the production of lactase rapidly declines, as there is a lesser need for its activity. Humans are unique as mammals because the domestication of milk-producing animals allows individuals access to milk and milk-products throughout one’s life. As such, humans continue to take in these types of food products beyond the lactation period, and thus, have a lifetime exposure to lactose. Over time humans developed a genetic polymorphism in the lactase gene resulting in sufficient production of lactase throughout adulthood when there is continuous exposure to lactose-containing foods. Because milk-producing agriculture is a recent event in regard to evolution, this...
polymorphism is thought to arise from a high-frequency haplotype due to the benefit of ingesting lactose in cultures that raise milk-producing animals. Individuals lacking this polymorphism will have a decline in lactase resulting in symptoms that indicate someone is intolerant to lactose as early as in the toddler life-stage. Symptoms include bloating, cramping, and diarrhea because lactose will not be properly digested for absorption and instead will travel to the large intestine where it can absorb water. Of note, it has also been evidenced that individuals who are lactase persistent but do not expose themselves to milk-containing products will have a steady decline of lactase production overtime and may also exhibit symptoms of lactose intolerance when reintroducing milk products.

Third Class of Carbohydrate: Polysaccharides

Polysaccharides contain 11 or more and up to 10,000,000 monosaccharide units. The monosaccharide units of the polysaccharide can be the same (homopolysaccharide) or have varying monosaccharide units (heteropolysaccharide). Another characteristic of polysaccharides are the degree of branching. Some are linear and contain zero branching units while others have varying degrees of branching. The branching units are significant for storage capacity, which will be discussed in more detail in the following subsections covering specific polysaccharides. There are three polysaccharides to discuss that have relevant implications in human nutrition—starch, glycogen, and cellulose. Common among these three polysaccharides is that they are all homopolysaccharides containing only glucose units.

Starch

Starch is the most abundant polysaccharide found in plants (e.g., tubers, seeds, roots). Starch is found in two forms, amylose and amylopectin. Amylose is linear, unbranched, and made of glucose connected by alpha 1,4 glycosidic bonds. Amylopectin is moderately branched and a homopolymer of glucose linked by alpha 1,4 bonds on the linear chains but by alpha 1,6 bonds at the branching points (Fig. 180-1). The typical lengths of a linear chain between branching points is 20–25 glucose units. In uncooked starch food sources, the linear structure of amylose allows it to be tightly packed. This creates a structure that is not as readily digestable as the branched less packed structure of amylopectin. In contrast, the processing and heating of amylose-containing foods (i.e., cooking) can loosen hydrogen bonds within the structure making it more accessible for digestion.

FIGURE 180-1

The structure of starch and glycogen. Amylose is a linear polymer of glucose residues linked α1→4, which coils into a helix. Amylopectin and glycogen consist of short chains of glucose residues linked α1→4 with branch points formed by α1→6 glycoside bonds. The glycogen molecule is a sphere ~21 nm in diameter that can be seen in electron micrographs. It has a molecular mass of ~10^7 Da and consists of polysaccharide chains, each containing about 13 glucose residues. The chains are either branched or unbranched and are arranged in 12 concentric layers. The branched chains (each has two branches) are found in the inner layers and the unbranched chains in the outermost layer. The blue dot at the center of the glycogen molecule is glycogenin, the primer molecule for glycogen synthesis. Carbohydrates of Physiological Significance, Rodwell VW, Bender DA, Botham KM, Kennelley PJ, Weil P. Harper's Illustrated Biochemistry, 31e; 2018. Available at: https://accessmedicine-mhmedical-com.arktos.nyit.edu/content.aspx?bookid=2386&sectionid=187832287&jumpsectionid=187832333 Accessed: March 05, 2020.
Glycogen

Glycogen is a highly branched, homopolymer of glucose. Glycogen is abundant in skeletal muscle and liver tissue of mammals. The glucose units are linked by alpha 1,4 bonds on the linear chains but by alpha 1,6 bonds at the branching points (just like amylpectin). The typical lengths of a linear chain between branching points is 10–14 glucose units. More branching allows for a higher degree of accessibility for metabolic enzymes, thus glycogen is a ready source of energy for humans (and other mammals).

Fibers

The structural components of a fiber are similar to that of a digestible carbohydrate except that the glycosidic bonds are resistant to enzymatic breakdown and forgo absorption in the gastrointestinal (GI) tract. There are many types of fibers we consume in food such as cellulose, resistant starch, bran, pectin, and inulin. Fibers are found in plants, specifically within the cellular walls. Common dietary sources of fiber include fruits, vegetables, grains, and legumes. Fibers can also be synthetically added to food sources such as cereals, yogurt, juices, and even artificial sweeteners. Fibers have an array of functions, characteristics, and physiological effects.

Characteristics (and Physiological Effects) Solubility

As the name of this characteristic suggests, fibers that are water-soluble will dissolve in water whereas fibers that are water-insoluble will not. The solubility of a fiber results in unique physiological effects. Fibers with a higher water-solubility form a more gel-like substance as it moves through the tract. They also tend to have a high viscosity, ability to adsorb, and are typically fermentable (see other characteristics sections below for more detail). Alternatively, insoluble fibers will stay intact as they travel through the digestive tract. Upon reaching the colon insoluble fiber will add to the bulk of fecal matter decreasing its transit time through the large intestine. This property of insoluble fibers helps to relieve constipation.10,11

Fermentable

Whether a fiber is fermentable depends on whether the bacteria in our large intestine can ferment it (i.e., metabolize it). Byproducts of fermentation include short-chained fatty acids (acetate, propionate, and butyrate), carbon dioxide, and hydrogen. The short-chained fatty acids (SCFA) that are produced through the fermentation process are either used as an energy source by colon cells or to support bacterial growth.

Other Characteristics

Water-soluble fibers are typically viscous. The viscosity turns the material more gel-like and slows the movement of food through the digestive tract. Viscous fibers delay gastric emptying leaving chyme in the stomach for a longer period of time and increasing the time of feeling full.12 The slower gastric emptying can play a role in the rate of glucose absorption at the small intestine which aids in the well-controlled flux of glucose levels into circulation following food intake. In addition to sequestering carbohydrates, viscous fibers can also sequester proteins and lipids inhibiting their
exposure to digestive enzymes. This can impede absorption of these macronutrients at the small intestine. Thus, fiber has been consistent as a staple food source to help with weight management and the control of blood sugar for type 1 and 2 diabetes.13–15

Some fibers have the ability to adsorb (i.e., to bind) to molecules and other nutrients. Relevant to human health, some fibers bind fatty acids, cholesterol, and bile acids within the digestive tract. Once bound the material travels to the large intestine and is added to the bulk of fecal matter to be excreted or bacteria in the large intestine can metabolize the bound molecules. Focusing on the potential of increased bile excretion via feces by fiber, the liver will need to synthesize more bile to keep up with lipid digestion and absorption. Part of the basic structure of bile includes cholesterol, thus low-density lipoprotein (LDL) cholesterol will be taken from circulation and incorporated into bile ultimately decreasing serum cholesterol.16 Although, this is a well-proposed mechanism, evidence shows that high intake of fiber (equivalent to > 3 servings of oatmeal per day) on a regular basis is needed to result in significant decrease in LDL blood cholesterol. Fiber can also adsorb specific minerals like calcium and iron. This can have either a positive or negative consequence. If the fiber is highly fermentable with bound minerals, the breakdown of the fiber by gut bacteria releases the minerals and allow for additional mineral absorption at the large intestine. Instead, if the fiber is poorly fermented the minerals will remain intact with the fiber material and be incorporated into and lost through fecal matter.

Other Considerations of Carbohydrates

Unrefined Versus Refined Carbohydrates

Although it is appropriate as a health professional to discuss carbohydrates in relation to their structures which will dictate their function in the body, often individuals broadly refer to carbohydrates as either refined or unrefined. Unrefined carbohydrates exist in whole food products, in other words, a food product that has undergone zero to minimal processing keeping its nutrients intact at the time of consumption. Examples of unrefined, whole food sources of carbohydrates are legumes, fresh fruits, fresh vegetables, and grains. The wheat grain is a great example of a carbohydrate that can be both unrefined and refined. The unrefined wheat grain contains layers including the bran, germ, and endosperm. The bran contains nutrients such as fiber and B vitamins. The germ contains polyunsaturated fatty acids, iron, zinc, magnesium, and vitamin E. The endosperm is rich in carbohydrates and contains protein. Thus, consumption of an unrefined wheat grain product provides an individual with a nutrient-rich food source with the potential to reap health benefits from these nutrients. The intake of unrefined grains has shown to be protective of the development of obesity, heart disease, hypertension, and type 2 diabetes.17,18 If a wheat grain were to undergo a refinement process, the nutrient-rich layers of the bran and germ are removed. This provides a food product that has an increased shelf life and an altered the taste but lacks nutrients that are essential to the body. Over the past century there has been an increase in the consumption of refined grains and is associated with lower fiber intake and increased risk of chronic disease like type 2 diabetes.19

Added Sugars

Added sugars are those that are intentionally added to food or beverages when they are being processed or prepared for the consumer. These sugars exclude naturally occurring sugars such as the sugar content existing in fruits and lactose-rich milk products. Over the past few decades there has been a rise in the consumption of added sugars in all life-stages, except during infancy, and has been closely associated with the rise in obesity and chronic disease in the United States especially in childhood and adolescence.20–22 Added sugars pose a threat to human health because they add on Calories to a food product without adding on any nutrient value. It has been estimated that about 15% of total daily Calories in adults come from added sugars alone; this is 10% higher than the recommendation from the World Health Organization.23,24 Added sugars will be listed in the food label under the ingredients section. Some examples of common added sugars include, but are not limited to: anhydrous dextrose, brown sugar, corn syrup, high-fructose corn syrup (HFCS), honey, invert sugar, malt syrup, maple syrup, molasses, nectars (e.g., peach nectar, pear nectar), and sugar.

Protein

Basic Definition and Dietary Sources

Proteins contain four Calories per gram. In the United States, protein deficiency is quite rare as sources of protein such as meat, eggs, grains, legumes, and dairy products are readily available. As such, protein is estimated to make up about 15% of the Calories consumed on a daily basis in the United States.5
**Protein Structure**

Protein molecules consist of amino acids linked together by peptide bonds. There are approximately 20 amino acids that are consistently found within dietary proteins (Table 180-1). Amino acids are molecules that are made of a central carbon attached to a hydrogen group, carboxyl group, amino group, and a side chain. The nitrogen present in the amino group differentiates its structural make-up from carbohydrates and lipids. The side chain is unique for each particular amino acid and is what differentiates each amino acid from one another. The make-up of the side-chain gives each amino acid specific properties, and thus, dictates the role of the protein.

**THE ESSENTIAL AND NONESSENTIAL AMINO ACIDS**

<table>
<thead>
<tr>
<th>Essential</th>
<th>Nonessential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine</td>
<td>Alanine</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Arginine&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Leucine</td>
<td>Asparagine</td>
</tr>
<tr>
<td>Lysine</td>
<td>Aspartate</td>
</tr>
<tr>
<td>Methionine</td>
<td>Cysteine&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Threonine</td>
<td>Glutamine&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Glycine&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Valine</td>
<td>Proline&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Serine&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Tyrosine&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Essential amino acids are required to obtain through the diet because the body cannot biosynthesize them.

<sup>b</sup> Conditionally essential amino acids.

The amino acids are linked together by the carboxyl group of one amino acid to the nitrogen of the amino group of another amino acid, otherwise known as a peptide bond. Proteins can be as small as two or three amino acids linked together (i.e., dipeptide or tripeptides, respectively) or more than three amino acids linked together (polypeptide). Dietary proteins are broken down to single amino acids, di- or tripeptides within the GI tract. Transporters at the small intestine are able to transfer these molecules from the GI tract to circulation. Once amino acids are present within the body they are available for protein synthesis. Polypeptides can stand-alone or form larger proteins with other polypeptides. The chemical properties of the amino acid side chains result in bending, folding, attraction, coiling, etc. of the polypeptide resulting in varying functional capabilities within the human body. The polypeptides that form take on the role of hormones, enzymes, and transporters and have structural properties within the body.

**Essentiality**

Of the 20 amino acids in Table 180-1, there are nine that are considered to be essential. Essential amino acids are required to be taken in through the diet.
diet because the body cannot biosynthesize them. Most proteins consist of at least some of each of the essential amino acids which means we cannot generate new proteins unless we have a dietary supply of the essential amino acids. The remaining 11 are nonessential and are not required to be taken in through the diet although they are commonly contained within animal food sources.

Although there are 11 nonessential amino acids, there are instances when they do become essential to take in through the diet. When this occurs, the amino acid is called “conditionally essential.” A clear example of a nonessential amino acid changing into a conditionally essential amino acid is in a condition referred to as phenylketonuria. This is a condition that results from a mutation on phenylalanine hydroxylase gene. Tyrosine is normally a nonessential amino acid that can be made when phenylalanine is available (Table 180-1). This conversion is stimulated by the enzyme phenylalanine hydroxylase. When the mutation in the enzyme’s gene is present, this conversion of phenylalanine to tyrosine is almost completely nonexistent resulting in tyrosine becoming conditionally essential. Other examples of conditionally essential amino acids are indicated in Table 180-1.

### Protein Quality

As stated, the amount of protein taken in through the Westernized diet is likely enough to satisfy an individual’s daily requirement. Needs are different dependent on life-stage, physical activity levels, and general size of a human. For example, infants and children need more protein per kilogram of body weight per day than adults due to the rapid tissue deposition occurring with normal growth and development (i.e., 1.5–0.95 g/kg body weight vs. 0.8 g/kg body weight, respectively).

Although the amount taken in is generally sufficient, the make-up of the protein, or quality of the protein, is something to consider, especially in a time when vegetarian and vegan diets are an option. A high-quality protein food source is one that contains all to most of the nine essential amino acids in proper proportions that once ingested, digested, and absorbed will adequately support protein synthesis. Animal sources are considered complete proteins. The types of proteins derived from animal muscles are myosin and actin. These form the contractile units of muscle and are the major component in both meat and in building muscle tissue. Since mammalian-derived meat and human skeletal muscle are similar in composition, these proteins contain high levels of all the essential amino acids needed for muscle growth. Whey and casein are also proteins that are animal-derived. Casein is abundant in milk products and makes up about 80% of all protein in cow’s milk. Whey is derived from leftover materials after milk is coagulated for cheese. Whey proteins are isolated from the leftover material and are digested efficiently. Although soy proteins are derived from plant sources, they contain adequate levels of amino acids and are considered to be a complete protein source.

On the other hand, incomplete proteins contain some essential amino acids; but not all, though two incomplete proteins can be put together to form a complete protein source. For example, wheat products contain all essential amino acids except they lack lysine. Alternatively, legumes are low in methionine. To overcome these essential amino acid deficiencies, individuals on a vegetarian or vegan diet often practice combining a wheat- and legume-derived protein to form a complete protein source (e.g., rice and beans).

### Celiac Disease

Celiac disease is an autoimmune reaction to gluten, a protein found in wheat, barley, semolina, farro, and rye. Celiac is prevalent worldwide with an estimated 1 in 100 people affected by this heritable disease. An individual carrying a HLA DQ2 or DQ8 allele is genetically predisposed and has a one in ten chance of developing Celiac in their lifetime.

Specifically, the disease is characterized by a response that occurs when the body is exposed to gliadin, a glycoprotein component of gluten. This triggers a T-cell mediated response resulting in the destruction of villi in the small intestine. Villi are essential for complete digestion and absorption of nutrients to occur. They house digestive enzymes that complete digestion as well as peptide and amino acid transporters that allow for absorption to circulation. With damaged villi resulting from the autoimmune response, nutrients are unable to be digested down to their absorbable forms and there is lack of surface area and transporters to allow of absorption even for completely digested nutrients. Unabsorbed nutrients then travel to the large intestine resulting in stomach discomfort and other related symptoms such as fatigue, bloating, and diarrhea. Long-term insufficient nutrient absorption depletes the body of essential nutrients and can result in unintentional weight loss, several types of anemia, osteoporosis, intestinal cancer, and, in children, failure to thrive.

Since this autoimmune response is triggered by exposure to gliadin, removing the gluten exposure through dietary sources, including medicine and foods manufactured in the same facilities as gluten-containing products, will eliminate the autoimmune response. Without this response occurring, the villi remain intact, functional, and can regenerate for those who have been exposed to gluten for any amount of time.
Lipids

Basic Definition and Dietary Sources

Lipids contain nine Calories per gram. Like carbohydrates and proteins, there are several different types of dietary fat with different functions and effects in regard to human health. Common types of dietary fat include triglycerides, saturated fatty acids, trans-fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, cholesteryl, and phospholipids. Foods often associated with higher fat content include red meats, cooking oils, butter, nuts, avocado, and certain fish. The energy that is taken in from lipids in the Westernized diet is about 33% on a daily basis. Of the percent of Calories coming from lipids about 11% of that is made up of saturated fatty acids which exceeds the recommendation of the 2015–20 Dietary Guidelines for Americans to consume less than 10% of Calories from saturated fatty acids. Instead of focusing on reducing lipid intake in the diet, there is an emphasis on focusing on specific types of lipids taken in through the diet to support body functioning and health.

Lipid Structure

Triglycerides and Fatty Acids

Triglycerides consist of a three-carbon chain (glycerol) with a fatty acid esterified to each carbon. Triglycerides are the most widely consumed type of lipid within the diet. The make-up of fatty acids vary and will dictate the properties that they give food (e.g., whether a lipid-containing food is liquid at room temperature or solid). Triglycerides are digested down to free fatty acids within the GI tract. The fatty acids are then absorbed to circulation and, once absorbed, will have different functions and effects on the human body dependent on their chemical make-up. Each differs by the number of carbons atoms on its chain (i.e., short-, medium-, or long-chain), number or existence of double bonds (e.g., monoo- or polyunsaturated), and the arrangement of double bonds (i.e., cis- versus trans- configuration). Fatty acids abundant in our dietary sources include saturated, trans, monounsaturated, and polyunsaturated, which will be discussed later in this chapter. The body can synthesize many fatty acids. Humans do lack an enzyme necessary to facilitate the double bond position in the omega-6 and -3 ends of the fatty acids making these types of fatty acids essential in terms of consumption within the diet.

Cholesterol

Cholesterol is a lipid that is only found in animal food sources, thus oils or plant-based foods do not contain cholesterol. The liver has the ability to synthesize cholesterol so it is not considered to be essential to obtain through the diet. Cholesterol consists of a steroid nucleus. In dietary sources, cholesterol is either found as such or esterified to a fatty acid. Because of the steroid nucleus, cholesterol is key for the synthesis of many steroid hormones such as estrogen or testosterone.

Phospholipids

Like triglycerides, phospholipids also consist of glycerol as its backbone but instead of three fatty acids attached to each carbon of the glycerol, there are only two. The third carbon consists of a phosphate group, thus the name, phospholipid. This structural make-up allows it to be amphipathic giving it the ability to act as an emulsifier allowing oils and water to mix giving a product a certain texture. In the human body phospholipids are integral parts of the cellular membrane and help regulate the substances that transport to and from a cell.

Lipid Properties and Their Significance on Select Health Outcomes

Saturated Fatty Acids

These fatty acids are considered saturated because the carbons along the fatty acid chain are bound to four atoms and thus is saturated. Over the past decades, saturated fatty acid intake has been deemed as a major influencer for the rise in cardiovascular disease resulting in health practitioners recommending limited saturated fatty acid intake for those at risk or recovering from a cardiovascular event. The results from a meta-analysis completed in 2010, caused researchers to question this long-time theory and expand research to look at the entire make-up of macro- and micronutrients within one's diet in regard to the risk of cardiovascular disease. Other patterns of the diet important to consider include high calcium intake, added or refined sugar intake, and high protein intake.
Trans Fatty Acids

When carbons along the fatty acid chain contain a double bond, the hydrogens attached to each carbon of the double bond either exist in a cis or trans formation. Trans fatty acids differ than other fatty acids containing double bonds because the hydrogens attached to the carbons are in the trans orientation versus cis. In the trans orientation the hydrogens are on the opposite sides of the double bonds. This trans configuration gives the fatty acid a higher melting point, and when present in food, can keep food solid at room temperature (e.g., margarine) or lengthen shelf life (e.g., chips, crackers, granola bars). There are few trans fatty acids found in natural food products but the majority of the human diet come from synthetic trans fatty acids. Fatty acids undergo a process called hydrogenation where double bonds become saturated. Between the saturation of double bonds and the arrangement of hydrogens, this configuration makes it shaped like a saturated fatty acid with similar properties. Research has illustrated a positive association between trans fatty acid intake and circulating cholesterol levels and inflammation making this type of fat a risk for cardiovascular disease. Studies have shown that even just a few grams of trans fatty acid intake per day can result in as much of a 23% increased risk of cardiovascular disease.32,33 Because of this heightened risk for cardiovascular events, the FDA has required that food labels present the amount of trans-fatty acids within a product.

Polyunsaturated—Omega-3 and Omega-6 Fatty Acids

A focus on dietary consumption of omega-3 and -6 fatty acids has been suggested by health officials and government agencies over the years as evidence has brought to light their protective affects against heart disease, cancers, and their anti-inflammatory properties. Omega-3 derivatives, EPA and DHA, from animal sources such as fish and fish oil supplements, reduce risk of coronary heart disease by lowering circulating LDL and triglycerides without affecting high-density lipoprotein (HDL) levels, which reduces the buildup of plaque leading to atherosclerosis. Omega-3 intake has also been associated with a reduced risk of thrombosis and arrhythmias.34 Low to moderate consumption of omega-6 fatty acids can stimulate inflammatory markers protective of coronary heart disease. The ratio of omega-6 to -3 intake has been evaluated over the years in terms of the resulting health outcomes. The typical Westernized diet results in a high omega-6 to -3 ratio (about 16:1).35 A high intake of omega-6 saturates the inflammatory response and there has been evidence that it can lead to the oxidation of circulating LDL, leading to atherosclerosis. Therefore, the current recommendations are to take in a ratio of 5–10:1 to reap the optimal health benefits from omega-6 and -3 fatty acids and their derivatives.36

Monounsaturated Fatty Acids

Monounsaturated fatty acids also have lowering effects of circulating LDL. There are certain regions in the world, like Mediterranean countries, with typical diets high in monounsaturated fat due to the high use of olive oils during the cooking and preparation process. Mediterranean populations have lower incidence of coronary heart disease in comparison to the United States. While intake of monounsaturated fats certainly plays a role in the mechanisms to reduce the risk of heart disease, it is likely not the only driver in Mediterranean diets as these diets are rich in fruits, vegetables, fatty fish, and nuts.

Cholesterol

The steroid core of cholesterol is not used for energy but rather is an essential component of all cellular membranes, aiding in their fluidity, as well as a component of other compounds in the body like hormones and bile. Cholesterol is found in animal products and is commonly taken in through the diet. Although cholesterol is consumed through the diet, our body is fully capable of biosynthesizing cholesterol within the liver in times of need. On the other hand, if much cholesterol is consumed through the diet, the liver suppresses the internal synthesis of cholesterol. Hypercholesterolemia, high blood cholesterol, arises when there is a mutation in the low-density lipoprotein receptor gene. When this mutation is present, there is inhibition of a negative feedback loop during cholesterol biosynthesis resulting in accelerated synthesis of internal cholesterol and high blood levels. Over the years, associations between circulating cholesterol and cardiovascular events suggested restrictions of dietary cholesterol to be prudent, but more recent research has shown that dietary cholesterol plays an insignificant role in modulating blood cholesterol levels.37 The evidence is strong enough that the 2015–20 Dietary Guidelines for Americans no longer recommend restricting dietary cholesterol.38

Water

Basic Definition and Dietary Sources
Water is essential for the human body to function. So much so that humans can survive weeks without food intake but only a few days without water. Water is a polar molecule and serves as an ideal solvent within the body. It is the medium in which chemical reactions occur, nutrients and hormones are transported, body temperature is regulated, and serves to regulate acid-base balance. Dietary consumption of water occurs through beverages like water, juice, coffee, and tea as well as foods containing water. Foods with high content of water include fruits, vegetables, and soups.

Distribution and Key Functions

In a normal healthy adult, water makes up about 60% of the total body weight. In other words, there is about 40 L of water in the body at any given time. About 66.7% (25 L) of that water is contained in intracellular environments, and the remaining 15 L is in extracellular compartments like plasma and interstitial fluid (i.e., surrounding cells). Each tissue type across the body has varying levels of water; for example, blood is about 90% water, muscle is about 75% water, bone is about 25% water, and adipose tissue is about 10% water.

Because water is the most abundant constituent of the human body, it plays an important role in maintaining cellular homeostasis, and thus, daily functioning. Water has many roles in metabolism, pH balance, and as a solvent (i.e., medium in which substances dissolve). Water holds heat so it affects body temperature. As part of the interstitial fluid, it provides a passageway for nutrients and other substances throughout the body. Water provides protection as a lubricant, rids toxicants via urine or foreign objects (e.g., tears), and provides buoyancy (e.g., to cushion walking).

Loss and Intake

The amount of water in the human body is not stored, yet the amount remains constant over time. Water is lost from our body (about 2500 mL per day) on a daily basis by obvious routes such as urine, feces, and sweat. Other routes of water loss include exhalation and skin diffusion. Because humans are constantly overturning water, individuals must obtain water by ingesting it. Dietary consumption of water occurs through beverages as well as water contained in food. Minimal amounts of water are also obtained from byproducts of metabolism (<10% of water “intake”).

Water Regulation

Glomerular Filtration

The filtering and excretion functions of the kidney help maintain fluid balance. The filtering process begins in the Bowman’s capsule, which encapsulates a series of capillaries called the glomerulus. The glomerulus receives blood (water, ions, amino acids, glucose, etc.) and filters it. Larger molecules like red blood cells return to circulation via the efferent arteriole. The filtered blood, called glomerular filtrate, crosses the wall of Bowman’s capsule and continues to the tubules along the nephron unit. The tubules have variable permeability along their length making them more pervious (or porous) to specific to certain solutes and water.

The formation of urine in the kidney rids the body of waste, potential toxins, and excess water and solutes. Urine is synthesized following reabsorption along the kidney. During reabsorption certain filtrates will reenter the blood stream, such as water and electrolytes, to ensure intra- and extracellular homeostasis. Of the glomerular filtrate that enters the kidney, only about 1% of it is actually incorporated into urine and excreted on a daily basis.

Osmolarity

Osmotic pressure plays a significant role in the intra- and extracellular distribution of water. Cellular membranes may be impermeable to solutes but not to water, thus, it will move from a high water concentration (low solute concentration) compartment to where there is a low water concentration. This gradient creates equilibrium of “water to solute.”

Vasopressin

Vasopressin is a hormone produced in the hypothalamus and released to the kidney by the pituitary gland. Its main function is to retain water levels in the body. Vasopressin is released in response to an increase of extracellular osmolality (low water volume) and increased sodium concentration in circulation. Upon reaching the kidney, vasopressin binds to V2 receptors on the basolateral end of the kidney tubules that trigger an increase of permeability to water by recruiting transport proteins called Aquaporin w and Aquaporin 3/4 to the apical and basolateral membranes of the kidney tubules, respectively. Aquaporins are selective water channels allowing for water reabsorption back to the bloodstream from the kidney.
MICRONUTRIENTS

Micronutrients are vitamins and minerals that, compared to macronutrients, are needed in smaller amounts by the body. Micronutrients are essential to human health and are used to maintain various systems in the body, including the brain, muscles, blood circulation, and the immune system. Although essential, humans are unable to produce micronutrients and therefore are required to intake them through dietary consumption.39

Vitamins

Basic Definition

Vitamins are mostly derived from the diet, although may also be partially generated by the body.39 However, since vitamins or their precursors must be obtained through the diet, all vitamins are considered essential. These organic compounds are needed to prevent disease and used in enzymatic reactions. Thirteen known vitamins exist today—the water-soluble vitamins B complex (B1, B2, B3, B6, B12, folic acid, biotin, pantothenic acid) and C, and the fat-soluble vitamins A, D, E, and K.

Water-soluble Vitamins

The body handles the water-soluble vitamins differently than that of the fat-soluble vitamins. Water-soluble vitamins are absorbed into the portal blood after digestion and are transported via proteins throughout the body by binding to enzymes. They are excreted through the urine when levels are in excess of what is needed by the body.

B-Complex Vitamins

The B-complex vitamins consist of B1 (thiamin), B2 (riboflavin), B3 (niacin), pantothenic acid (B5), biotin (B7), B6 (pyridoxine), folate (B9), and B12 (cobalamin). Each of these has different structures and functions in maintaining health.

Thiamin Basic Definition and Dietary Sources

Vitamin B1, also known as thiamin, was the first B vitamin to be identified. The structure of thiamin is a pyrimidine ring (2,5-dimethy-6-aminopyrimidine) joined to a thiazolium ring (4-methyl-5-hydroxy ethyl thiazole) by a methylene bridge. Among multiple functions, thiamin is required by transketolase, an enzyme essential for the pentose shunt that supplies NADP for synthetic pathways.40

Thiamin is naturally found in many foods, including meats (especially pork), legumes, sunflower seeds, vegetables, and whole grains and has been added to enriched grain products.41 Processing and heating foods will reduce the thiamin content. Foods containing antithiamin factors, such as thiaminases in raw fish, can cleave and destroy thiamin. Polyhydroxyphenols can also inactivate thiamin through oxyreductive processes, and are found in coffee, tea, betel nuts, blueberries, black currents, brussels sprouts, and red cabbage.42

Most dietary thiamin is in phosphorylated forms, freed by intestinal phosphatases prior to absorption in the jejunum. Thiamin is stored in the liver, but in small amounts, and is needed in a continuous supply from the diet.

Key Functions

About 80% of the thiamin in the body exists as thiamin pyrophosphate (TPP, also known as thiamin diphosphate),36 which is the main metabolically active form of thiamin. TPP has many roles in energy metabolism. First, it is a cofactor for reactions that cleave alpha-ketoacids and decarboxylation of pyruvate to form acetyl CoA. This then goes onto the pyruvate pathway to oxidize glucose. TPP also is a cofactor in decarboxylation of alpha-ketoglutarate dehydrogenase, used in the citric acid cycle (also known as TCA cycle or Krebs cycle),40 a cascade of chemical reactions that releases stored energy from carbohydrates, proteins, and fats, into adenosine triphosphate (ATP) and carbon dioxide.

Deficiency

Thiamin deficiency can be caused by low dietary intakes, low absorption or high excretion rates due to alcoholism, dialysis, chronic diarrhea, and long-term use of high doses of diuretics. Although rare, thiamin deficiency can be caused by genetic mutations. Early symptoms of thiamin deficiency include weight loss and anorexia, confusion, short-term memory loss, muscle weakness, and cardiovascular symptoms.43 Beriberi is the most common
effect of a thiamin deficiency, which is characterized by peripheral neuropathy, wasting, and impaired sensory motor and reflex functions. Rarely does it result in congestive heart failure, edema in lower limbs, and death. Wernicke-Korsakoff syndrome more commonly occurs concurrently with thiamin deficiency, and is more common in people with chronic alcoholism, severe gastric disorders, drug use disorders, or AIDS. Most patients experience two phases, the first being acute, life-threatening Wernicke’s encephalopathy, characterized by peripheral neuropathy. Those who survive this stage develop Korsakoff’s psychosis, which is due to chronic thiamin deficiency and characterized by severe short-term memory loss, disorientation, and confabulation.  

Riboflavin Basic Definition and Dietary Sources

Riboflavin, also known as vitamin B2, is a yellow, fluorescent compound, necessary for redox reactions. Its structure, 7,8-dimethyl-10-ribitylisoalloxazine, lends itself to be essential for two major coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Both of these coenzymes are critical in energy production and electron transport, cell function and development, and metabolism of fats and drugs. Riboflavin is key to the 2-electron acceptor/donor and 1-electron acceptor/donor complexes in the electron transport chain (complexes I-IV and coenzyme Q10).  

The majority of dietary riboflavin is in the form of FMN or FAD. Foods rich in riboflavin include eggs, organ meat, lean meats, dairy products, and green vegetables, as well as fortified cereals and grains.  

Key Functions
Riboflavin, as the form of FMN and FAD, are distributed widely to body tissues. It is involved in the metabolism of macronutrients and the production of some other B complex vitamins, which make it an essential vitamin in growth and development. Riboflavin also serves as an antioxidant because its role in the regeneration of glutathione, a free radical scavenger.  

Deficiency
Riboflavin deficiency is characterized by a sore throat, hyperemia, and edema of the pharyngeal and oral mucous membranes, cheliosis, angular stomatitis, glossitis, seborrheic dermatitis, and normochromic normocytic anemia. People with riboflavin deficiency often present with other nutrient deficiencies as well.  

Niacin Basic Definition and Dietary Sources

Niacin (vitamin B3) encompasses several forms, including nicotinic acid (NA), nicotinamide (nicotinic acid amide, NM), nicotinic acid (pyridine-3-carboxylic acid), and the biologically active derivatives of nicotinamide. Niacin is initially incorporated into nicotinamide adenine dinucleotide (NAD), which can be phosphorylated to form nicotinamide adenine dinucleotide phosphate (NADP) for more than 400 enzymatic activities. The redox potential of NAD and NADP is used in energy production, the Krebs cycle, glycolysis, ethanol oxidation, and other reactions.  

Food sources of niacin include animal products, including milk, eggs, fish, lean meats, poultry; legumes, rice; and enriched grains. The amino acid, tryptophan, is a precursor of niacinamide and the conversion requires two major steps: metabolic conversion of tryptophan to α-amino-β-carboxymuconate-ε-semialdehyde (ACMS), then metabolic conversion of ACMS to nicotinamide. However, the conversion of tryptophan into nicotinamide is effected at low efficiency. The concept of niacin equivalents (NEs) is estimated as total food NE = mg niacin +1/60 mg tryptophan.  

Key Functions
All tissues in the body are able to convert absorbed niacin into its main metabolically active form. As one of the water-soluble vitamins, urinary excretion, not a blood sample, is the most sensitive and reliable measure of niacin status. Niacin, in the form of nicotinic acid, is used pharmacologically to reduce serum LDL cholesterol and increase serum HDL cholesterol. In patients with dyslipidemia, niacin intake has shown to correct the HDL:LDL cholesterol ratio and improve markers for atherosclerosis. High doses of NA leads to the “niacin flush,” characterized by an intense itching or burning sensation on the skin.  

Deficiency
Niacin deficiency results in pellagra. The classic manifestation of pellagra is a pigmented rash the develops in areas exposed to sunlight; digestive conditions such as vomiting, constipation, diarrhea; a bright red tongue; and neurological symptoms such as depression, apathy, headache, fatigue, and loss of memory. Pellagra is common when corn is the dietary staple because corn is low in tryptophan and digestible niacin. It usually requires
alkaline food to release the niacin from niacytin, so the human body can digest and absorb appropriately. Pellagra has largely disappeared in developed countries thanks to niacin-enriched cereals and refined grain products. Individuals with chronic alcoholism or tryptophan pathway disruptions may develop secondary pellagra.

**Vitamin B6 Basic Definition and Dietary Sources**

Vitamin B6 is the generic name for a group of six compounds with vitamin B6 activity: pyridoxal (PL), pyridoxine (PN), pyridoxamine (PM), and their respective 5'-phosphates, pyridoxal 5'-phosphate (PLP), pyridoxine 5'-phosphate (PNP), and pyridoxamine 5'-phosphate (PMP). PLP and PMP are coenzymes for more than 100 enzymatic reactions, including amino acid metabolism, heme biosynthesis, transsulfuration, and methyl group transfer. PLP is also involved with the metabolism of one-carbon units, carbohydrates, and lipids. Vitamin B6 is found in a variety of foods, including fish, organ meats, potatoes and other starchy vegetables, and noncitrus fruits. The majority of vitamin B6 in the United States comes from fortified foods, potatoes, and noncitrus fruits.

**Key Functions**
The human body absorbs vitamin B6 in the jejunum through passive diffusion. Vitamin B6 is essential in cognitive development through biosynthesis of neurotransmitters, including serotonin, dopamine, epinephrine, norepinephrine, and gamma-aminobutyric acid (GABA). Vitamin B6 also plays an important role in gluconeogenesis, glycogenolysis, as well as biosynthesis of sphingolipids and ceramide. Additionally, vitamin B6 serves as a coenzyme in the synthesis of hemoglobin and humoral, cell-mediated immune responses. Some current evidence also suggests that vitamin B6 might decrease the risks of cardiovascular disease and cancer as well as alleviate premenstrual syndrome and “morning sickness” in pregnancy.

**Deficiency**
Deficiency of vitamin B6 is uncommon, but inadequate B6 status is usually associated with inadequacies of other B vitamins. Deficiency is associated with microcytic anemia, electroencephalographic abnormalities, dermatitis with cheilosis and glossitis, depression and confusion, and weakened immune function. Mild deficiency patients may not have symptoms or signs for months or years.

**Folate Basic Definition and Dietary Sources**

Folate is found in the forms folate and folic acid. Folic acid consists of a p-aminobenzoic molecule linked to a pteridine ring and one molecule of glutamic acid. Folate is a coenzyme or cosubstrate in single-carbon transfers in the synthesis of nucleic acids, metabolism of amino acids, and purine synthesis. Folic acid is the fully oxidized monoglutamate form of the folate that is used in fortified foods and dietary supplements.

Folate is found naturally in vegetables (especially dark green leafy vegetables), fruits and fruit juices, nuts, beans, peas, dairy products, poultry and meat, eggs, seafood, and grains. The highest levels of folate are found in spinach, liver, yeast, asparagus, and brussels sprouts. Fortified bread, flour, cornmeal, pasta, rice, and cereals are also good sources of folic acid. Dietary folate equivalents (DFEs) adjust for bioavailability of food folate versus folic acid, and 1 ug DFE = 0.6 ug of folic acid from fortified foods or supplement with meals = 1 ug of food folate = 0.5 ug of supplement on empty stomach.

**Key Functions**
Folate is essential in making red and white blood cells in the bone marrow, converting carbohydrates into energy, and producing DNA and RNA. Folate-dependent one-carbon metabolism is also required for de novo synthesis of purine nucleotides, thymidylate (dTMP), and methylation of homocysteine into methionine.

**Deficiency**
Deficiency of folate exists with other nutrient deficiencies in poor diets, alcoholism, and malabsorptive disorders. Folate deficiencies are characterized by megaloblastic anemia; soreness and shallow ulcerations in the tongue and oral mucosa; and changes in skin and hair pigmentation. Women with low intakes of folate are at higher risk for giving birth to infants with neural tube defects.

**Cobalamin Basic Definition and Dietary Sources**

Cobalamin, also known as vitamin B12, consists of a cobalt atom coordinated by four nitrogens from four pyrrole rings (or tetrapyrrole) collectively. Methylcobalamin and 5-deoxyadenosylcobalamin are the active forms of vitamin B12. Food sources of vitamin B12 include animal products, such as fish, meat, poultry, eggs, milk and milk products, and fortified grains. Vegetarians and vegans need to eat supplemented B12 or nutritional yeast to
ensure adequate intake. As B12 is bound to protein in food, hydrochloric acid and gastric protease in the stomach are needed to release B12. Fortified foods and supplements are in the free form and thus do not require this step. B12 is then bound to intrinsic factor for absorption from the small intestine.

**Key Functions**

B12 is essential for red blood cell formation, neurological function, and DNA synthesis. Vitamin B12 is a cofactor for methionine synthase, which is used to catalyze homocysteine to methionine to form S-adenosylmethionine. Vitamin B12 is also critical for converting L-methylmalonyl-coenzyme A (CoA) to succinyl-CoA needed for hemoglobin synthesis.

**Deficiency**

Pernicious anemia, an autoimmune disease, affects the gastric mucosa and leads to failure of production of intrinsic factor, which is necessary for absorption of vitamin B12. This results in B12 deficiency, megaloblastic anemia, and neurological disorders. Other symptoms of deficiency include difficulty maintaining balance, depression, confusion, dementia, poor memory, and soreness of mouth or tongue. In infants with deficiency, failure to thrive, movement disorders, developmental delays, and megaloblastic anemia can be present.  

**Vitamin C Basic Definition and Dietary Sources**

Also known as ascorbic acid, vitamin C is required for collagen and neurotransmitter synthesis, protein metabolism, and wound healing. Vitamin C cannot be made within the body, and therefore dietary intake is essential. Fruits and vegetables are the best sources, with high concentrations of vitamin C in citrus fruits, tomatoes, red and green peppers, strawberries, kiwi, and broccoli. Many foods are also fortified with vitamin C, such as breakfast cereals and grains. Ascorbic acid may be reduced through prolonged storage and can be destroyed by heat.

The bioavailability of vitamin C is dependent on intestinal absorption and renal excretion. When ascorbic acid levels are high, the kidney will filter it out for excretion. When serum vitamin C levels are low, small intestinal absorption increases and renal tubule reabsorption of ascorbic acid increases.

**Key Functions**

Vitamin C is a co-factor in many enzymes used for biosynthesis of collagen, carnitine, and neurotransmitters. Two enzymes involved with procollagen biosynthesis require vitamin C for formation and secretion of stable collagen helices. Without vitamin C, the collagen structures weaken and lead to tooth loss, joint pain, bone and connective tissue disorders, and poor wound healing. The biosynthesis of carnitine is essential for transporting long-chain fatty acids; without vitamin C, the body may feel fatigued and lethargic. Vitamin C is also essential in converting dopamine to norepinephrine. Mood changes, depression, and hypochondria can occur with vitamin C deficiency.

Vitamin C is also an essential antioxidant. As defined by the Panel on Dietary Antioxidants and Related Compounds of the Food and Nutrition Board, "a dietary antioxidant is a substance in foods that significantly decreases adverse effects of reactive oxygen species, reactive nitrogen species, or both on normal physiological function in humans." Vitamin C has low one-electron reduction potential and is stable in the ascorbyl radical form when ascorbate reacts with reactive oxygen or nitrogen species. Vitamin C is therefore a free radical scavenger and helps to protect cells against reactive oxygen molecules. Furthermore, vitamin C is a co-antioxidant with vitamin E, as it can help regenerate α-tocopherol.

**Deficiency**

Scurvy results from acute vitamin C deficiency, with signs appearing within one month of low or no vitamin C intake. Symptoms include fatigue, lethargy, inflammation of gums, weakened connective tissues, petechiae, joint pain, poor wound healing, hyperkeratosis, and corkscrew hairs. Vitamin C deficiency is rare in developed countries; however those with limited food variety and supply can still develop scurvy. Smokers need 35 mg more vitamin C per day due to their increased oxidative stress decreasing vitamin C levels.

**Disease Prevention**

Vitamin C's function as an antioxidant has led to research into vitamin C’s role in cancer prevention. Vitamin C can limit the formation of carcinogens, and case-control studies have found an inverse association between dietary vitamin C intake and lung, breast, colon, rectum, stomach, oral cavity, larynx, pharynx, and esophageal cancers. However, prospective cohort studies on dietary vitamin C intake and clinical trials of supplemental vitamin C intake show mixed to no results on cancer prevention.

The common cold is often attributed to requiring high levels of vitamin C intake. In the general population, evidence shows vitamin C levels of 200
mg/day or more do not reduce the risk of developing the common cold; however, in populations with extreme exercise or cold environments, higher doses may be helpful.\(^{52}\)

**Fat-soluble Vitamins**

In contrast to the water-soluble vitamins previously described, the fat-soluble vitamins are absorbed and transported with lipids throughout the body. Their absorption in the digestive tract requires bile salts and transport by chylomicrons,\(^{42}\) where they are then stored in lipids until they are utilized by the body.

**Vitamin A Basic Definition and Dietary Sources**

Vitamin A is a group of retinoids, including retinol, retinal, and retinyl esters. Vitamin A exists in two forms in the diet: preformed vitamin A (retinol and retinyl ester) and provitamin A carotenoids (beta-carotene, alpha-carotene, and beta-cryptoxanthin). The body converts both forms into retinal and retinoic acid to become active and function. Vitamin A contains a beta-ionone ring, a conjugated polyene side chain and a terminal functional group. All-trans-retinol is the parent molecule that can be esterified with long chain fatty acids into retinyl esters. Retinol is also sequentially oxidized in the body to retinal then to retinoic acid; different forms of retinoic acid modulate the function of retinol in the body.

Vitamin A needs can be met with preformed vitamin A or provitamin A. Preformed vitamin A is found in animal sources, such as dairy products, fish, meat, and organ meats such as liver. Provitamin A can be found in plants, fungi, and bacteria. Foods are often enriched with retinyl ester or beta-carotene, such as fortified milk and breakfast cereals.

**Key Functions**

Vitamin A is required for many key functions in the body. Most notable is the use of retinal in the transduction of light in the eye for vision. Retinoic acid is necessary for differentiation of the cornea and conjunctival membranes to prevent xerophthalmia and essential for rod and cone cells in the retina. The retinal in the rods are photoisomerized when light is absorbed to trigger the signaling of neurons. The photoisomerized retinal is then released and through a series of steps is added to the storage pool of retinyl esters for another photo cycle.

Vitamin A is also essential in epithelial cells to regulate genes for structural proteins such as keratin, enzymes such as alcohol dehydrogenase, extracellular matrix proteins and retinol binding proteins. Retinoic acid is also necessary in the embryonic development of the hindbrain, limbs, heart, eyes, and ears. Retinoids are needed for immune function through cell differentiation, antiviral and antitumor activity, phagocytic activity, and production of cytokines during inflammation.

**Deficiency**

Although rare in the United States, vitamin A deficiency is common in many developing countries due to limited access to preformed vitamin A from animal sources and beta-carotene foods. During infancy, childhood, pregnancy, and lactation, vitamin A requirements increase, and therefore deficiency is mostly found in these populations. Other groups at risk for vitamin A deficiency include premature infants and patients with cystic fibrosis.

Most common symptoms of vitamin A deficiency include xerophthalmia, which includes night blindness or inability to see in low light, and Bitot’s spots. Vitamin A deficiency is often seen with low iron status, which can lead to anemia.

**Vitamin D Basic Definition and Dietary Sources**

Vitamin D is unique in that it can be synthesized endogenously or through dietary intake. Vitamin D has two major forms, vitamin D\(_2\) (ergocalciferol), which is added to foods, and vitamin D\(_3\) (cholecalciferol), synthesized in the skin and consumed from animal-based foods. Both forms of vitamin D are considered inactive until converted into calcitriol [1,25-dihydroxyvitamin D, or 1,25(OH)\(_2\)D\(_3\)] through two enzymatic reactions. The precursor to calcitriol, 25-hydroxyvitamin D (25(OH)D), is the major circulating form of vitamin D and binds to vitamin D binding protein throughout the body.

Since endogenous vitamin D synthesis varies due to location and sun exposure, most people require dietary vitamin D to maintain adequate vitamin D stores. Dietary sources include food and supplements. Natural sources high in vitamin D include fatty fish, fish liver oil, and egg yolks. In the United...
States and Canada, milk and infant formula are also fortified with vitamin D.

Vitamin D is absorbed with other dietary fats in the small intestine, and its absorption is dependent on fat in the lumen. Bile acids assist in the formation of chylomicrons in the intestines, which packages lipids and vitamin D for transport across the intestinal lining. Adipose and skeletal tissues then take up vitamin D during chylomicron hydrolysis, with the remaining vitamin D taken up by the liver.

**Key Functions**

Vitamin D, in its biologically active form, 25(OH)D, formed in the liver, is required for bone mineralization through its mechanisms associated with calcium homeostasis. Calcitriol elevates ionized calcium levels through stimulating intestinal calcium absorption in the intestine when calcium levels are low. Furthermore, calcitriol mobilizes calcium from bone stimulating the formation and activation of osteoclasts. Calcitriol also works with parathyroid hormone (PTH) to stimulate the renal distal tubule reabsorption of calcium for retention. These three actions increase serum calcium levels, which in turn decreases PTH secretion, closing the feedback loop. Calcitriol also suppresses the parathyroid gene expression to decrease PTH when calcium levels are high through the vitamin D receptor (VDR).

Vitamin D also plays a role in phosphorous homeostasis. Phosphate deficiency stimulates production of calcitriol, which then stimulates phosphate absorption in the small intestine and induces the secretion of FGF23 by osteocytes to reabsorb phosphate in the kidney.

**Deficiency**

Low vitamin D levels can be associated with inadequate dietary intake or insufficient sun exposure. Vitamin D is synthesized in the skin to contribute to serum 25(OH)D levels, but seasonal effects, latitude, and skin pigmentation can all impact 7-dehydrocholesterol’s role in producing 25(OH)D.

Vitamin D deficiency can result in low bone mineralization, and can lead to rickets and osteomalacia (see “Calcium” below).

**Vitamin E Basic Definition and Dietary Sources**

Vitamin E structures consist of a chromanol ring and a saturated tocopherol or unsaturated tocotrienol side chain. Natural vitamin E comes in eight forms (alpha-, beta-, gamma- and delta-tocopherol, and alpha-, beta-, gamma- and delta-tocotrienol). The term “vitamin E” refers to these eight forms, yet alpha-tocopherol is the only form of vitamin E that is required for humans, and the only form used to determine the DRI for vitamin E. Alpha-tocopherol is high in foods such as nuts, seeds, and plant-based oils, and is also available in green leafy vegetables and fortified grains and cereals.

Since vitamin E is fat soluble, it is absorbed through the intestine via chylomicrons and is taken up by the liver via the hepatic alpha-tocopherol transfer protein. Vitamin E is then metabolized into other forms for its antioxidant properties. All forms of vitamin E are absorbed and incorporated into chylomicrons, and no one form appears to be preferentially absorbed from the intestine. However, the liver preferentially releases alpha-tocopherol into plasma, regulated by alpha-tocopherol transfer protein (alpha-TTP).

**Key Functions**

As previously stated, vitamin E acts as a key antioxidant in the body. Vitamin E scavenges for reactive oxygen species and stops their production as fat undergoes oxidation. Vitamin E breaks chains to prevent propagation of free-radical reactions and protects polyunsaturated fatty acids (PUFAs) from reacting with peroxyl radicals by binding to the reactive species. The resulting tocopheroxyl radical can be reduced by other antioxidants to tocopherol, react with another tocopheroxyl radical to form nonreactive products, undergo further oxidation to tocopheryl quinone, or act as a prooxidant and oxidize other lipids.

Furthermore, alpha-tocopherol is involved in immune function, cell signaling, and gene expression. It inhibits protein kinase C activity to inhibit cell proliferation and differentiation. It also decreases adhesion of blood cell components to the endothelium and increases production of phospholipases to inhibit platelet aggregation and increase vasodilation.

**Deficiency**

Vitamin E deficiency is rare in humans, but is accompanied by symptoms of peripheral neuropathy, spinocebellar ataxia, skeletal myopathy, and
pigmented retinopathy. \textsuperscript{64} Neurologic symptoms could progress in children who have deficiency within their first 10 years of life.

**Disease Prevention**

Vitamin E is found to inhibit low-density lipoprotein (LDL) oxidation, \textsuperscript{65} smooth muscle proliferation, \textsuperscript{66} plasma generation of \textit{thrombin} to reduce platelet aggregation, as well as induces synthesis of prostacyclin for vasodilation. \textsuperscript{59} Although several observational studies have shown inverse associations between vitamin E intake and risk of heart disease, \textsuperscript{67,68} randomized clinical trials have not found associations between supplementation of vitamin E and prevention of coronary heart disease. \textsuperscript{69–71}

The antioxidant nature of vitamin E has led to the hypothesis proposing that vitamin E protects against the damaging effects of free radicals leading to cancers. However, trials have not shown such an association for breast, \textsuperscript{72,73} lung, \textsuperscript{74} or prostate cancers, \textsuperscript{74,75} but have shown a slight inverse association between risk of colon \textsuperscript{76} and esophageal cancers \textsuperscript{77} with vitamin E supplementation.

**Vitamin K Basic Definition and Dietary Sources**

Vitamin K is a group of compounds with the 2-methyl-1,4-naphthoquinone structure, which is primarily present as phyloquinone (K\textsubscript{1}) or menaquinones (K\textsubscript{2}) in the diet. \textsuperscript{78}

Phyloquinone is present in green leafy vegetables, such as spinach and collards. Darker leaves have higher concentrations. Other plant sources include soybean, canola, cottonseed, and olive oils. Menaquinones are found in modest amounts in animal-based products, such as dairy products like milk, butter, and cheeses, and fermented foods, such as the Japanese soy-product \textit{natto}. \textsuperscript{79} The bacteria in the human digestive tract also produce menaquinones.

**Key Functions**

As a fat soluble vitamin, vitamin K is incorporated into micelles once ingested for absorption from the small intestine, which is then delivered to chylomicrons and transported to the liver for repackaging into very low-density lipoproteins before being transported to the liver, brain, heart, pancreas, and bone. Due to its nature, only small amounts of vitamin K circulate in the blood; it is quickly metabolized and excreted via urine and feces. \textsuperscript{79}

Vitamin K functions as a coenzyme for vitamin K-dependent carboxylase, which is required for synthesis of proteins needed for blood clotting and bone metabolism. Prothrombin is a protein that is involved with blood clotting, and in vitamin K deficiency; prothrombin time increases and can lead to hemorrhagic events. Vitamin K-dependent proteins include matrix Gla-protein and osteocalcin. Matrix Gla-protein is used in vascular smooth muscle, bone, and cartilage while osteocalcin is needed for bone mineralization. \textsuperscript{80}

Vitamin D and calcium intake throughout the lifespan is important for bone mass and to reduce the risk of osteoporosis, a condition characterized by porous and fragile bones. Vitamin K's role in the prevention of osteoporosis is less well-known, but studies have shown that supplementation of vitamin K can improve bone mineral density and reduce fractures by inducing osteocalcin synthesis. \textsuperscript{81–86}

**Deficiency**

Vitamin K deficiency can occur in the first few weeks of life due to low placental transfer, low clotting factor levels, and low vitamin K content in breast milk. Deficiency is rare in adults and can be attributed to malabsorption or medications that interfere with vitamin K metabolism. Patients on anticoagulants, such as \textit{Warfarin} (Coumadin), should maintain a consistent vitamin K intake to avoid increased prothrombin time. \textsuperscript{79}

In vitamin K deficiency, prothrombin time increases due to the decrease in prothrombin activity. This leads to bleeding and, in severe cases, hemorrhaging. As vitamin K is necessary for bone mineralization, reduction in mineralization and osteoporosis can also occur. \textsuperscript{81}

**Minerals**
Minerals can be divided into major and trace minerals, depending on their essential quantity within the body. Major minerals are required in amounts greater than 100 mg per day, where as adults need trace minerals in less than 100 mg per day. Minerals are obtained via the diet and are used in maintaining electrolyte balance, enzymatic reactions, and ensuring normal functioning throughout the body.

**Calcium**

**Basic Definition and Dietary Sources**

Calcium is known to build strong bones and teeth, but the mineral’s functions encompass more than just bone health. Calcium in the body is fundamental to shape proteins for catalytic and mechanical functions, regulates body processes, and acts as a signal transmitter for cells. The calcium ion (Ca²⁺) is unique for its ability to fit into the folds of peptide chains to allow for triggering the shaping for protein function.

Dairy sources provide more than 70% of the calcium in the diet within the United States. Milk and milk products, canned fish with bones, greens such as broccoli, kale, and mustard greens, as well as legumes, are considered great natural sources of calcium. Food items that have been fortified with calcium, including fortified tofu, soy milk, orange juice, and enriched grain products also contribute to a large portion of the calcium intake in the United States. For example, some ethnic groups receive most of their calcium from calcium-fortified corn tortillas with lime and dried beans.

Calcium intake can be impacted by its bioavailability. Inhibitors of calcium absorption include oxalic acid, which is high in spinach, rhubarb, sweet potatoes, and dried beans. Phytic acid also is an inhibitor of calcium absorption, which is the storage form of phosphorous in beans, and can be found in wheat bran and dried beans.

**Distribution and Key Functions**

Calcium performs key functions in the body: calcium acts as an intracellular messenger, cofactor for enzymes and proteins, and maintains the structure of bones and teeth.

As a signal transmitter, calcium can bind to both extracellular and intracellular proteins. When a stimulus occurs, the cell releases a store of calcium and, depending on the action necessary, is released from the cell or to enter the cell. Calcium is critical for the mediation of vascular contraction, vasodilation, muscle function, nerve transmission, and hormonal secretion.

Calcium also maintains bone and teeth structure and function. About 50–70% of bone is mineral, most of which is calcium hydroxyapatite. Calcium is required for both bone formation and remodeling and is deposited into the organic matrix of the skeletal for rigidity, strength, and elasticity.

**Deficiency**

Rickets and osteomalacia develop when calcium levels are low. In young children and infants, rickets is the end-stage condition when bones and cartilage fail to mature and lead to irreversible changes in the skeletal structure. Children with rickets present with symptoms of stunted growth and bowing of the extremities. Osteomalacia is seen in adults and children and is the defective mineralization of bone and softening of bone. Bone pain, muscle weakness, and impaired bone mineralization are key symptoms, and results in the undermineralization of bone.

Osteoporosis is associated with aging and reduced bone mass and bone quality. Low bone mineral density increases bone fragility, and in turn, increases the risk of fractures. Menopause can initiate osteoporosis through increased bone remodeling in women, and men experience comparable bone loss 5–10 years later than women.

**Sodium**

**Basic Definition and Dietary Sources**

Sodium (Na⁺) is one of the major minerals and an essential electrolyte that plays an important role in a host of normal metabolic functions. The major source of sodium is sodium chloride, commonly known as table salt. Protein foods generally contain more naturally existing sodium than vegetables, fruits, or grains. High sodium content can be found in most convenience and fast-food products, as addition of table salts, flavored salts, preservatives, etc.
The 2015–20 Dietary Guidelines for Americans recommend consuming less than 2300 mg of sodium per day as part of a healthy eating pattern, though collected statistics present that the vast majority of adults in America eat an average of more than 3400 mg sodium each day. Healthy kidneys are usually able to excrete excess sodium intake, but persistent excessive sodium intake has been found to be associated with elevated risks of hypertension and osteoporosis.

Distribution and Key Functions

Approximately 35–40% of the total body sodium is in the skeleton, and the normal sodium concentration in serum is 136–145 mEq/L. Secretions such as bile and pancreatic juice also contain substantial amounts of sodium. Sodium is a cation of extracellular fluid and is needed for proper fluid balance, maintenance of acid-base balance, nerve transmission, and muscle contraction. The Na/K ATPase pump is an active transport system that requires sodium, potassium, and energy for proper function, and works to keep sodium extracellular through exchange with potassium. Exportation of sodium from the cell is the driving force for facilitated transporters that import glucose, amino acids, and other nutrients into the cells.

Regulation of Sodium Balance

Changes in either intracellular or extracellular sodium concentrations can have a major effect on bodily functions. Sodium balance involves the function of the kidneys, the renin-angiotensin-aldosterone system, the sympathetic nervous system, circulating catecholamines, certain hormone concentrations, and blood pressure. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one of the medical situations caused by disrupted sodium and fluid regulations.

Potassium

Basic Definition and Dietary Sources

Potassium (K+) is the major cation of intracellular fluid and is present in all body tissues.

Potassium can be found in a wide variety of plant and animal foods and beverages. Fresh fruits, vegetables, meat, and dairy products are all good sources of potassium. Insufficient potassium intake has been associated with hypertension and cardiac arrhythmia.

Distribution and Key Functions

The total amount of potassium in the average adult body is about 45 mmol/kg body weight, and most potassium resides intracellularly. The potassium concentration difference between intracellular and extracellular fluids forms a transmembrane electrochemical gradient that is maintained via the sodium-potassium (Na+/K+) ATPase transporter. Therefore, sodium and potassium together, play an essential role in maintaining a normal water balance, osmotic equilibrium, acid-base balance, nerve transmission, and muscle contraction. In addition, potassium promotes cellular growth, and an adequate supply is essential when muscle is being formed.

Phosphorus

Basic Definition and Dietary Sources

Phosphorus is an essential mineral that is required in cell function, acid-base balance, as well as energy and bone metabolism. Approximately 85% of phosphorus in adult is present in the skeleton and teeth as calcium phosphate crystals. Almost 50% of phosphorus that is present in serum exists as free ions (H2PO4- and H2PO4-2-), and the remainder is bound to protein or other compounds. Phosphorus can be found in almost all protein sources, mainly in the form of phosphates and phosphate esters, such as meat, fish, poultry, eggs, milk, nuts, legumes, and grains. Phosphorus in seeds and unleavened breads is in the form of phytic acid. It can also be found in processed foods and soda soft drinks.

Distribution and Key Functions

Approximately 700 g of phosphorus exists in adult tissues. Of this amount, 85% is stored in bones and teeth, and the other 15% is distributed in the blood and soft tissues. In the form of phosphates, phosphorus is an essential component of DNA, RNA, ATP, and cAMP. In the form of phospholipids, phosphorus is a component of every cell membrane in the body. Phosphorus also plays key roles in gene transcription regulation, enzyme activation, and protein synthesis.
energy production, and extracellular fluid pH maintenance.

Deficiency

Phosphorus deficiency is very rare because first, its hemostasis is efficiently and effectively regulated by the kidneys, bones, and intestines, as well as hormones such as estrogen and adrenaline; and secondly, it is so widely available from both natural sources and processed foods. However, phosphate deficiency could develop in individuals who take phosphate binders for renal disease, use phosphate-binding antacids long term, or have poor intake in general. Severe phosphate depletion could lead to neural, muscular, skeletal, hematologic, and renal dysfunction and damage.88

Magnesium

Basic Definition and Dietary Sources

Magnesium (Mg²⁺) is the second-most abundant intracellular cation after potassium in the human body. The adult human body, on average, contains approximately 20–28% of magnesium.86 The unique chemical structure and properties of magnesium allow it to position H₂O in a manner that promotes catalytic activity. It is also able to induce a conformational rearrangement that exposes catalytic sites and provides stability as the phosphate backbone is hydrolyzed.

Magnesium is fairly ubiquitous in whole, unrefined foods. Major food sources include nuts and seeds, legumes, leafy vegetables, seafood, chocolate, and artichokes.

Distribution and Key Functions

An abundance of total magnesium is found in bones (60–65%) and in muscle (26%) with most of the remainder in soft tissues and body fluids. Less than 1% of total magnesium is in blood serum, making it difficult to assess magnesium status. Magnesium homeostasis is tightly controlled by the kidneys, which typically excrete about 120 mg magnesium in the urine per day.

Key functions of magnesium are threefold. First, magnesium is a required cofactor for over 300 enzymes that are involved in the metabolism of food, synthesis of fatty acids and proteins, phosphorylation of glucose, as well as the formation of cyclic adenosine monophosphate (cAMP). In these metabolic pathways, magnesium usually acts as a stabilizer to neutralize the (-) charge of ATP and regulate ATP-dependent enzyme reactions. Secondly, magnesium plays an important role in regulating calcium flux from intracellular organelles as well as extracellular calcium flux into a cell. Healthy function of vascular and other smooth cells requires a balanced ratio of calcium and magnesium in the blood.88 Lastly, animal studies and human observational studies have found that magnesium has an effect on maintenance of healthy learning and memory functions.

Deficiency

Serum magnesium concentration is commonly stable, under well-adjusted absorption, excretion, and transmembranous cation flux systems. Although very rare, severe magnesium deficiency symptoms such as tremors, muscle spasms, anorexia, nausea, vomiting, and personality changes have been observed in patients with diabetes, chronic renal failure, nephrolithiasis, osteoporosis, aplastic osteopathy, and heart and vascular diseases.88 Moderate depletion of magnesium is prevalent in older populations in Western nations due to low intake of magnesium-rich foods, increased loss of electrolytes, or certain chronic diseases.

Sulfur

Basic Definition and Dietary Sources

Sulfur is one of the most abundant mineral elements found in the human body, and it exists as a constituent of cystine, cysteine, and methionine amino acids. Methionine and cysteine provide nearly 100% of the sulfur in the human diet.88 Sulfur functions almost entirely as a component of organic molecules in cells and extracellular compartments.88 The unique tertiary structure of proteins indicate sulfur results from many biochemical reactions and structural modifications, which is essential for the activity of insulin, certain enzymes, proteins, and cellular reactions. Sulfur can be obtained almost exclusively from protein-rich food items including meats, poultry, fish, eggs, milk, legumes, and nuts. A very small proportion of sulfur
Distribution and Key Functions

The body contains approximately 140 grams of sulfur, and it is mostly distributed in proteins. Since sulfur is contained in so many amino acids, and plays a role in the synthesis of a very large number of key metabolic intermediates, sulfur has many key health functions. Sulfur can be considered as an antioxidant because glutathione (a tripeptide-containing cysteine) serves as a donor for the reduction of hydrogen peroxide and organic peroxides. Taurine, another sulfur-containing amino acid made by liver cells, helps to regulate lipid metabolism. Studies have found that taurine supplementation is linked to a significant decrease in total hepatic lipid content and slightly increased bile flow and secretion of bile salts. Sulfur is also part of the molecule known as S-adenosylmethionine, which serves as a cosubstrate in methyl group transfer, trans-sulfuration, and aminopropylation.

Trace Elements

Trace elements are minerals present in living tissues in small amounts; some of them are considered to be nutritionally essential, and the remainder are nonessential. Trace elements function primarily as catalysts in enzyme systems and include iron, zinc, copper, iodine, manganese, cobalt, fluoride, and selenium. In this section, we will concentrate our discussion on the first four trace minerals since the deficiency and/or toxicity of these four elements are relatively more common and have significant and close associations with the development of chronic diseases as well as other health dysfunctions.

Iron

Basic Definition and Dietary Sources

Iron is a mineral essential to catalytic reactions in the body. Two oxidative states of iron exist, the ferrous form (Fe²⁺) and the ferric form (Fe³⁺). These two states allow for redox reactions to occur, with ferrous iron oxidizing to ferric iron. In the body, iron can exist in one of three forms: bound to protein as heme, such as in hemoglobin or myoglobin; as heme enzymes; or as nonheme compounds such as in storage. Ferritin is the storage form of iron and consists of 24 protein units surrounding a ferric core. Ferritin releases iron when blood levels are low. Transferrin functions as a transport mechanism by binding to iron and can limit its toxic effects when levels of iron are high.

Iron can take two forms in food, heme and nonheme iron. Heme iron is derived from hemoglobin or myoglobin and is found in animal products, mostly red meats, fish, and poultry. In contrast, nonheme iron is found in plant foods, along with enriched and fortified foods. Nonheme iron is less bioavailable than heme iron, with only 2–20% of nonheme iron assimilated into the body compared to 15–35% of heme iron. Iron absorption is facilitated by ascorbate and citrate, while inhibited by phytates, polyphenols, and calcium.

Distribution and Key Functions

About 66% of the body’s iron is found as hemoglobin, 15% bound to myoglobin in the muscle for oxygen, and 25% in the storage form. Iron homeostasis is tightly regulated as its use in the body is diverse. As iron is not actively excreted from the body, absorption through the gastrointestinal system regulates iron balance. Through a feedback loop, iron is transferred across the intestines during iron deficiency and is then transported to cells or bone marrow by transferrin. When iron levels are high, the divalent metal transporter 1 in the intestines decreases transport of iron.

In addition to transferrin, hepcidin is a hepatic peptide hormone that assists with iron homeostasis. Hepcidin binds to ferroportin in the intestines, macrophages, and placenta. Ferroportin is a transport protein of iron, and when bound to hepcidin, is degraded and leads to lower iron transport into plasma. This decrease in iron levels leads to lower saturation of transferrin and a feedback loop to decrease hepcidin production by the liver.

Iron is essential for metabolic processes, including oxygen transport, electron transport, cell differentiation, and DNA and RNA synthesis. Iron is a key component of many enzymes for electron transport and DNA synthesis, and is used in oxidases, catalases, peroxidases, cytochromes, ribonucleotide reductases, aconitases, and nitric oxide synthases.
Iron Deficiency and Anemia

Iron deficiency is prevalent in 39% of children less than 5 years of age, 48% of 5–14 year olds, and 52% of women in developing countries. Deficiency can be categorized in terms of severity and can present with or without anemia. Mild iron deficiency results in increased oxygen delivery due to lower hemoglobin and myoglobin status and redistribution of blood flow that results in enhanced cardiac output. Severe iron deficiency can result in acidosis and affects cognitive development and immune function. Iron deficiency can be caused by low iron absorption, blood loss, increased iron requirements due to pregnancy or menstruation, and poor dietary intake.

Anemia occurs when the count of red blood cells is low or the amount of hemoglobin is below normal. Hemoglobin delivers oxygen from the lungs to other cells and when hemoglobin or red blood cells are not functioning at full capacity, fatigue, shortness of breath, and increased heart rate can occur. The most common cause of anemia is iron deficiency, which can result from poor dietary intake.

Zinc

Basic Definition and Dietary Sources

Zinc is an intracellular ion, required for catalytic activity in more than 300 different enzymes. Though zinc is abundant in the cytosol, almost all of it is bound to proteins that form “zinc fingers.” Good food sources of zinc include red meats, poultry, shellfish, cereals, milk, and milk products. Zinc intestinal absorption does not appear to be influenced by total body zinc levels, but phytates readily bind to zinc and inhibit its absorption.

Distribution and Key Functions

The human body has approximately 2–3 g of zinc, with the highest concentrations stored in the liver, pancreas, kidneys, bone, and muscles. Zinc homeostasis is maintained largely through pancreatic secretions regulated by zinc transporters. Metallothionein is the most abundant, nonenzymatic, zinc-containing protein and serves as an intracellular reservoir that donates zinc ions to other proteins.

Zinc has structural, catalytic, and regulatory functions in the cell, including gene expression, cell signaling, and cell proliferation and differentiation. It plays essential structural roles as components of many enzymes that are involved in either synthesis or degradation of carbohydrates, lipids, proteins, and nucleic acids. In addition, zinc stabilizes RNA and DNA structure, and is required for the activity of RNA polymerases. It also protects against age-related macular degenerative disease, and is able to stimulate bone formation.

Deficiency

Zinc deficiency is very rare in Western nations because of the abundance of fortified breads, cereals, and refined grains. However, zinc deficiency is one of the ten major factors contributing to disease in developing countries. The clinical signs of zinc deficiency include short stature, hypogonadism, mild anemia, and low plasma zinc levels. Additional symptoms are delayed sexual maturation, poor wound healing, impaired taste acuity, immune dysfunction, alopecia, and dermatitis-like lesions.

Copper

Basic Definition and Dietary Sources

Copper is another essential trace mineral that serves as a normal constituent of blood. Copper has two oxidative statuses: cuprous (Cu⁺) and cupric (Cu²⁺), with cupric the most common biological form of copper. The redox capability of copper is utilized in numerous enzymatic reactions.

Most copper in the diet is bound to proteins, and good food sources of copper include shellfish, nut/seeds, cocoa powder, legumes, the germ component of grains, and organ meats. Some studies have shown that high ascorbic acid intake, high zinc intake, and therapeutic doses of iron may lead to a poorer copper status.

Distribution and Key Functions

Copper does not exist as a free ion in the body. Approximately 90% of the copper in serum is incorporated into ceruloplasmin, a copper-containing
Copper deficiency is characterized by anemia, neutropenia, skeletal demineralization, subperiosteal hemorrhages, hair and skin depigmentation, and defective elastin formation. Failure of erythropoiesis because of copper deficiency may lead to death. Copper deficiency is extremely rare among healthy humans consuming a balanced diet. However, premature infants and infants who were poorly nourished are likely to have copper deficiency. Two genetic disorders, known as Menkes’ syndrome and Wilson’s disease, could result in an abnormal distribution of copper among organs and within cells. Menke’s syndrome is an X-linked recessive defect that affects the gene-encoding ATP7A. Menke’s syndrome leads to generalized copper deficiency and marked cerebral degeneration, and is fatal by about three years of age. Wilson’s disease, in contrast, is an autosomal recessive gene disorder that affects the gene encoding ATP7B. Wilson’s disease leads to accumulated copper toxicity because the body is unable to excrete copper in bile or export copper from neuronal tissue. The onset of Wilson’s disease is variable but usually presents with liver dysfunction by 30 years of age, accompanied with neuropsychiatric symptoms. Wilson’s disease is usually treated by limiting copper in the diet and administering chelating agents and high doses of zinc.

Iodine

Basic Definition and Dietary Sources

Iodine is a trace mineral of crucial importance to health and well-being and diet is the sole source. Iodine is required at all stages of life, with fetal life and early childhood being the most critical phases for its availability. Good food sources of iodine are seafood (fish, shellfish, and seaweed), iodized salt, meats, and eggs. Vegetables and grains also contain iodine, but their content level depends on exposure to iodine through rain, glaciation, and soil.

Distribution and Key Functions

Dietary iodine is primarily needed for the synthesis of thyroid hormones, which are involved in numerous metabolic and developmental processes. Iodine is stored in the thyroid gland, and is used in synthesis of triiodothyronine (T3) and thyroxine (T4). Three types of deiodinases regulate plasma and intracellular iodine levels, and thyroid hormone actions.

Deficiency and Toxicity

Iodine deficiency in the developed Western nations has practically been eliminated with the use of iodized salt. Yet, people living in many mountainous areas or developing countries of the world may still have low intake because of the low iodine content in the soil or high consumption of goitrogens (substances that disrupt the production of thyroid hormones by interfering with iodine uptake). Very low iodine intake is associated with the development of endemic goiter. Iodine deficiency during gestation and early postnatal growth can result in mental deficiency, deaf-mutism, and shortened stature.

Acute excessive intake of iodine results in the Wolff-Chaikoff effect, characterized by short-term, high intracellular iodine levels and decreased organization. Chronic excessive intake of iodine can disturb the thyroid gland’s regulatory mechanisms and lead to hypothyroidism.

DIETARY REFERENCE INTAKE

Dietary reference intakes (DRIs), developed and published by the National Academy of Medicine (formerly the Institute of Medicine or IOM), are reference values that provide quantitative estimates of macro- and micronutrient intake, serving as a guide for good nutrition among healthy
populations and provide the scientific basis for the development of dietary guidelines in the United States and Canada. DRI is an umbrella term that includes at least four nutrient-based reference values: Recommended Dietary Allowance (RDA), Estimated Average Requirement (EAR), Adequate Intake (AI), and Tolerable Upper Intake Level (UL). These recommendations include over 40 nutrients taken in through diet for ten different age groups across the life course, in addition to significant life-stages in females including pregnancy (taking into consideration different needs for each trimester) and lactation (addressing different needs for the age of the infant or child). The RDA is the average daily dietary intake level that is sufficient to meet the nutrient requirements of 9–98% of healthy individuals in a particular life stage and gender group. The EAR is the daily intake value that is estimated to meet half of the healthy individuals (median usual intake value) by life stage and gender group. The AI is based on experimentally derived intake levels or approximations of observed mean nutrient intake by a group or groups of healthy people. The UL is the highest level of daily nutrient intake that is unlikely to pose risks of adverse health effects in almost all individuals in the specified life-stage group.\(^95\)

There are four overarching steps of the DRI development: (1) Indicator review and selection; (2) Intake-response assessment and specification of reference values; (3) Intake assessment; and (4) Discussion of implications and special concerns. The “indicator” that initiates the entire process refers to clinical endpoints, surrogate endpoints, biomarkers, or risk factors for a chronic disease. Selecting an appropriate indicator for a given nutrient and DRI usually starts with a review and interpretation of published literature by the DRI committee. After the selection of indicators, the intake-response relationships is determined, which includes responses of nutrient adequacy, excess, or relationship to a chronic disease outcome. Then, these values are compared to current levels of intake and implications of the determined reference values, and special concerns will be thoroughly discussed. Afterward, adjustments for special groups are conducted and risk assessments surrounding the DRIs will be included before publication.

Nutrient assessment for DRI review and update is based on annual nutrient nominations. Then, DRI committees are jointly prioritizing nutrients for government-funded review and subsequent commissioning of an expert review to re-establish reference values. The most recent DRI activity update is the DRI for sodium and potassium in the 2019 report.\(^96\)

**DIETARY GUIDELINES FOR AMERICANS**

The history of USDA nutrition guides includes over 100 years of American nutrition advice. Both the Dietary Goals and the Dietary Guidelines for Americans have been updated over time, to reflect evolving scientific evidence, changed historical focus on nutrient adequacy, and new public health marketing techniques. There have been many versions of USDA food guides. For example, the influential MyPyramid food guide was introduced along with the Dietary Guidelines for Americans in 2005. It continued the “pyramid concept,” which was first introduced in the 1992 Food Guide with a more simplified illustration. This version also added the concept of physical activity. The most recent USDA food guides, the MyPlate, was introduced along with an update of USDA food patterns for the 2010 Dietary Guidelines for Americans. It used a general plate shape and different colors on the plate to help grab consumers’ attention and emphasize the importance of portion size.

The Dietary Guidelines for Americans have been developed jointly by the U.S. Department of Health and Human Services (HHS) and the U.S. Department of Agriculture (USDA) since 1980. Starting in 1985, the Dietary Guidelines Advisory Committee was established. A Federal advisory committee of nine nutrition scientists selected from outside the Federal Government was convened to review and make recommendations to HHS and USDA about the first edition of the Dietary Guidelines. New Advisory Committees are established every 5 years for each revision of the dietary guidelines. HHS and USDA collaborate during a three-stage process: review the science, develop the dietary guidelines, and implement the dietary guidelines. In the first stage, an external Dietary Guidelines Advisory Committee (Advisory Committee) is appointed. The advisory committee used four state-of-the-art approaches to review and analyze the available evidence, summarizing all of the evidence in a comprehensive scientific report. In the second stage, the scientific report is translated into more consumer-friendly language to create the actual dietary guidelines used by HHS and USDA. The most recent 2015–20 Dietary Guidelines is built around five Guidelines and Key Recommendations that provide detail on the elements of healthy eating patterns. In the third and final stage, the Federal Government implements the recommendations in the Dietary Guidelines. Federal programs apply the Dietary Guidelines to meet the needs of Americans and specific population groups through food, nutrition, and health policies and programs and in nutrition education materials for the public.

Nutrient recommendations in the United States have obviously evolved substantially over the past 100 plus years. They were first established with a focus solely on recommendations for macronutrients because knowledge about micronutrients was widely lacking. They also initially focused more on preventing infectious disease like polio or tuberculosis, leading causes of illness and death at that time. Because of medical advances including the use of vaccines, antibiotics and improvements in public health, the recommendations have now shifted to focus on chronic diseases like obesity and heart disease. Currently, the overarching goals of the recommendations are to prevent over- or undernutrition, ensure normal development and health
status and to support pregnancy and lactation when nutritional needs are altered.

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Nonpersistence

55. Oxygen

Basic Definition and Dietary Sources

52. Copper

Second stage, the scientific report is translated into more consumer-friendly language to create the actual dietary guidelines used by HHS and USDA. With an update of USDA food patterns for the 2010

meet half of the healthy individuals (median usual intake value) by life stage and gender group. The AI is based on experimentally derived intake levels

oxidase), iron oxidation, synthesis of

Iron is essential for metabolic processes, including

bioavailable than heme iron, with only 2–20% of nonheme iron assimilated into the body compared to 15–35% of heme iron. Iron absorption is

free ions (H2PO4- and H2PO42-), and the remainder is bound to protein or other compounds.

Minerals can be divided into major and trace minerals, depending on their essential quantity within the body. Major minerals are required in amounts

chylomicrons, and no one form appears to be preferentially absorbed from the intestine. However, the liver preferentially releases alpha-tocopherol

extracellular matrix proteins and retinol binding proteins. Retinoic acid is also necessary in the embryonic development of the hindbrain, limbs, heart,

Deficiency

foods and supplements are in the free form and thus do not require this step. B12 is then bound to intrinsic factor for absorption from the small

glutamic acid. Folate is a coenzyme or cosubstrate in single-carbon transfers in the synthesis of nucleic acids, metabolism of amino acids, and purine

isoalloxaine, lends itself to be essential for two major coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Both of these

added to enriched grain products.

homeostasis. Of the glomerular filtrate that enters the kidney, only about 1% of it is actually incorporated into urine and excreted on a daily basis.

that the 2015–20

typical diets high in monounsaturated fat due to the high use of olive oils during the cooking and preparation process. Mediterranean populations

trans fatty acids found in natural food products but the majority in the human diet come from synthetic trans

completed in 2010,

legume-derived protein to form a complete protein source (e.g., rice and beans).

nonessential amino acid that can be made when phenylalanine is available (e.g., tyrosine). These amino acids are nonessential for the body because

diet because the body cannot biosynthesize them. Most proteins consist of at least some of each of the amino acids which means we cannot generate

contains protein. Thus, consumption of an unrefined wheat grain product provides an individual with a nutrient-rich food source with the potential to

Alternatively, insoluble fibers will stay intact as they travel through the digestive tract. Upon reaching the colon insoluble fiber will add to the bulk of

consist of short chains of glucose residues linked

Second Class of Carbohydrates: Oligosaccharides

Carbohydrate Structure

Maxcy-Rosenau-Last Public Health & Preventive Medicine, 16e

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