6

Dietary Carbohydrates: Sugars and Starches

SUMMARY

The primary role of carbohydrates (sugars and starches) is to provide energy to cells in the body, particularly the brain, which is the only carbohydrate-dependent organ in the body. The Recommended Dietary Allowance (RDA) for carbohydrate is set at 130 g/d for adults and children based on the average minimum amount of glucose utilized by the brain. This level of intake, however, is typically exceeded to meet energy needs while consuming acceptable intake levels of fat and protein (see Chapter 11). The median intake of carbohydrates is approximately 220 to 330 g/d for men and 180 to 230 g/d for women. Due to a lack of sufficient evidence on the prevention of chronic diseases in generally healthy individuals, no recommendations based on glycemic index are made.

BACKGROUND INFORMATION

Classification of Dietary Carbohydrates

Carbohydrates can be subdivided into several categories based on the number of sugar units present. A *monosaccharide* consists of one sugar unit such as glucose or fructose. A *disaccharide* (e.g., sucrose, lactose, and maltose) consists of two sugar units. *Oligosaccharides*, containing 3 to 10 sugar units, are often breakdown products of *polysaccharides,* which contain more than 10 sugar units. Oligosaccharides such as raffinose and stachyose are found in small amounts in legumes. Examples of polysaccharides include starch and glycogen, which are the storage forms of carbohydrates in plants and

animals, respectively. Finally, *sugar alcohols*, such as sorbitol and mannitol, are alcohol forms of glucose and fructose, respectively.

Definition of Sugars

The term "sugars" is traditionally used to describe mono- and disaccharides (FAO/WHO, 1998). Sugars are used as sweeteners to improve the palatability of foods and beverages and for food preservation (FAO/WHO, 1998). In addition, sugars are used to confer certain functional attributes to foods such as viscosity, texture, body, and browning capacity. The monosaccharides include glucose, galactose, and fructose, while the disaccharides include sucrose, lactose, maltose, and trehalose. Some commonly used sweeteners contain trisaccharides and higher saccharides. Corn syrups contain large amounts of these saccharides; for example, only 33 percent or less of the carbohydrates in some corn syrups are mono- and disaccharides; the remaining 67 percent or more are trisaccharides and higher saccharides (Glinsmann et al., 1986). This may lead to an underestimation of the intake of sugars if the trisaccharides and higher saccharides are not included in an analysis.

Extrinsic and Intrinsic Sugars

The terms extrinsic and intrinsic sugars originate from the United Kingdom Department of Health. Intrinsic sugars are defined as sugars that are present within the cell walls of plants (i.e., naturally occurring), while extrinsic sugars are those that are typically added to foods. An additional phrase, "non-milk extrinsic sugars," was developed due to the lactose in milk also being an extrinsic sugar (FAO/WHO, 1998). The terms were developed to help consumers differentiate sugars inherent to foods from sugars that are not naturally occurring in foods.

Added Sugars

The U.S. Department of Agriculture (USDA) has defined "added sugars" for the purpose of analyzing the nutrient intake of Americans using nationwide surveys, as well as for use in the Food Guide Pyramid. The Food Guide Pyramid, which is the food guide for the United States, translates recommendations on nutrient intakes into recommendations for food intakes (Welsh et al., 1992). Added sugars are defined as sugars and syrups that are added to foods during processing or preparation. Major sources of added sugars include soft drinks, cakes, cookies, pies, fruitades, fruit punch, dairy desserts, and candy (USDA/HHS, 2000). Specifically, added sugars include white sugar, brown sugar, raw sugar, corn syrup, corn-syrup

solids, high-fructose corn syrup, malt syrup, maple syrup, pancake syrup, fructose sweetener, liquid fructose, honey, molasses, anhydrous dextrose, and crystal dextrose. Added sugars do not include naturally occurring sugars such as lactose in milk or fructose in fruits.

The Food Guide Pyramid places added sugars at the tip of the pyramid and advises consumers to use them sparingly (USDA, 1996). Table 6-1 shows the amounts of added sugars that could be included in diets that meet the Food Guide Pyramid for three different calorie levels.

Since USDA developed the added sugars definition, the added sugars term has been used in the scientific literature (Bowman, 1999; Britten et al., 2000; Forshee and Storey, 2001; Guthrie and Morton, 2000). The 2000 *Dietary Guidelines for Americans* used the term to aid consumers in identifying beverages and foods that are high in added sugars (USDA/HHS, 2000). Although added sugars are not chemically different from naturally occurring sugars, many foods and beverages that are major sources of added sugars have lower micronutrient densities compared with foods and beverages that are major sources of naturally occurring sugars (Guthrie and Morton, 2000). Currently, U.S. food labels contain information on total sugars per serving, but do not distinguish between sugars naturally present in foods and added sugars.

Definition of Starch

Starch consists of less than 1,000 to many thousands of α-linked glucose units. Amylose is the linear form of starch that consists of α-(1,4) linkages of glucose polymers. Amylopectin consists of the linear

TABLE 6-1 Amount of Sugars That Can Be Added for Three Different Energy Intakes That Meet the Food Guide Pyramid

Food Guide Pyramid Patterns at Three Calorie Levels	Pattern A	Pattern B	Pattern C
Kilocalories (approximate)	1,600	2,200	2,800
Bread/grain group (servings)	6	9	11
Vegetable group (servings)	3	4	5
Fruit group (servings)	2	3	4
Milk group (servings)	2–3	2–3	2–3
Meat group (oz)	5	6	7
Total fat (g)	53	73	93
Total added sugars (tsp)[a]	6	12	18

[a] 1 tsp added sugars = 4 g added sugars.
SOURCE: USDA (1996).

α-(1,4) glucose polymers, as well as branched 1-6 glucose polymers. The amylose starches are compact, have low solubility, and are less rapidly digested. They are prone to retrogradation (hydrogen bonding between amylose units) to form resistant starches (RS_3). The amylopectin starches are digested more rapidly, presumably because of the more effective enzymatic attack of the more open-branched structure.

Definition of Glycemic Response, Glycemic Index, and Glycemic Load

Foods containing carbohydrate have a wide range of effects on blood glucose concentration during the time course of digestion (glycemic response), with some resulting in a rapid rise followed by a rapid fall in blood glucose concentration, and others resulting in a slow extended rise and a slow extended fall. Prolonging the time over which glucose is available for absorption in healthy individuals greatly reduces the postprandial glucose response (Jenkins et al., 1990). Holt and coworkers (1997), however, reported that the insulin response to consumption of carbohydrate foods is influenced by the level of the glucose response, but varies among individuals and with the amount of carbohydrate consumed. Adults with type 1 or type 2 diabetes have been shown to have similar glycemic responses to specific foods (Wolever et al., 1987), whereas glycemic responses were shown to vary with severity of diabetes (Gannon and Nuttall, 1987). Individuals with lactose maldigestion have reduced glycemic responses to lactose-containing items (Maxwell et al., 1970).

The glycemic index (GI) is a classification proposed to quantify the relative blood glucose response to foods containing carbohydrate (Jenkins et al., 1981). It is defined as the area under the curve for the increase in blood glucose after the ingestion of a set amount of carbohydrate in an individual food (e.g., 50 g) in the 2-hour postingestion period as compared with ingestion of the same amount of carbohydrate from a reference food (white bread or glucose) tested in the same individual, under the same conditions, using the initial blood glucose concentration as a baseline. The average daily dietary GI of a meal is calculated by summing the products of the carbohydrate content per serving for each food, times the average number of servings of that food per day, multiplied by the GI, and all divided by the total amount of carbohydrate (Wolever and Jenkins, 1986). Individual foods have characteristic values for GI (Foster-Powell and Brand Miller, 1995), although within-subject and between-subject variability is relatively large (Wolever et al., 1991). Because GI has been determined by using 50-g carbohydrate portions of food, it is possible that there is a nonlinear response between the amount of food ingested, as is the case for fructose (Nuttall et al., 1992) and the glycemic response.

The average glycemic load is derived the same way as the GI, but without dividing by the total amount of carbohydrate consumed. Thus, glycemic load is an indicator of glucose response or insulin demand that is induced by total carbohydrate intake.

GI is referred to throughout this chapter because many studies have used this classification system. This does not imply that it is the best or only system for classifying glycemic responses or other statistical associations. The GI approach does not consider different metabolic responses to the ingestion of sugars versus starches, even though they may have the same GI values (Jenkins et al., 1988b).

Utilization of the Glycemic Index

Several food characteristics that influence GI are summarized in Table 6-2. Broadly speaking, the two main factors that influence GI are carbohydrate type and physical determinants of the rate of digestion, such as whether grains are intact or ground into flour, food firmness resulting from cooking, ripeness, and soluble fiber content (Wolever, 1990). Intrinsic factors such as amylose:amylopectin ratio, particle size and degree of gelatinization, as well as extrinsic factors such as enzyme inhibitors and food preparation and processing, affect GI in their ability to interact with digestive enzymes and the consequent production of monosaccharides. With progressive ripeness of foods, there is a decrease in starch and an increase in free sugar content. The ingestion of fat and protein has been shown to decrease the GI of foods by increasing plasma glucose disposal through the increased secretion of insulin and possibly other hormones (Gannon et al., 1993; Nuttall et al., 1984). Significantly high correlations between GI and protein, fat, and total caloric content were observed and

TABLE 6-2 Factors That Reduce the Rate of Starch Digestibility and the Glycemic Index

Intrinsic	Extrinsic
High amylose:amylopectin ratio	Protective insoluble fiber seed coat as in whole intact grains
Intact grain/large particle size	Viscous fibers
Intact starch granules	Enzyme inhibitors
Raw, ungelatinized or unhydrated starch	Raw foods (vs. cooked foods)
Physical interaction with fat or protein	Minimal food processing
	Reduced ripeness in fruit
	Minimal (compared to extended) storage

explained 87 percent of the variation in glycemic response among foods (Hollenbeck et al., 1986). In addition to these factors, the GI of a meal can affect the glycemic response of the subsequent meal (Ercan et al., 1994; Wolever et al., 1988). Examples of published values for the GI of pure carbohydrates and other food items are shown in Table 6-3.

A number of research groups have reported a significant relationship between mixed-meal GI predicted from individual food items and either the GI measured directly (Chew et al., 1988; Collier et al., 1986; Gulliford et al., 1989; Indar-Brown et al., 1992; Järvi et al., 1995; Wolever and Jenkins, 1986; Wolever et al., 1985, 1990) or metabolic parameters such as high

TABLE 6-3 Glycemic Index (GI) of Common Foods

Food Item	GI (White Bread = 100)
Rice, white, low-amylose	126
Baked potato	121
Corn flakes	119
Rice cakes	117
Jelly beans	114
Cheerios	106
Carrots	101
White bread	101
Wheat bread	99
Soft drink	97
Angel food cake	95
Sucrose	92
Cheese pizza	86
Spaghetti (boiled)	83
Popcorn	79
Sweet corn	78
Banana	76
Orange juice	74
Rice, Uncle Ben's converted long-grain	72
Green peas	68
Oat bran bread	68
Orange	62
All-Bran cereal	60
Apple juice	58
Pumpernickel bread	58
Apple	52
Chickpeas	47
Skim milk	46
Kidney beans	42
Fructose	32

SOURCE: Foster-Powell and Brand Miller (1995).

density lipoprotein cholesterol concentration that are known to be influenced by GI (Liu et al., 2001). Although the glycemic response of diabetics is distinctly higher than that of healthy individuals, the relative response to different types of mixed meals is similar (Indar-Brown et al., 1992; Wolever et al., 1985). The prediction of GI in mixed meals by Wolever and Jenkins (1986) is shown in Figure 6-1. In contrast, some studies reported no such relationship between the calculated and measured GI of mixed meals (Coulston et al., 1984; Hollenbeck et al., 1986; Laine et al., 1987).

There are a number of reasons why different groups have reported different findings on the calculation of GI in mixed meals. As previously discussed, there are a number of intrinsic (e.g., particle size) and extrinsic (e.g., ingestion of fat and protein, degree of food preparation) factors that can affect the glycemic response of a meal (Table 6-2), some of which are known to also affect the absorption of other nutrients such as vitamins and minerals. For instance, coingestion of dietary fat and protein can sometimes have a significant influence on the glucose response of a carbohydrate-containing food, with a reduction in the glucose response generally seen with increases in fat or protein content (Gulliford et al., 1989; Holt et al.,

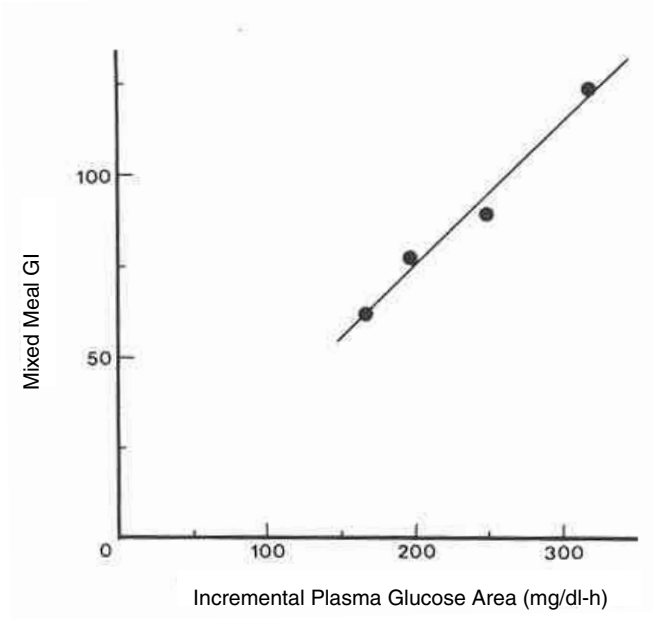

FIGURE 6-1 Correlation between calculated glycemic index (GI) of four test meals (•) and incremental blood glucose response areas. Based on data from Coulston et al. (1984). Reproduced, with permission, from Wolever and Jenkins (1986). Copyright 1986 by the American Society for Clinical Nutrition.

1997). Palatability can have an influence on GI, independent of food type and composition (Sawaya et al., 2001). Furthermore, there are expected inherent biological variations in glucose control and carbohydrate tolerance that are unrelated to the GI of a meal. Finally, varied experimental design and methods for calculating the area under the blood glucose curve can result in a different glycemic response to meals of a similar predicted GI (Coulston et al., 1984; Wolever and Jenkins, 1986). For instance, it is important that the incremental area, rather than the absolute area, under the blood glucose curve be measured (Wolever and Jenkins, 1986). Taken together, the results from these different studies indicate that the GI of mixed meals can usually be predicted from the GI of individual food components.

Physiology of Digestion, Absorption, and Metabolism

Digestion

Starch. The breakdown of starch begins in the mouth where salivary amylase acts on the interior α-(1,4) linkages of amylose and amylopectin. The digestion of these linkages continues in the intestine where pancreatic amylase is released. Amylase digestion produces large oligosaccharides (α-limit dextrins) that contain approximately eight glucose units of one or more α-(1,6) linkages. The α-(1,6) linkages are cleaved more easily than the α-(1,4) linkages.

Oligosaccharides and Sugars. The microvilli of the small intestine extend into an unstirred water layer phase of the intestinal lumen. When a limit dextrin, trisaccharide, or disaccharide enters the unstirred water layer, it is rapidly hydrolyzed by enzymes bound to the brush border membrane. These limit dextrins, produced from starch digestion, are degraded by glucoamylase, which removes glucose units from the nonreducing end to yield maltose and isomaltose. Maltose and isomaltose are degraded by intestinal brush border disaccharidases (e.g., maltase and sucrase). Maltase, sucrase, and lactase digest sucrose and lactose to monosaccharides prior to absorption.

Intestinal Absorption

Monosaccharides first diffuse across to the enterocyte surface, followed by movement across the brush border membrane by one of two mechanisms: active transport or facilitated diffusion.

Active Transport. The intestine is one of two organs that vectorially transports hexoses across the cell into the bloodstream. The mature enterocytes capture the hexoses directly ingested from food or produced from the digestion of di- and polysaccharides. Active transport of sugars involves sodium dependent glucose transporters (SGLTs) in the brush border membrane (Díez-Sampedro et al., 2001). Sodium is pumped from the cell to create a gradient between the interior of the cell and the lumen of the intestine, requiring the hydrolysis of adenosine triphosphate (ATP). The resultant gradient results in the cotransport of one molecule each of sodium and glucose. Glucose is then transported across the basolateral membrane of the small intestine by glucose transporter (GLUT) 2. Similar to glucose, galactose utilizes SGLT cotransporters and basolateral GLUT 2. Fructose is not transported by SGLT cotransporters.

Facilitated Diffusion. There are also transporters of glucose that require neither sodium nor ATP. The driving force for glucose transport is the glucose gradient and the energy change that occurs when the unstirred water layer is replaced with glucose. In this type of transport, called facilitated diffusion, glucose is transported down its concentration gradient (from high to low). Fructose is also transported by facilitated diffusion. One facilitated glucose transporter, GLUT 5, has been identified in the small intestine (Levin, 1999). GLUT 5 appears to transport glucose poorly and is the main transporter of fructose.

Metabolism

Cellular Uptake. Absorbed sugars are transported throughout the body to cells as a source of energy. The concentration of glucose in the blood is highly regulated by the release of insulin. Uptake of glucose by the adipocyte and muscle cell is dependent upon the binding of insulin to a membrane-bound insulin receptor that increases the translocation of intracellular glucose transporters (GLUT 4) to the cell membrane surface for uptake of glucose. GLUT 1 is the transporter of the red blood cell; however, it is also present in the plasma membrane of many other tissues (Levin, 1999). Besides its involvement in the small intestine, GLUT 2 is expressed in the liver and can also transport galactose, mannose, and fructose (Levin, 1999). GLUT 3 is important in the transport of glucose into the brain (Levin, 1999).

Intracellular Utilization of Galactose. Absorbed galactose is primarily the result of lactose digestion. The majority of galactose is taken up by the liver where it is metabolized to galactose-1-phosphate, which is then con-

verted to glucose-1-phosphate. Most of the glucose-1-phosphate derived from galactose metabolism is converted to glycogen for storage.

Intracellular Utilization of Fructose. Absorbed fructose, from either direct ingestion of fructose or digestion of sucrose, is transported to the liver and phosphorylated to fructose-1-phosphate, an intermediate of the glycolytic pathway, which is further cleaved to glyceraldehyde and dihydroxyacetone phosphate (DHAP). DHAP is an intermediary metabolite in both the glycolytic and gluconeogenic pathways. The glyceraldehyde can be converted to glycolytic intermediary metabolites that serve as precursors for glycogen synthesis. Glyceraldehyde can also be used for triacylglycerol synthesis, provided that sufficient amounts of malonyl coenzyme A (CoA) (a precursor for fatty acid synthesis) are available.

Intracellular Utilization of Glucose. Glucose is a major fuel used by most cells in the body. In muscle, glucose is metabolized anaerobically to lactate via the glycolytic pathway. Pyruvate is decarboxylated to acetyl CoA, which enters the tricarboxylic acid (TCA) cycle. Reduced coenyzmes generated in the TCA cycle pass off their electrons to the electron transport system, where it is completely oxidized to carbon dioxide and water. This results in the production of the high-energy ATP that is needed for many other metabolic reactions. After the consumption of carbohydrates, fat oxidation is markedly curtailed, allowing glucose oxidation to provide most of the body's energy needs. In this manner, the body's glucose and glycogen content can be reduced toward more normal concentrations.

Gluconeogenesis. Glucose can be synthesized via gluconeogenesis, a metabolic pathway that requires energy. Gluconeogenesis in the liver and renal cortex is inhibited via insulin following the consumption of carbohydrates and is activated during fasting, allowing the liver to continue to release glucose to maintain adequate blood glucose concentrations.

Glycogen Synthesis and Utilization. Glucose can also be converted to glycogen (glycogenesis), which contains α-(1-4) and α-(1-6) linkages of glucose units. Glycogen is present in the muscle for storage and utilization and in the liver for storage, export, and maintenance of blood glucose concentrations. Glycogenesis is activated in skeletal muscle by a rise in insulin concentration following the consumption of carbohydrate. In the liver, glycogenesis is activated directly by an increase in circulating glucose, fructose, galactose, or insulin concentration. Muscle glycogen is mainly used in the muscle. Following glycogenolysis, glucose can be exported from the liver for maintenance of normal blood glucose concentrations and for use by other tissues.

Formation of Amino Acids and Fatty Acids from Carbohydrates. Pyruvate and intermediates of the TCA cycle are precursors of certain nonessential amino acids. A limited amount of carbohydrate is converted to fat because de novo lipogenesis is generally quite minimal (Hellerstein, 1999; Parks and Hellerstein, 2000). This finding is true for those who are obese, indicating that the vast majority of deposited fat is not derived from dietary carbohydrate when consumed at moderate levels.

Insulin. Based on the metabolic functions of insulin discussed above, the ingestion of carbohydrate produces an immediate increase in plasma insulin concentrations. This immediate rise in plasma insulin concentration minimizes the extent of hyperglycemia after a meal. The effects of insulin deficiency (elevated blood glucose concentration) are exemplified by type 1 diabetes. Individuals who have type 2 diabetes may or may not produce insulin and insulin-dependent muscle and adipose tissue cells may or may not respond to increased insulin concentrations (insulin resistant); therefore, circulating glucose is not effectively taken up by these tissues and metabolized.

Clinical Effects of Inadequate Intake

The lower limit of dietary carbohydrate compatible with life apparently is zero, provided that adequate amounts of protein and fat are consumed. However, the amount of dietary carbohydrate that provides for optimal health in humans is unknown. There are traditional populations that ingested a high fat, high protein diet containing only a minimal amount of carbohydrate for extended periods of time (Masai), and in some cases for a lifetime after infancy (Alaska and Greenland Natives, Inuits, and Pampas indigenous people) (Du Bois, 1928; Heinbecker, 1928). There was no apparent effect on health or longevity. Caucasians eating an essentially carbohydrate-free diet, resembling that of Greenland natives, for a year tolerated the diet quite well (Du Bois, 1928). However, a detailed modern comparison with populations ingesting the majority of food energy as carbohydrate has never been done.

It has been shown that rats and chickens grow and mature successfully on a carbohydrate-free diet (Brito et al., 1992; Renner and Elcombe, 1964), but only if adequate protein and glycerol from triacylglycerols are provided in the diet as substrates for gluconeogenesis. It has also been shown that rats grow and thrive on a 70 percent protein, carbohydrate-free diet (Gannon et al., 1985). Azar and Bloom (1963) also reported that nitrogen balance in adults ingesting a carbohydrate-free diet required the ingestion of 100 to 150 g of protein daily. This, plus the glycerol obtained from triacylglycerol in the diet, presumably supplied adequate substrate

for gluconeogenesis and thus provided at least a minimal amount of completely oxidizable glucose.

The ability of humans to starve for weeks after endogenous glycogen supplies are essentially exhausted is also indicative of the ability of humans to survive without an exogenous supply of glucose or monosaccharides convertible to glucose in the liver (fructose and galactose). However, adaptation to a fat and protein fuel requires considerable metabolic adjustments.

The only cells that have an absolute requirement for glucose as an oxidizable fuel are those in the central nervous system (i.e., brain) and those cells that depend upon anaerobic glycolysis (i.e., the partial oxidation of glucose to produce lactate and alanine as a source of energy), such as red blood cells, white blood cells, and medulla of the kidney. The central nervous system can adapt to a dietary fat-derived fuel, at least in part (Cahill, 1970; Sokoloff, 1973). Also, the glycolyzing cells can obtain their complete energy needs from the indirect oxidation of fatty acids through the lactate and alanine-glucose cycles.

In the absence of dietary carbohydrate, de novo synthesis of glucose requires amino acids derived from the hydrolysis of endogenous or dietary protein or glycerol derived from fat. Therefore, the marginal amount of carbohydrate required in the diet in an energy-balanced state is conditional and dependent upon the remaining composition of the diet. Nevertheless, there may be subtle and unrecognized, untoward effects of a very low carbohydrate diet that may only be apparent when populations not genetically or traditionally adapted to this diet adopt it. This remains to be determined but is a reasonable expectation.

Of particular concern in a Western, urbanized society is the long-term consequences of a diet sufficiently low in carbohydrate such that it creates a chronically increased production of β-hydroxybutyric and acetoacetic acids (i.e., keto acids). The concern is that such a diet, deficient in water-soluble vitamins and some minerals, may result in bone mineral loss, may cause hypercholesterolemia, may increase the risk of urolithiasis (Vining, 1999), and may affect the development and function of the centra1 nervous system. It also may adversely affect an individual's general sense of well being (Bloom and Azar, 1963), although in men starved for an extended period of time, encephalographic tracings remained unchanged and psychometric testing showed no deficits (Owen et al., 1967). It also may not provide for adequate stores of glycogen. The latter is required for hypoglycemic emergencies and for maximal short-term power production by muscles (Hultman et al., 1999).

EVIDENCE CONSIDERED FOR ESTIMATING THE AVERAGE REQUIREMENT FOR CARBOHYDRATE

The endogenous glucose production rate, and thus the utilization rate, depends on the duration of starvation. Glucose production has been determined in a number of laboratories using isotopically labeled glucose (Amiel et al., 1991; Arslanian and Kalhan, 1992; Bier et al., 1977; Denne and Kalhan, 1986; Kalhan et al., 1986; King et al., 1982; Patel and Kalhan, 1992). In overnight fasted adults (i.e., postabsorptive state), glucose production is approximately 2 to 2.5 mg/kg/min, or approximately 2.8 to 3.6 g/kg/d. In a 70-kg man, this represents approximately 210 to 270 g/d. In the postabsorptive state, approximately 50 percent of glucose production comes from glycogenolysis in liver and 50 percent from gluconeogenesis in the liver (Chandramouli et al., 1997; Landau et al., 1996).

The minimal amount of carbohydrate required, either from endogenous or exogenous sources, is determined by the brain's requirement for glucose. The brain is the only true carbohydrate-dependent organ in that it oxidizes glucose completely to carbon dioxide and water. Normally, the brain uses glucose almost exclusively for its energy needs. The endogenous glucose production rate in a postabsorptive state correlates very well with the estimated size of the brain from birth to adult life. However, not all of the glucose produced is utilized by the brain (Bier et al., 1977; Felig, 1973). The requirement for glucose has been reported to be approximately 110 to 140 g/d in adults (Cahill et al., 1968). Nevertheless, even the brain can adapt to a carbohydrate-free, energy-sufficient diet, or to starvation, by utilizing ketoacids for part of its fuel requirements. When glucose production or availability decreases below that required for the complete energy requirements for the brain, there is a rise in ketoacid production in the liver in order to provide the brain with an alternative fuel. This has been referred to as "ketosis." Generally, this occurs in a starving person only after glycogen stores in the liver are reduced to a low concentration and the contribution of hepatic glycogenolysis is greatly reduced or absent (Cahill et al., 1968). It is associated with approximately a 20 to 50 percent decrease in circulating glucose and insulin concentration (Carlson et al., 1994; Owen et al., 1998; Streja et al., 1977). These are signals for adipose cells to increase lipolysis and release nonesterified fatty acids and glycerol into the circulation. The signal also is reinforced by an increase in circulating epinephrine, norepinephrine, glucagon, and growth hormone concentration (Carlson et al., 1994). The nonesterified fatty acids are removed by the liver and converted into ketoacids, which then diffuse out of the liver into the circulation. The increase in nonesterified fatty acids results in a concentration-dependent exponential increase in ketoacids (Hanson et al., 1965); glucagon facilitates this process (Mackrell and Sokal, 1969).

In an overnight fasted person, the circulating ketoacid concentration is very low, but with prolonged starvation the concentration increases dramatically and may exceed the molar concentration of glucose (Cahill, 1970; Streja et al., 1977). In individuals fully adapted to starvation, ketoacid oxidation can account for approximately 80 percent of the brain's energy requirements (Cahill et al., 1973). Thus, only 22 to 28 g/d of glucose are required to fuel the brain. This is similar to the total glucose oxidation rate integrated over 24 hours determined by isotope-dilution studies in these starving individuals (Carlson et al., 1994; Owen et al., 1998).

Overall, the key to the metabolic adaptation to extended starvation is the rise in circulating nonesterified fatty acid concentrations and the large increase in ketoacid production. The glycerol released from the hydrolysis of triacylglycerols stored in fat cells becomes a significant source of substrate for gluconeogenesis, but the conversion of amino acids derived from protein catabolism into glucose is also an important source. Interestingly, in people who consumed a protein-free diet, total nitrogen excretion was reported to be in the range of 2.5 to 3.5 g/d (35 to 50 mg/kg), or the equivalent of 16 to 22 g of catabolized protein in a 70-kg man (Raguso et al., 1999). Thus, it is similar to that in starving individuals (3.7 g/d) (Owen et al., 1998). Overall, this represents the minimal amount of protein oxidized through gluconeogenic pathways (Du Bois, 1928). This amount of protein is considerably less than the Recommended Dietary Allowance (RDA) of 0.8 g/kg/d for adults with a normal body mass index (Chapter 10). For a 70-kg lean male, this equals 56 g/d of protein, which is greater than the estimated obligate daily loss in body protein from the shedding of cells, secretions, and other miscellaneous functions (approximately 6 to 8 g/d for a 70-kg man; see Chapter 10) and has been assumed to be due to inefficient utilization of amino acids for synthesis of replacement proteins and other amino acid-derived products (Gannon and Nuttall, 1999). In part, it also may represent the technical difficulty in determining a minimal daily protein requirement (see Chapter 10).

If 56 g/d of dietary protein is required for protein homeostasis, but the actual daily loss of protein is only approximately 7 g, then presumably the remaining difference (49 g) is metabolized and may be utilized for new glucose production. It has been determined that for ingested animal protein, approximately 0.56 g of glucose can be derived from every 1 g of protein ingested (Janney, 1915). Thus, from the 49 g of protein not directly utilized to replace loss of endogenous protein or not used for other synthetic processes, approximately 27 g (0.56×49) of glucose may be produced. In people on a protein-free diet or who are starving, the 16 to 22 g of catabolized protein could provide 10 to 14 g of glucose.

If the starving individual's energy requirement is 1,800 kcal/d and 95 percent is supplied by fat oxidation either directly or indirectly through

oxidation of ketoacids (Cahill et al., 1973), then fat oxidation represents 1,710 kcal/d, or 190 g based upon approximately 9 kcal/g fat. The glycerol content of a typical triacylglycerol is 10 percent by weight, or in this case 19 g of glycerol, which is equivalent to approximately 19 g of glucose. This, plus the amount of glucose potentially derived from protein, gives a total of approximately 30 to 34 g ([10 to 14] + 19). Thus, a combination of protein and fat utilization is required to supply the small amount of glucose still required by the brain in a person fully adapted to starvation. Presumably this also would be the obligatory glucose requirement in people adapted to a carbohydrate-free diet. Thus, the normal metabolic adaptation to a lack of dietary protein, as occurs in a starving person in whom the protein metabolized is in excess of that lost daily, is to provide the glucose required by the brain. Nevertheless, utilization of this amount of glucose by the brain is vitally important. Without it, function deteriorates dramatically, at least in the brain of rats (Sokoloff, 1973).

The required amount of glucose could be derived easily from ingested protein alone if the individual was ingesting a carbohydrate-free, but energy-adequate diet containing protein sufficient for nitrogen balance. However, ingested amounts of protein greater than 30 to 34 g/d would likely stimulate insulin secretion unless ingested in small amounts throughout a 24-hour period. For example, ingestion of 25 to 50 g of protein at a single time stimulates insulin secretion (Krezowski et al., 1986; Westphal et al., 1990), despite a lack of carbohydrate intake. This rise in insulin would result in a diminution in the release of fatty acids from adipose cells and as a consequence, reduce ketoacid formation and fatty acid oxidation. The ultimate effect would be to increase the requirement for glucose of the brain and other organs. Thus, the minimal amount of glucose irreversibly oxidized to carbon dioxide and water requires utilization of a finely balanced ratio of dietary fat and protein.

Azar and Bloom (1963) reported that 100 to 150 g/d of protein was necessary for maintenance of nitrogen balance. This amount of protein could typically provide amino acid substrate sufficient for the production of 56 to 84 g of glucose daily. However, daily infusion of 90 g of an amino acid mixture over 6 days to both postoperative and nonsurgical starving adults has been reported to reduce urinary nitrogen loss without a significant change in glucose or insulin concentration, but with a dramatic increase in ketoacids (Hoover et al., 1975). Thus, the issue becomes complex in nonstarving people.

Glucose utilization by the brain has been determined either by measuring arteriovenous gradients of glucose, oxygen, lactate, and ketones across the brain and the respiratory quotient (Kety, 1957; Sokoloff, 1973), or with estimates of brain blood flow determined by different methods (e.g., NO_2 diffusion). A major problem with studies based on arteriovenous

differences is the limited accuracy of the blood flow methods used (Settergren et al., 1976, 1980). Using ^{18}F-2-fluoro-2-deoxyglucose and positron emission tomography, the rate of glucose accumulation in the brain also has been determined (Chugani, 1993; Chugani and Phelps, 1986; Chugani et al., 1987; Hatazawa et al., 1987). This is an indirect method for measuring glucose utilization, and also has limitations (Hatazawa et al., 1987). Brain O_2 consumption in association with the brain respiratory quotient also has been used as an indirect estimate of glucose utilization (Kalhan and Kiliç, 1999).

Only data determined by direct measurement of glucose arteriovenous difference across the brain in association with determination of brain blood flow can be considered for setting an Estimated Average Requirement (EAR), although the other, indirect methods yield similar results. The glucose consumption by the brain can be used along with information from Dobbing and Sands (1973) and Dekaban and Sadowsky (1978), which correlated weight of the brain with body weight to calculate glucose utilization.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Infants Ages 0 Through 12 Months

Methods Considered to Set the AI

Carbohydrate Utilization by the Brain. In infants, the brain size relative to body size is greater than that in adults. The brain utilizes approximately 60 percent of the infant's total energy intake (Gibbons, 1998). Therefore, the turnover of glucose per kilogram of body weight can be up to fourfold greater in the infant compared to the adult (Kalhan and Kiliç, 1999).

The infant brain is fully capable of using ketoacids as fuel. In species in which the mothers' milk is very high in fat, such as in rats, the circulating ketoacid concentration is very high in the suckling pups, and the ketoacids are an important source of fuel for the developing brain (Edmond et al., 1985; Sokoloff, 1973). In addition, the gluconeogenic pathway is well developed even in premature human infants (Sunehag et al., 1999). Indeed, provided that adequate lipid and protein substrates are supplied, gluconeogenesis can account for the majority of glucose turnover. Whether gluconeogenesis can account for the entire glucose requirement in infants has not been tested.

Growth. Studies have been performed using artificial formula feedings and varying the fat and carbohydrate content while keeping the protein

content constant (9 percent) (Fomon et al., 1976). Fomon and coworkers (1976) provided infants with formulas containing either 34 or 62 percent of energy from carbohydrate for 104 days. There were no significant differences in the length or weight of the infants fed the two formulas. Interestingly, it also did not affect the total food energy consumed over the 6 or 12 months of life. From the limited data available, the lowest intake that has been documented to be adequate is 30 percent of total food energy. However, it is likely that infants also may grow and develop normally on a very low or nearly carbohydrate-free diet since their brains' enzymatic machinery for oxidizing ketoacids is more efficient than it is in adults (Sokoloff, 1973).

Human Milk. The lower limit of dietary carbohydrate compatible with life or for optimal health in infants is unknown. Human milk is recognized as the optimal milk source for infants throughout at least the first year of life and is recommended as the sole nutritional milk source for infants during the first 4 to 6 months of life (IOM, 1991). Carbohydrate in human milk is almost exclusively lactose (Table 6-4). The only source of lactose in the animal kingdom is from the mammary gland and therefore is found only in mammals. Lactose is readily hydrolyzed in the infant intestine. The resulting glucose and galactose also readily pass into the portal venous system. They are carried to the liver where the galactose is converted to glucose and either stored as glycogen or released into the general circulation and oxidized. The net result is the provision of two glucose molecules for each lactose molecule ingested. The reason why lactose developed as the carbohydrate fuel produced by the mammary gland is not understood. One reason may be that the provision of a disaccharide compared to a monosaccharide reduces the osmolality of milk. Lactose has also been reported to facilitate calcium absorption from the gut, which otherwise is not readily absorbed from the immature infant intestine (Condon et al., 1970; Ziegler and Fomon, 1983). However, isotopic tracer data have not confirmed this (Kalhan and Kiliç, 1999).

The lactose content of human milk is approximately 74 g/L and changes little over the total nursing period (Dewey and Lönnerdal, 1983; Dewey et al., 1984; Lammi-Keefe et al., 1990; Nommsen et al., 1991) (Table 6-4). However, the volume of milk consumed by the infant decreases gradually over the first 12 months of life as other foods are gradually introduced into the feeding regimen. Over the first 6 months of life, the volume consumed is about 0.78 L/d (see Chapter 2); therefore approximately 60 g of carbohydrate represents about 37 percent of total food energy (see Chapter 5) (Nommsen et al., 1991). This amount of carbohydrate and the ratio of carbohydrate to fat in human milk can be assumed to be optimal for infant growth and development over the first 6 months of life.

TABLE 6-4 Total Carbohydrate Content of Human Milk

Reference	Stage of Lactation	Total Carbohydrate Content (g/L)	Total Lactose Content (g/L)	Total Glucose Content (g/L)
Anderson et al., 1981	3–5 d		51.4 ± 2.2	
	8–11 d		59.8 ± 2.3	
	26–29 d		65.1 ± 2.3	
Anderson et al., 1983	3 d	62 ± 9		
	7 d	67 ± 5		
	14 d	67 ± 6		
Dewey and Lönnerdal, 1983	1 mo		70.5 ± 5.6	
	2 mo		72.1 ± 6.2	
	3 mo		71.3 ± 7.9	
	4 mo		76.1 ± 4.0	
	5 mo		76.2 ± 3.3	
	6 mo		77.5 ± 2.7	
Dewey et al., 1984	4–6 mo		77.1 ± 3.0	
	7–11 mo		75.7 ± 3.6	
	12–20 mo		72.3 ± 4.3	
Neville et al., 1984	33–210 d Median 115 d		Mid-feed: 72.1 Pooled pumped: 71.8	Mid-feed: 0.27 Pooled pumped: 0.27
Ferris et al., 1988	2 wk		62.5 ± 6.5	
	6 wk		67.8 ± 6.4	
	12 wk		68.5 ± 7.3	
	16 wk		70.0 ± 6.5	
Lammi-Keefe et al., 1990	8 wk		76.2 ± 3.2	0.26 ± 0.05
			73.6 ± 3.8	0.31 ± 0.05
			77.4 ± 6.7	0.33 ± 0.06
			74.2 ± 4.7	0.33 ± 0.08
			80.1 ± 4.6	0.33 ± 0.06
Allen et al., 1991	21 d		63.4 ± 0.7	0.27 ± 0.01
	45 d		65.6 ± 0.4	0.27 ± 0.01
	90 d		67.7 ± 0.7	0.31 ± 0.01
	180 d		68.8 ± 1.4	0.32 ± 0.02
Nommsen et al., 1991	3 mo		74.4 ± 1.5	
	6 mo		74.4 ± 1.9	
	9 mo		73.5 ± 2.9	
	12 mo		74.0 ± 2.7	

continued

TABLE 6-4 Continued

Reference	Stage of Lactation	Total Carbohydrate Content (g/L)	Total Lactose Content (g/L)	Total Glucose Content (g/L)
Coppa et al., 1993	4 d	78.1 ± 8.08	56.0 ± 6.06	
	10 d	83.8 ± 6.45	62.5 ± 5.74	
	30 d	80.6 ± 6.90	64.1 ± 6.45	
	60 d	79.8 ± 7.01	66.2 ± 6.88	
	90 d	79.3 ± 7.03	66.3 ± 7.08	
	120 d	82.2 ± 10.31	68.9 ± 8.16	

The method used to set the Adequate Intake (AI) for older infants is carbohydrate intake from human milk and complementary foods (see Chapter 2). According to the Third National Health and Nutrition Examination Survey, the median carbohydrate intake from weaning food for ages 7 through 12 months was 50.7 ± 5 g/d (standard error of the mean). Based on an average volume of 0.6 L/d of human milk that is secreted (Chapter 2), the carbohydrate intake from human milk is 44 g/d (0.6 L/d × 74 g/L). Therefore, the total intake of carbohydrate from human milk and complementary foods is 95 g/d (44 + 51).

Carbohydrate AI Summary, Ages 0 Through 12 Months

The AI is based on the average intake of carbohydrate consumed from human milk and complementary foods.

AI for Infants

0–6 months	**60 g/d of carbohydrate**
7–12 months	**95 g/d of carbohydrate**

Special Considerations

The carbohydrate content of milk protein-based formulas for term infants is similar to that of human milk (70 to 74 g/L). Whole cow milk contains lower concentrations of carbohydrate than human milk (48 g/L) (Newburg and Neubauer, 1995). In addition to lactose, conventional infant formulas can also contain sucrose or glucose polymers.

Children and Adolescents Ages 1 Through 18 Years

Evidence Considered in Estimating the Average Requirement

In the newborn, the brain weight is approximately 380 g; by age 1 year this has increased to approximately 1,000 g in boys and approximately 980 g in girls (Dekaban and Sadowsky, 1978; Dobbing and Sands, 1973), with a corresponding increase in energy requirement. After 1 year of age, there is a further increase in brain weight up to 5 years of age (approximately 1,300 g in boys and 1,150 g in girls). Subsequently, the brain size increases only modestly. The consumption of glucose by the brain after age 1 year also remains rather constant or increases modestly and is in the range reported for adults (approximately 31 μmol/100 g of brain/min) (Kennedy and Sokoloff, 1957; Sokoloff et al., 1977). Therefore, the Estimated Average Requirement (EAR) for carbohydrate is set based on information used for adults (see "Adults Ages 19 Years and Older"). As for adults, the EAR is the same for both genders since differences in brain glucose utilization are small.

The amount of glucose produced from obligatory endogenous protein catabolism in children is not known. Therefore, this information was not considered in the derivation of the EAR for children. Children ages 2 to 9 years have requirements for carbohydrate that are similar to adults. This is based on population data in which animal-derived foods are ingested exclusively (e.g., Alaska and Greenland natives), as well as in children with epilepsy who have been treated with ketogenic diets for extended periods of time (Swink et al., 1997; Vining, 1999). In these children, the ketoacid concentration was in the range of 2 to 3 mmol/L (i.e., similar to that in a starving adult) (Nordli et al., 1992).

Carbohydrate EAR and RDA Summary, Ages 1 Through 18 Years

EAR for Children

1–3 years	**100 g/d of carbohydrate**
4–8 years	**100 g/d of carbohydrate**

EAR for Boys

9–13 years	**100 g/d of carbohydrate**
14–18 years	**100 g/d of carbohydrate**

EAR for Girls

9–13 years	**100 g/d of carbohydrate**
14–18 years	**100 g/d of carbohydrate**

The Recommended Dietary Allowance (RDA) for carbohydrate is set by using a coefficient of variation (CV) of 15 percent based on the variation in brain glucose utilization. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for carbohydrate the RDA is 130 percent of the EAR).

RDA for Children

1–3 years	**130 g/d of carbohydrate**
4–8 years	**130 g/d of carbohydrate**

RDA for Boys

9–13 years	**130 g/d of carbohydrate**
14–18 years	**130 g/d of carbohydrate**

RDA for Girls

9–13 years	**130 g/d of carbohydrate**
14–18 years	**130 g/d of carbohydrate**

Adults Ages 19 Years and Older

Evidence Considered in Estimating the Average Requirement

Glucose Utilization by the Brain. Long-term data in Westernized populations, which could determine the minimal amount of carbohydrate compatible with metabolic requirements and for optimization of health, are not available. Therefore, it is provisionally suggested that an EAR for carbohydrate ingestion in the context of overall food energy sufficiency be based on an amount of digestible carbohydrate that would provide the brain (i.e., central nervous system) with an adequate supply of glucose fuel without the requirement for additional glucose production from ingested protein or triacylglycerols. This amount of glucose should be sufficient to supply the brain with fuel in the absence of a rise in circulating acetoacetate and β-hydroxybutyrate concentrations greater than that observed in an individual after an overnight fast (see "Evidence Considered for Estimating the Average Requirement for Carbohydrate"). This assumes the consumption of an energy-sufficient diet containing an Acceptable Macronutrient Distribution Range of carbohydrate intake (approximately 45 to 65 percent of energy) (see Chapter 11).

Brain glucose utilization based on O_2 consumption is summarized in Table 6-5. Only data determined by direct measurement of glucose arteriovenous difference across the brain in association with determination of

TABLE 6-5 Indirect Estimates of Glucose Utilization by Measuring Brain Oxygen (O_2) Consumption

Reference	Study Population	O_2 Consumption (mL/100 g/min)	O_2 Consumption (L/100 g/d)
Kennedy and Sokoloff, 1957	2 children, 3 y	6.2	8.93
		5.6	8.06
Kennedy and Sokoloff, 1957	5 children, 4–7 y	5.3	7.63
		4.3	6.19
		4.4	6.34
		5.7	8.21
		4.4	6.34
Kennedy and Sokoloff, 1957	2 children, 10 and 11 y	5.7	8.21
		4.9	7.06
Kennedy and Sokoloff, 1957	12 adults	4.18	6.02

[a] For males, based on Dekaban and Sadowsy (1978) and Dobbing and Sands (1973).
[b] O_2 = 4.8 kcal/L = 1.2 g of glucose/L.

brain blood flow (Table 6-6) were considered for setting an EAR, although both methods yielded similar results. Data on glucose consumption by the brain for various age groups using information from Dobbing and Sands (1973) and Dekaban and Sadowsky (1978) were also used, which correlated weight of the brain with body weight. The average rate of brain glucose utilization in the postabsorptive state of adults based on several studies is approximately 33 μmol/100 g of brain/min (5.5 mg/100 g of brain/min or 8.64 g/100 g of brain/d) (Table 6-6). Based on these data, the brain's requirement for carbohydrate is in the range of approximately 117 to 142 g/d (Gottstein and Held, 1979; Reinmuth et al., 1965; Scheinberg and Stead, 1949; Sokoloff et al., 1977). Regardless of age and the associated change in brain mass, the glucose utilization rate/100 g of brain tissue remains rather constant, at least up to age 73 years (Reinmuth et al., 1965). In 351 men (aged 21 to 39 years), the average brain weight at autopsy was reported to be 1.45 kg, with a standard deviation of only 0.02 kg. In 201 women of the same age range, the average brain weight was 1.29 kg with a standard deviation of 0.03 kg. There was excellent correlation between body weight and height and brain weight in adults of all ages.

The glucose produced from the obligatory turnover of protein plus the glucose produced from glycerol is approximately 30 g/d (see "Evi-

Estimated Brain Weight (g)[a]	O_2 Consumption (L/d)	Glucose Consumption (g/d)[b]
1,200	107.1	129
1,200	96.8	116
1,260	96.2	115
1,260	78.0	94
1,300	82.4	99
1,300	109.2	131
1,300	84.3	101
1,360	111.6	134
1,360	96.0	115
1,450	84.3	101

dence Considered for Estimating the Average Requirement for Carbohydrate"). Therefore, the overall dietary carbohydrate requirement in the presence of an energy-adequate diet would be approximately 87 (117 – 30) to 112 (142 – 30) g/d. This amount of carbohydrate is similar to that reported to be required for the prevention of ketosis (50 to 100 g) (Bell et al., 1969; Calloway, 1971; Gamble, 1946; Sapir et al., 1972) and to that reported to have a maximal protein sparing effect when glucose was ingested daily (Gamble, 1946). The carbohydrate requirement is modestly greater than the potential glucose that can be derived from an amount of ingested protein required for nitrogen balance in people ingesting a carbohydrate-free diet (Azar and Bloom, 1963).

This amount of carbohydrate will not provide sufficient fuel for those cells that are dependent on anaerobic glycolysis for their energy supply (e.g., red and white blood cells). For glycolyzing cells, approximately 36 g/d are necessary (Cahill, 1970). Glycolyzing cells can obtain energy through the functioning of the Cori cycle (i.e., lactate to glucose to lactate) and the alanine-glucose cycle. That is, the cyclic interconversion of glucose with lactate or alanine occurs without a net loss of carbon.

In the absence of carbohydrate in the diet, and in the absence of a rise in ketoacids above the overnight fasting reference range, ingested protein

TABLE 6-6 Direct Estimates of Glucose Utilization by Measuring Brain Glucose Consumption

Reference	Study Population	Glucose Consumption (μmol/100 g of brain/min)	Estimated Brain Weight (g)[a]	Glucose Consumption	
				(mg/min)	(g/d)
Settergren et al., 1976	12 infants, average 5 mo	27	400	19.4	28
Mehta et al., 1977	10 infants, average 11 mo	66	1,000	118	170
Settergren et al., 1980	42 infants and children, 3 wk–14 y	25	400–1,450	18–65	26–94
Scheinberg and Stead, 1949	18 adults, 18–36 y	34	1,450	88	127
Reinmuth et al., 1965	13 adults, 21–29 y	38	1,450	99	142
Sokoloff et al., 1977	Adults	31	1,450	81	117
Gottstein and Held, 1979	24 adults, 21–43 y	31	1,450	81	117

[a] Based on Dekaban and Sadowsy (1978) and Dobbing and Sands (1973).

sufficient to provide the brain with glucose fuel is theoretically possible, but is not likely to be acceptable. The amount of dietary protein required approaches the theoretical maximal rate of gluconeogenesis from amino acids in the liver (135 g of glucose/24 h) (Brosnan, 1999).

In summary, the EAR for total carbohydrate is set at 100 g/d. This amount should be sufficient to fuel central nervous system cells without having to rely on a partial replacement of glucose by ketoacids. Although the latter are used by the brain in a concentration-dependent fashion (Sokoloff, 1973), their utilization only becomes quantitatively significant when the supply of glucose is considerably reduced and their circulating concentration has increased several-fold over that present after an overnight fast.

Diets contain a combination of carbohydrate, fat, and protein, and therefore available glucose is not limiting to the brain unless carbohydrate energy intake is insufficient to meet the glucose needs of the brain. Nevertheless, it should be recognized that the brain can still receive enough glucose from the metabolism of the glycerol component of fat and from the gluconeogenic amino acids in protein when a very low carbohydrate diet is consumed.

Aging. It is well known that the overall rate of energy metabolism decreases with aging (Roberts, 2000a). Also, the total body glucose oxidation rate is decreased, but only modestly. In adults 70 years of age or older, the glucose oxidation rate was only about 10 percent less than in young adults between 19 and 29 years of age (Robert et al., 1982).

The actual brain mass slowly decreases after age 45 to 55 years. In 76- to 80-year-old men, the average brain mass was 1.33 kg, and for women in the same age range it was 1.19 kg (i.e., a loss of 8 to 9 percent of mass) (Dekaban and Sadawosky, 1978). This decrease is similar to that reported from autopsy data in Japan (mean 1,422 to 1,336 g) (Yamaura et al., 1980). Whether glucose oxidation changes out of proportion to brain mass remains a controversial issue (Gottstein and Held, 1979; Leenders et al., 1990). In any case, the decrease in brain glucose oxidation rate is not likely to be substantially less. Therefore, the EAR is the same for all adults. There is no evidence to indicate that a certain amount of carbohydrate should be provided as starch or sugars. However, most individuals do not choose to eat a diet in which sugars exceed approximately 30 percent of energy (Nuttall and Gannon, 1981).

Carbohydrate EAR and RDA Summary, Ages 19 Years and Older

EAR for Men

19–30 years	**100 g/d of carbohydrate**
31–50 years	**100 g/d of carbohydrate**
51–70 years	**100 g/d of carbohydrate**
> 70 years	**100 g/d of carbohydrate**

EAR for Women

19–30 years	**100 g/d of carbohydrate**
31–50 years	**100 g/d of carbohydrate**
51–70 years	**100 g/d of carbohydrate**
> 70 years	**100 g/d of carbohydrate**

The RDA for carbohydrate is set by using a CV of 15 percent based on the variation in brain glucose utilization. The RDA is defined as equal to the

EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for carbohydrate the RDA is 130 percent of the EAR).

RDA for Men

19–30 years	**130 g/d of carbohydrate**
31–50 years	**130 g/d of carbohydrate**
51–70 years	**130 g/d of carbohydrate**
> 70 years	**130 g/d of carbohydrate**

RDA for Women

19–30 years	**130 g/d of carbohydrate**
31–50 years	**130 g/d of carbohydrate**
51–70 years	**130 g/d of carbohydrate**
> 70 years	**130 g/d of carbohydrate**

Pregnancy

Evidence Considered in Estimating the Average Requirement

Pregnancy results in an increased metabolic rate and thus an increased fuel requirement. This increased fuel requirement is due to the establishment of the placental–fetal unit and an increased energy supply for growth and development of the fetus. It is also necessary for the maternal adaptation to the pregnant state and for moving about the increased mass of the pregnant woman. This increased need for metabolic fuel often includes an increased maternal storage of fat early in pregnancy, as well as sufficient energy to sustain the growth of the fetus during the last trimester of pregnancy (Knopp et al., 1973).

In spite of the recognized need for increased energy-yielding substrates imposed by pregnancy, the magnitude of need, as well as how much of the increased requirement needs to be met from exogenous sources, remains incompletely understood and is highly variable (Tables 5-23 through 5-27). There is general agreement that the additional food energy requirement is relatively small. Several doubly labeled water studies indicate a progressive increase in total energy expenditure over the 36 weeks of pregnancy (Forsum et al., 1992; Goldberg et al., 1993; Kopp-Hoolihan et al., 1999) (Table 5-27). The mean difference in energy expenditure between week 0 and 36 in the studies was approximately 460 kcal/d and is proportional to body weight.

The developing fetus utilizes glucose as an energy-yielding substrate. However, there is some evidence that the fetus can utilize maternally pro-

vided ketoacids. The fetus does not utilize significant amounts of free fatty acids (Rudolf and Sherwin, 1983).

As part of the adaptation to pregnancy, there is a decrease in maternal blood glucose concentration, a development of insulin resistance, and a tendency to develop ketosis (Burt and Davidson, 1974; Cousins et al., 1980; Phelps et al., 1981; Rudolf and Sherwin, 1983; Ryan et al., 1985).

A higher mean respiratory quotient for both the basal metabolic rate and total 24-hour energy expenditure has also been reported in pregnant women when compared to the postpartum period. This indicates an increased utilization of glucose by the maternal–fetal unit. The increased glucose utilization rate persists after fasting, indicating an increased endogenous production rate as well (Assel et al., 1993; Kalhan et al., 1997) (see Chapter 5). Thus, irrespective of whether there is an increase in total energy expenditure, these data indicate an increase in glucose utilization. Earlier, it was reported that the glucose turnover in the overnight fasted state based on maternal weight gain remains unchanged from that in the nonpregnant state (Cowett et al., 1983; Kalhan et al., 1979).

The fetus reportedly uses approximately 8 ml O_2/kg/min or 56 kcal/kg/d (Sparks et al., 1980). For a 3-kg term fetus, this is equivalent to 168 kcal/d. The transfer of glucose from the mother to the fetus has been estimated to be 17 to 26 g/d in late gestation (Hay, 1994). If this is the case, then glucose can only account for approximately 51 percent of the total oxidizable substrate transferred to the fetus at this stage of gestation.

The mean newborn infant brain weight is reported to be approximately 380 g (Dekaban and Sadowsky, 1978). Assuming the glucose consumption rate is the same for infants and adults (approximately 33 μmol/100 g of brain/min or 8.64 g/100 g of brain/d) (see "Adults Ages 19 Years and Older"), and that ketoacids do not supply a significant amount of oxidizable substrate for the fetal brain in utero, the glucose requirement at the end of pregnancy would be approximately 32.5 g/d. This is greater than the total amount of glucose transferred daily from the mother to the fetus.

Data obtained in newborns indicate that glucose oxidation can only account for approximately 70 percent of the brain's estimated fuel requirement (Denne and Kalhan, 1986). Whether this is the case in the late-term fetus is not known. However, the fetal brain can clearly utilize ketoacids (Patel et al., 1975). In addition, an increase in circulating ketoacids is common in pregnant women (Homko et al., 1999). Taken together, these data suggest that ketoacids may be utilized by the fetal brain in utero. If nonglucose sources (largely ketoacids) supply 30 percent of the fuel requirement of the fetal brain, then the brain glucose utilization rate would be 23 g/d (32.5 g × 0.70). This is essentially the same as the average maternal–fetal glucose transfer rate (mean 22 g, range 17 to 26 g) (Hay,

1994). These data also indicate that the fetal brain utilizes essentially all of the glucose derived from the mother.

In order to assure provision of glucose to the fetal brain (approximately 33 g/d) as a fuel in the absence of utilization of a lipid-derived fuel, as well as to supply the glucose fuel requirement for the mother's brain independent of utilization of ketoacids (or other substrates), the EAR for metabolically available dietary carbohydrate is the EAR for nonpregnant women (100 g/d) plus the additional amount required during the last trimester of pregnancy (35 g/d), or 135 g/d. There is no evidence to indicate that a certain portion of the carbohydrate must be consumed as starch or sugars.

EAR and RDA Summary, Pregnancy

EAR for Pregnancy

14–18 years	**135 g/d of carbohydrate**
19–30 years	**135 g/d of carbohydrate**
31–50 years	**135 g/d of carbohydrate**

The RDA for carbohydrate is set by using a CV of 15 percent based on the variation in brain glucose utilization. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for carbohydrate the RDA is 130 percent of the EAR). The calculated values for the RDAs have been rounded.

RDA for Pregnancy

14–18 years	**175 g/d of carbohydrate**
19–30 years	**175 g/d of carbohydrate**
31–50 years	**175 g/d of carbohydrate**

Lactation

Evidence Considered in Estimating the Average Requirement

The requirement for carbohydrate is increased during lactation. The lactose content of human milk is approximately 74 g/L; this concentration changes very little during the nursing period. Therefore, the amount of precursors necessary for lactose synthesis must increase. Lactose is synthesized from glucose and as a consequence, an increased supply of glucose must be obtained from ingested carbohydrate or from an increased supply of amino acids in order to prevent utilization of the lactating woman's endogenous proteins. Glycerol derived from endogenous or exogenous

fat may contribute to the increased production of glucose through gluconeogenesis. However, the amount of fat that can be oxidized daily greatly limits the contribution of glycerol to glucose production and thus lactose formation.

The EAR during lactation is the sum of the carbohydrate intake necessary to replace the carbohydrate secreted in human milk (60 g/d) and the EAR for adolescent girls and women (100 g/d). The EAR for carbohydrate during lactation is set at 160 g/d.

EAR and RDA Summary, Lactation

EAR for Lactation

14–18 years	**160 g/d of carbohydrate**
19–30 years	**160 g/d of carbohydrate**
31–50 years	**160 g/d of carbohydrate**

The RDA for carbohydrate is set by using a CV of 15 percent based on the variation in brain glucose utilization. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for carbohydrate the RDA is 130 percent of the EAR). The calculated values for the RDAs have been rounded.

RDA for Lactation

14–18 years	**210 g/d of carbohydrate**
19–30 years	**210 g/d of carbohydrate**
31–50 years	**210 g/d of carbohydrate**

Special Considerations

Individuals adapted to a very low carbohydrate diet can perform adequately for extended periods of time at power outputs represented by exercise at less than 65 percent O_2 max (Miller and Wolfe, 1999). For extended periods of power output exceeding this level, the dependence on carbohydrate as a fuel increases rapidly to near total dependence (Miller and Wolfe, 1999). Therefore, for such individuals there must be a corresponding increase in carbohydrate derived directly from carbohydrate-containing foods. Additional consumption of dietary protein may assist in meeting the need through gluconeogenesis, but it is unlikely to be consumed in amounts necessary to meet the individual's need. A requirement for such individuals cannot be determined since the requirement for carbohydrate will depend on the particular energy expenditure for some defined period of time (Brooks and Mercier, 1994).

INTAKE OF CARBOHYDRATES

Food Sources

White, brown, and raw sugars represent different forms and purification of sucrose. Corn syrups are the hydrolytic products of starch digestion. They are composed of various proportions of glucose (dextrose), maltose, trisaccharides, and higher molecular-weight products including some starch itself. Another source of carbohydrate, high fructose corn syrup, is often misunderstood. These syrups are also derived from cornstarch through the conversion of a portion of the glucose present in starch into fructose. The fructose content present in corn syrup is 42, 55, or 90 percent. The great majority of the remaining content is glucose. Other sources of sugars include malt syrup, comprised largely of sucrose; honey, which resembles sucrose in its composition but is composed of individual glucose and fructose molecules; and molasses, a by-product of table sugar production.

With the introduction of high fructose corn sweeteners in 1967, the amount of "free" fructose in the diet of Americans has increased considerably (Hallfrisch, 1990). Nonalcoholic beverages (e.g., soft drinks and fruit-flavored drinks) are the major dietary sources of added fructose; fruits and fruit products are the major dietary sources of naturally occurring fructose (Park and Yetley, 1993).

Using 1994–1996 U.S. Department of Agriculture food consumption survey data, nondiet soft drinks were the leading source of added sugars in Americans' diets, accounting for one-third of added sugars intake (Guthrie and Morton, 2000). This was followed by sugars and sweets (16 percent), sweetened grains (13 percent), fruit ades/drinks (10 percent), sweetened dairy (9 percent), and breakfast cereals and other grains (10 percent). Together, these foods and beverages accounted for 90 percent of Americans' added sugars intake. Gibney and colleagues (1995) reported that dairy foods contributed 31 percent of the total sugar intakes in children, and fruits contributed 17 percent of the sugars for all ages.

Grains and certain vegetables are the major contributors of starch. The majority of carbohydrate occurs as starch in corn, tapioca, flour, cereals, popcorn, pasta, rice, potatoes, and crackers. Fruits and darkly colored vegetables contain little or no starch.

Dietary Intake

Data from the 1994–1996, 1998 Continuing Food Survey of Intakes by Individuals (CSFII) indicates that the median intake of carbohydrate was approximately 220 to 330 g/d for men and 180 to 230 g/d for women in the United States (Appendix Table E-2). This represents 49 to 50 percent

of energy intake (Appendix Table E-3). Between 10 and 25 percent of adults consumed less than 45 percent of energy from carbohydrate. Less than 5 percent of adults consumed more than 65 percent of energy from carbohydrate (Appendix Table E-3).

Median carbohydrate intakes of Canadian men and women during 1990 to 1997 ranged from approximately 47 to 50 percent of energy intake (Appendix Table F-2). More than 25 percent of men consumed less than 45 percent of energy from carbohydrate, whereas between 10 and 25 percent of women consumed below this level. Less than 5 percent of Canadian men and women consumed more than 65 percent of energy from carbohydrate.

Data from the Third National Health and Nutrition Examination Survey shows that the median intake of added sugars widely ranged from 10 to 30 tsp/d for adults, which is equivalent to 40 to 120 g/d of sugars (1 tsp = 4 g of sugar) (Appendix Table D-1). Based on data from CFSII, the mean intake of added sugars in the U.S. population aged 2 and older was 82 g, accounting for 15.8 percent of the total energy intake (Guthrie and Morton, 2000).

ADVERSE EFFECTS OF OVERCONSUMPTION

Hazard Identification

Sugars such as sucrose (e.g., white sugar), fructose (e.g., high-fructose corn syrup), and dextrose that are present in foods have been associated with various adverse effects. These sugars may be either naturally occurring or added to foods. Potential adverse effects from consuming a high carbohydrate diet, including sugars and starches, are discussed in detail in Chapter 11.

Behavior

The concept that sugars might adversely affect behavior was first reported by Shannon (1922). The notion that intake of sugars is related to hyperactivity, especially in children, is based on two physiological theories: (1) an allergic reaction to refined sugars (Egger et al., 1985; Speer, 1954) and (2) a hypoglycemic response (Cott, 1977). A number of studies have been conducted to find a correlation between intake of sugars and adverse behavior; some have been reviewed by White and Wolraich (1995). Most of the intervention studies looked at the behavior effects of sugars within a few hours after ingestion, and therefore the long-term effects are unclear. The cross-sectional studies are not capable of determining if the sugars caused adverse behavior or adverse behavior resulted in increased sugar

consumption. A meta-analysis of 23 studies conducted over a 12-year period concluded that sugar intake does not affect either behavior or cognitive performance in children (Wolraich et al., 1995) (Figure 6-2). Therefore, altered behavior cannot be used as an adverse effect for setting a Tolerable Upper Intake Level (UL) for sugars.

Dental Caries

Sugars play a significant role in the development of dental caries (Walker and Cleaton-Jones, 1992), but much less information is known about the role of starch in the development of dental caries (Lingstrom et al., 2000). Early childhood dental caries, also known as baby-bottle tooth decay or nursing caries, affects about 3 to 6 percent of children (Fitzsimons et al., 1998). This is associated with frequent, prolonged use of baby bottles containing fermentable sugars (e.g., cow's milk, infant formula, fruit juice, soft drinks, and other sweetened drinks), at-will breast-feeding, and continual use of a sweetened pacifier (Fitzsimons et al., 1998). Increased consumption of sugar-containing foods has been associated with a deterioration of dental health in 5-year-old children (Holbrook et al., 1995). Children 5 or 8 years of age who consumed sweet snacks between meals more than five times a day had significantly higher mean decayed and missing teeth and filled scores than children with a lower consumption (Kalsbeek and Verrips, 1994). Root caries in middle-aged and elderly adults was significantly associated with sucrose consumption (Papas et al., 1995).

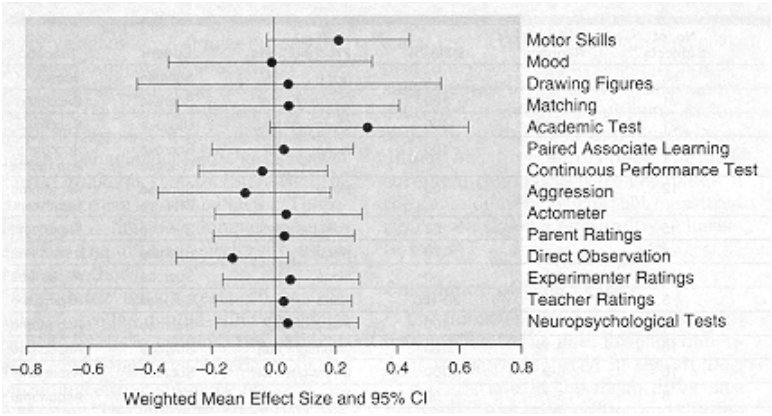

FIGURE 6-2 Weighted mean effect sizes and 95 percent confidence intervals (CI) by measurement construct following meta-analysis of 23 studies on the effect of sugar intake on behavior and cognition. Reprinted, with permission, from Wolraich et al. (1995). Copyright 1995 by the American Medical Association.

Dental caries is a disorder of multifactorial causation. Hence, it is difficult to rationalize the relationship of sugars and dental caries as simply "cause-and-effect" (Walker and Cleaton-Jones, 1992). Caries occurrence is influenced by frequency of meals and snacks, oral hygiene (tooth-brushing frequency), water fluoridation, fluoride supplementation, and fluoride toothpaste (Holbrook et al., 1995; Mascarenhas, 1998; McDonagh et al., 2000; Shaw, 1987). Fluoride alters the sugars–caries dose–response curve. Caries has declined in many industrialized countries and in areas with water fluoridation (McDonagh et al., 2000). Because of the various factors that can contribute to dental caries, it is not possible to determine an intake level of sugars at which increased risk of dental caries can occur.

Triacylglycerol, LDL, and HDL Cholesterol Concentration

Sugars. Fructose is more lipogenic than glucose or starches (Cohen and Schall, 1988; Reiser and Hallfrisch, 1987); however, the precise biochemical basis for this mechanism has not been elucidated (Roche, 1999). There is some evidence that increased intake of sugars is positively associated with plasma triacylglycerol and low density lipoprotein (LDL) cholesterol concentrations (Table 6-7). The data on triacylglycerol concentration is mixed with a number of studies showing an increase in concentration with increased sucrose, glucose, or fructose concentration (Albrink and Ullrich, 1986; Hayford et al., 1979; Kaufmann et al., 1966; Mann et al., 1973, Rath et al., 1974; Reiser et al., 1979a, 1989; Yudkin et al., 1986), whereas other studies have shown no effect (Bossetti et al., 1984; Crapo and Kolterman, 1984; Dunnigan et al., 1970; Hallfrisch et al., 1983; Mann and Truswell, 1972; Surwit et al., 1997; Swanson et al., 1992).

Smith and colleagues (1996) demonstrated that hypertriacylglycerolemia could be reduced in some people with the reduction (73 percent) of extrinsic sucrose in the diet. The investigators reported reduced plasma triacylglycerol concentrations in 32 hypertriacylglycerolemic individuals by greater than 20 percent, and the reduction remained significant with the control of weight loss. Parks and Hellerstein (2000) published an exhaustive review of carbohydrate-induced hypertriacylglycerolemia and concluded that it is more extreme if the carbohydrate content of a high carbohydrate diet consists primarily of monosaccharides, particularly fructose, rather than oligo- and polysaccharides. Purified diets, whether based on starch or monosaccharides, induce hypertriacylglycerolemia more readily than diets higher in fiber in which most of the carbohydrate is derived from unprocessed whole foods, and possibly result in a lower glycemic index and reduced postprandial insulin response (Jenkins et al., 1987b).

TABLE 6-7 Dietary Sugars and Blood Lipid Concentrations in Healthy Subjects

Reference	Study Population/ Dietary Intervention	Triacylglycerol Concentration (mmol/L)			
Kaufmann et al., 1966	3 men and 1 woman, 10–35 d/diet	2 males: no difference between diets			
	30% starch	1 male (ad lib to sucrose to fructose): 0.98–1.98 to 2.76 to 4.50			
	30% sucrose	1 female (starch to fructose): 1.32–1.78 to 2.30–2.58			
	30% fructose				
Dunnigan et al., 1970	9 men and women, 4-wk crossover				
	31% sucrose	1.05[a]			
	sucrose-free	1.04[a]			
Mann and Truswell, 1972	9 men, 2-wk crossover				
	23% sucrose	1.10[a]			
	23% starch	1.11[a]			
Mann et al., 1973	9 men, 2-wk crossover				
	17% sucrose	1.66[a]			
	34% sucrose	1.84[b]			
	34% sucrose + polyunsaturated fatty acids	1.50[a]			
Rath et al., 1974	6 men, 2- to 5-wk crossover	Significant increase with 52% sucrose			
	17% sucrose				
	52% sucrose				
Hayford et al., 1979	8 men, 10-d crossover				
	45% sucrose	0.87[a]			
	65% sucrose	1.31[b]			
	45% glucose	0.80[a]			
	65% glucose	1.33[b]			
Reiser et al., 1979a	19 men and women, 6-wk crossover	Men		Women	
		Baseline	6 wk	Baseline	6 wk
	30% starch	1.28[a]	1.42[a]	1.06[a]	0.98[a]
	30% sucrose	1.54[a]	1.86[b]	1.06[a]	1.23[b]
Hallfrisch et al., 1983	12 men, 5-wk crossover				
	0% fructose, 15% starch	0.97[a]			
	7.5% fructose, 7.5% starch	1.07[a]			
	15% fructose, 0% starch	1.04[a]			
Bossetti et al., 1984	8 men and women, 140-d crossover	Baseline	14 d		
	11–16% sucrose	0.60[a]	0.63[a]		
	11–16% fructose	0.80[a]	0.56[a]		

Low Density Lipoprotein Cholesterol Concentration (mmol/L)	High Density Lipoprotein Cholesterol Concentration (mmol/L)
3.52^a	1.01^a
3.76^b	1.05^a
3.70^b	1.07^a

Baseline	14 d
2.38^a	2.35^a
2.59^a	2.48^a

Baseline	14 d
1.42^a	1.37^a
1.42^a	1.40^a

continued

TABLE 6-7 Continued

Reference	Study Population/ Dietary Intervention	Triacylglycerol Concentration (mmol/L)	
Crapo and Kolterman, 1984	11 men and women, 14-d crossover 24% sucrose 24% fructose	No significant difference	
Albrink and Ullrich, 1986	6 men per group, 11 d 0% sucrose 18% sucrose 36% sucrose 52% sucrose	Significant increase when fed 36% or 52% sucrose and a diet containing less than 14 g of fiber	
Yudkin et al., 1986	14 men, 14-d crossover 18% sucrose 37% sucrose 19% sucrose 26 men, 14-d crossover 23% sucrose 9% sucrose 24% sucrose	 1.02[a] 1.11[a] 1.09[a] 1.33[a] 1.05[b] 1.23[a]	
Reiser et al., 1989	11 men, 5-wk crossover 20% fructose 20% starch	 0.84[a] 0.70[b]	
Swanson et al., 1992	14 men and women, 4-wk crossover	Baseline	4 wk
	19% fructose, 25% starch	1.16[a]	0.96[a]
	< 3% fructose, 39% starch	1.02[a]	0.94[a]
Surwit et al., 1997	42 women, 6-wk intervention 4% sucrose 43% sucrose	 1.05[a] 1.08[a]	
Marckmann et al., 2000	20 women, 2-wk crossover 2.5% sucrose, 59% carbohydrate 23.2% sucrose, 59% carbohydrate	 0.81[a] 0.96[b]	
Saris et al., 2000	390 adults, 6-mo parallel 18.8% sugar, 52% carbohydrate 29.5% sugar, 56% carbohydrate	 1.29[a] 1.46[a]	

[a,b] Different lettered superscripts within each study indicate that values were significantly different.

Low Density Lipoprotein Cholesterol Concentration (mmol/L)	High Density Lipoprotein Cholesterol Concentration (mmol/L)
	Significant reduction in high density lipoprotein concentration with fructose
Significant decline observed for 0% and 18% sucrose diets	Significantly lower for 18%, 36%, and 52% sucrose diets
	1.27^a 1.07^b 1.42^a
	1.30^a 1.27^a 1.26^a
3.06^a 2.73^b	1.16^a 1.11^a
Baseline 4 wk 2.62^a 2.73^a 2.65^a 2.46^b	Baseline 4 wk 1.28^a 1.30^a 1.32^a 1.22^a
2.38^a 2.60^b	1.03^a 1.06^a
2.43^a	1.34^a
2.72^b	1.38^a
3.68^a	1.20^a
3.61^a	1.15^a

Increases in LDL cholesterol concentration have been observed more consistently with increases in sugar intake (Table 6-7). Increases in LDL cholesterol concentration were reported when 7.5 and 15 percent fructose replaced an equal amount of starch (Hallfrisch et al., 1983), 36 and 52 percent sucrose were fed compared with 0 and 18 percent sucrose (Albrink and Ullrich, 1986), 20 percent fructose replaced an equal amount of starch (Reiser et al., 1989), and 19 percent fructose was fed compared with less than 3 percent fructose (Swanson et al., 1992).

In general, most epidemiological studies have shown an inverse relationship between sugar intake and high density lipoprotein (HDL) cholesterol concentration (Archer et al., 1998; Bolton-Smith et al., 1991; Ernst et al., 1980; Tillotson et al., 1997). Of the nine intervention studies reviewed, five showed no difference in HDL cholesterol concentration with varying intakes of sugars (Bossetti et al., 1984; Hallfrisch et al., 1983; Reiser et al., 1989; Swanson et al., 1992; Surwit et al., 1997). A significant decrease in HDL cholesterol concentration was observed when 24 percent fructose replaced the same amount of sucrose (Crapo and Kolterman, 1984); 37 percent sucrose was fed compared with 18 or 19 percent sucrose (Yudkin et al., 1986); and 18, 36, and 52 percent sucrose was fed compared with 0 percent sucrose (Albrink and Ullrich, 1986).

Kant (2000) used the Third National Health and Nutrition Examination Survey (NHANES III) survey to examine the association between the consumption of energy-dense, nutrient-poor (EDNP) foods on lipid profiles. EDNP foods such as visible fats, nutritive sweeteners and sweetened beverages, desserts, and snacks have high fat and/or high carbohydrate and poor micronutrient content. HDL cholesterol concentration was inversely related and serum homocysteine concentration was positively related to EDNP food intake. Both serum homocysteine and HDL cholesterol concentrations are independent risk factors for cardiovascular disease (Aronow and Ahn, 1998; Boushey et al., 1995).

GI. In controlled studies, the consumption of high glycemic index (GI) diets has generally resulted in modest increases in circulating concentrations of hemoglobin A_{1c}, total serum cholesterol, and triacylglycerols, as well as decreased circulating HDL cholesterol and urinary C-peptide concentrations in diabetic and hyperlipidemic individuals (Table 6-8). Furthermore, studies on dyslipidemic individuals show that a low GI diet can reduce cholesterol and triacylglycerol concentrations (Jenkins et al., 1985, 1987b). Data are limited for healthy individuals as only one study has measured the effect of predicted GI on blood lipid concentrations (Jenkins et al., 1987a). This study showed a 15 and 13 percent reduction in total cholesterol and LDL cholesterol concentration, respectively, when the GI was reduced by 41 (Jenkins et al., 1987a).

A significant negative relationship between GI and HDL cholesterol concentration was reported in two epidemiological studies (Ford and Liu, 2001; Frost et al., 1999) (Table 6-9 and Figure 6-3). Only the negative relationship to glycemic load was significant for postmenopausal women (Liu et al., 2001). HDL cholesterol concentrations were more responsive to changes in GI in women than in men (Figure 6-3). In contrast, Ford and Liu (2001) reported a more pronounced response in men than in women. Thus, although there is evidence for an association between high GI and risk factors for cardiovascular disease (Haffner et al., 1988a; Morris and Zemel, 1999), further controlled studies are needed.

CHD. Four epidemiological studies have shown no risk of coronary heart disease (CHD) from consuming naturally occurring or added sugars (Bolton-Smith and Woodward, 1994a; Kushi et al., 1985; Liu et al., 1982, 2000; McGee et al., 1984) (see Table 11-7). Two epidemiological studies have been conducted to relate the risk of CHD with GI (Liu et al., 2000; van Dam et al., 2000) (Table 6-9). One study showed increased risk of CHD with increasing GI, but for only those with a body mass index greater than 23 (Liu et al., 2000). van Dam and coworkers (2000) observed no association between GI and risk of CHD in elderly men. Thus, there are insufficient data for setting a UL based on increased risk for CHD.

Insulin Sensitivity and Type 2 Diabetes

Sugars. Insulin has three major effects on glucose metabolism: it decreases hepatic glucose output, it increases glucose utilization in muscle and adipose tissue, and it enhances glycogen production in the liver and muscle. Insulin sensitivity measures the ability to do these effectively. Individuals vary genetically in their insulin sensitivity, some being much more efficient than others (Reaven, 1999). Obesity is related to decreased insulin sensitivity (Kahn et al., 2001), which can also be influenced by fat intake (see Chapter 11) and exercise.

Two prospective cohort studies showed no risk of diabetes from consuming increased amounts of sugars (Colditz et al., 1992; Meyer et al., 2000). Furthermore, a negative association was observed between increased sucrose intake and risk of diabetes (Meyer et al., 2000). Intervention studies that have evaluated the effect of sugar intakes on insulin concentration and insulin resistance portray mixed results. Dunnigan and coworkers (1970) reported no difference in glucose tolerance and plasma insulin concentration after 0 or 31 percent sucrose was consumed for 4 weeks. Reiser and colleagues (1979b) reported that when 30 percent starch was replaced with 30 percent sucrose, insulin concentration was significantly elevated; however, serum glucose concentration did not differ.

TABLE 6-8 Controlled Studies of Low Glycemic Index (GI) Diets on Carbohydrate and Lipid Metabolism in Healthy, Diabetic, and Hyperlipidemic Subjects

Reference	Study Design	Change in Diet GI	Type of Glycated Proteins
Healthy subjects			
Jenkins et al., 1987a	6 men, 2 wk	–41	Fructosamine
Kiens and Richter, 1996	7 young men, 30 d	–24	Not reported
Frost et al., 1998	25 women, 3 wk	–18	Not reported
Diabetic subjects			
Collier et al., 1988	7 type I children, 6 wk	–12	Albumin
Fontvieille et al., 1988	8 type I men and women, 3 wk	–14	Fructosamine
Jenkins et al., 1988a	8 type II men and women, 2 wk	–23	HbA_{1c} Fructosamine
Brand et al., 1991	16 type II men and women, 12 wk	–14	HbA_{1c}
Fontvieille et al., 1992	18 type I and II men and women, 5 wk	–26	Fructosamine
Wolever et al., 1992a	15 type II men and women, 2 wk	–27	Fructosamine
Wolever et al., 1992b	6 type II overweight men and women, 6 wk	–28	Fructosamine

Change in Glycated Proteins (%)	Change in Blood Lipids[a] (%)	Comments[b]
–7[c,d]	–15[c,d] TC –13[c,d] LDL-C	–32%[c,e] urinary C-peptide excretion –10%[c,e] creatinine clearance during the day
Not reported	Not reported	Euglycemic hyperinsulinemic clamp showed no difference in glucose uptake between high and low GI diets at low plasma insulin, but glucose uptake was reduced at high plasma insulin with low GI diet
Not reported	Not reported	Using short insulin tolerance test, in vivo insulin sensitivity improved after low GI diet
–19[c,d]	–14[c,d] TC	Reduced postprandial glucose response to standard test meal with low GI diet
–18.1[c,d]	–5.8[c,d] TAG	–8.9%[c,d] plasma phospholipids –6.1%[c,d] daily insulin needs
–6.6[c,d] –6.6[c,d]	–5.8[c,d] TC	–30%[c,d] fasting blood glucose
–11[c,e]	Not significant	–11%[c,e] plasma glucose response to standard meal
–12.1[c,e]	–21.1[c,e] TAG	–11%[c,e] fasting blood glucose –13.3%[c,e] mean daily blood glucose
–3.4[c,e]	–7[c,e] TC	–30%[c,e] urinary C-peptide excretion –29%[c,e] postbreakfast blood glucose TAG rose on high GI diet ($p = 0.027$) and fell on low GI diet, but the difference between the two diets was not significant
–8[c,e]	–6.8[c,e] TC	–22.4%[c,e] TAG for the 5 subjects with TAG > 2.2 mmol/L

continued

TABLE 6-8 Continued

Reference	Study Design	Change in Diet GI	Type of Glycated Proteins
Frost et al., 1994	25 type II men and women, 12 wk	–5	Fructosamine
Järvi et al., 1999	20 type II men and women, 2 d	–26	HbA_{1c} Fructosamine
Luscombe et al., 1999	21 type II men and women, 4 wk	–20	Fructosamine
Hyperlipidemic subjects			
Jenkins et al., 1987b	30 men and women, 4 wk	–17	Fructosamine

[a] TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, TAG = triacylglycerols, HDL-C = high density lipoprotein cholesterol.
[b] PAI-1 = plasminogen activator inhibitor-1.

GI. There are well-recognized, short-term effects of high versus low GI carbohydrates on several key hormones and metabolites. In particular, compared to regular consumption of low GI carbohydrates, regular consumption of high GI carbohydrates results in high concentrations of circulating glucose and insulin (Table 6-8). In healthy individuals, there also appears to be an amplification of glucose and insulin responses to consumption of high GI foods with repeated consumption (Liljeberg et al., 1999). Based on associations between these metabolic parameters and risk of disease (DeFronzo et al., 1992; Groop and Eriksson, 1992; Haffner et al., 1988b, 1990; Martin et al., 1992; Rossetti et al., 1990; Warram et al., 1990), further controlled studies on GI and risk factors for diabetes are needed. Furthermore, studies are needed on the extent to which consumption of high GI diets might influence the development of diabetes compared to other putative dietary variables that also influence insulin secretion (e.g., dietary fiber).

In prospective epidemiological studies, three of the four published studies support an association between GI and the development of type 2 diabetes (Table 6-9). Data from the Nurses' Health Study illustrated a significant association between the dietary glycemic index and risk of type 2 diabetes that was significant both with and without an adjustment for

Change in Glycated Proteins (%)	Change in Blood Lipids[a] (%)	Comments[b]
–15.8[c,d]	–11.3[c,d] TC –26.3[c,d] TAG	–21.3%[c,d] fasting blood glucose
–5.9[c,d] –2.5[c,e]	–5.2[c,e] TC –8.3[c,e] LDL-C	–31%[c,e] 9-h blood glucose profile –53%[c,d] PAI-1 activity
Not significant	+5.7[c,e] HDL-C	Fasting plasma glucose did not significantly differ between the diets
Not significant	When TAG > 2 mmol/L –8.8[c,e] TC –9.1[c,e] LDL-C –19.3[c,e] TAG	24-h urinary C-peptide was not significantly different Changes in weight loss and fat intake did not explain the lipid effects

[c] Significant effect ($p < 0.05$).
[d] Treatment difference (across treatment).
[e] Endpoint difference (between treatment).

cereal fiber intake (Salmerón et al., 1997b). In contrast, the Iowa Women's Health Study showed no significant relationship between GI and the development of type 2 diabetes after adjusting for total dietary fiber, although the association was positive in the GI range of 59 to 71 and then declined with GI values greater than 71 (Meyer et al., 2000). The reasons for the discrepancy between studies are not known, but may be related to the accuracy of dietary intake records, the imprecision in calculating GI from reported diets, and the age of individuals entering the investigations. There are currently no intervention trials in which dietary GI is manipulated and development of chronic diseases monitored; such studies are needed.

Obesity

Sugars. Several studies have been conducted to determine the relationship between total (intrinsic plus added) and added sugars intake and energy intake (Table 6-10). The Department of Health Survey of British School Children showed that as total sugar intake increased from less than 20.7 percent of energy to up to 25.2 percent of energy, intake increased by approximately 100 kcal/d (Gibson, 1993). In contrast, the Bogalusa Heart

TABLE 6-9 Cross-Sectional and Cohort Studies on the Relation of Glycemic Index (GI) to the Risk of Diabetes, Coronary Heart Disease (CHD), and Cancer and Its Association with High Density Lipoprotein Cholesterol (HDL-C) Concentration and Glucated Hemoglobin (HbA_{lc}) in Diabetes

References	Study Design	GI
Diabetes		
Salmerón et al., 1997a	42,759 healthy, male health professionals Cohort, 6-y follow-up	Quintile mean 65 70 73 75 79
Salmerón et al., 1997b	65,173 healthy, female nurses Cohort, 6-y follow-up	Quintile mean 64 68 71 73 77
Meyer et al., 2000	35,988 postmenopausal women Cohort, 6-y follow-up	< 58 59–65 66–71 72–80 > 80
Buyken et al., 2001	2,810 type I diabetic men and women Cross-sectional study	58.2–77.7 79.8–81.5 81.5–85.5 85.5–111.5
Hu et al., 2001	84,941 healthy, female nurses Cohort, 16-y follow-up	
CHD and related parameters		
Frost et al., 1999	1,420 British adults Cross-sectional study	Mean: 86

Main Effect[a]	Comments[b]
RR of diabetes 1.00 1.16 1.19 1.20 1.37	p for trend = 0.03 after adjustment for cereal fiber intake For high GL plus low cereal fiber intake, the RR of diabetes was 2.17 (1.04–4.54)
RR of diabetes 1.00 1.21 1.37 1.37 1.37	p for trend = 0.005 after adjustment for cereal fiber intake Significant association between glycemic load and risk of diabetes (RR = 1.47 for 5th quintile)
RR of diabetes 1.00 1.19 1.26 0.96 0.89	GI and GL were not associated with risk of diabetes
HbA_{1c} (%) 6.05 6.27 6.59 6.55	Using bivariate model, serum HDL-C was inversely associated with GI (p for trend = 0.0001), and TAG was positively associated with GI (p for trend = 0.01) Significant association between GL and risk of diabetes (p trend < 0.001); this is an updated analysis from Salmerón et al. (1997b) that includes 3,300 new cases of type 2 diabetes
Negative relationship between GI and HDL-C ($p < 0.0001$)	

continued

TABLE 6-9 Continued

References	Study Design	GI
Liu et al., 2000	75,521 female nurses Cohort, 10-y follow-up	GI quintile mean by GL score 72 75 77 78 80
van Dam et al., 2000	646 elderly Dutch men Prospective analysis	Tertile median 77 82 85
Ford and Liu, 2001	13,907 men and women Cross-sectional study	 < 76 76–79 80–83 84–87 > 87
Liu et al., 2001	280 postmenopausal women Prospective analysis	Quintile mean 68 73 75 77 81
Cancer		
Franceschi et al., 2001	Italian men and women with colon cancer 1,953 cases 4,154 controls	 < 70.8 70.8–73.8 73.9–76.5 76.6–79.6 > 79.6

[a] RR = relative risk, OR = odds ratio.
[b] GL = glycemic load, TAG = triacylglycerol, BMI = body mass index.

Study reported a significant decrease in energy intake with increased total sugar intake (Nicklas et al., 1996). A negative correlation between total sugar intake and body mass index (BMI) has been consistently reported for children and adults (Bolton-Smith and Woodward, 1994b; Dreon et al., 1988; Dunnigan et al., 1970; Fehily et al., 1984; Gibson, 1993, 1996b; Miller

Main Effect[a]		Comments[b]
RR of CHD		RR of CHD associated with high glycemic load only for those with BMI > 23
1.00		
1.01		
1.25		
1.51		
1.98		
RR of CHD		No association between GI and risk of CHD (p for trend = 0.7)
1.00		
1.12		
1.11		
Serum HDL-C (mmol/L)		p for trend < 0.001
1.36		The decrease in HDL-C was similar for subjects with BMI < 25 and those with BMI ≥ 25
1.31		
1.30		
1.27		
1.28		
Plasma HDL-C (mmol/L)	Plasma TAG (mmol/L)	Nonsignificant negative association between GI and HDL-C concentration (p for trend = 0.1)
1.45	1.16	
1.42	1.20	Nonsignificant positive association between GI and TAG concentration (p for trend = 0.03)
1.42	1.14	
1.40	1.27	
1.29	1.37	
OR of colon and rectum cancer		p for trend < 0.001 Similar findings for glycemic load
1.0		
1.3		
1.6		
1.5		
1.7		

et al., 1990) (Table 6-11). A study of 42 women compared the effects of a high sucrose (43 percent of total energy) and low sucrose (4 percent of total energy), low fat (11 percent total energy) hypoenergetic diet (Surwit et al., 1997). There were no significant differences between groups in total body weight lost during the intervention. On the other hand, a study using

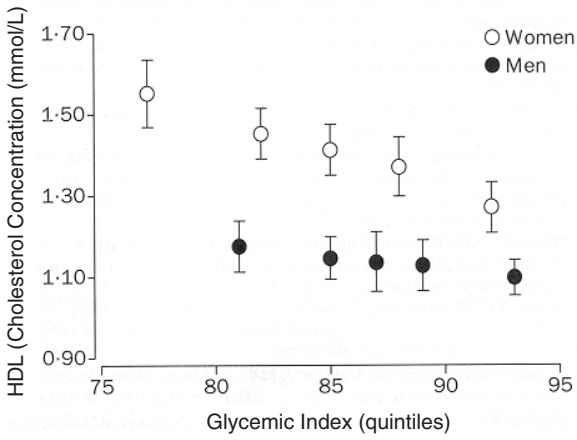

FIGURE 6-3 Relation between high density lipoprotein (HDL) cholesterol concentration and five quintiles of glycemic index in men and women. Reprinted, with permission, from Frost et al. (1999). Copyright 1999 by Elsevier Science (*The Lancet*).

23 lean men, 23 obese men, 17 lean women, and 15 obese women found that lean and obese individuals of the same gender had similar total sugar intake (Miller et al., 1994). However, the obese individuals derived a greater percentage (38.0 to 47.9 percent) of their sugar intake from added sugars compared with lean individuals (25.2 to 31.4 percent).

Increased added sugars intakes have been shown to result in increased energy intakes for children and adults (Bowman, 1999; Gibson 1996a, 1997; Lewis et al., 1992). Despite these observations, a negative correlation between added sugars intake and BMI has been observed (Bolton-Smith and Woodward, 1994b; Gibson, 1996a; Lewis et al., 1992). For adolescents, nonconsumers of soft drinks consumed 1,984 kcal/d in contrast to 2,604 kcal/d for those teens who consumed 26 or more oz of soft drinks per day (Harnack et al., 1999). Using NHANES III data, Troiano and colleagues (2000) found that soft drinks contributed a higher proportion of daily energy intake for overweight than for nonoverweight children and adolescents. Kant (2000) demonstrated a positive association between energy-dense, micronutrient-poor food and beverage consumption (visible fats, nutritive sweeteners, sweetened beverages, desserts, and snacks) and energy intake.

Ludwig and colleagues (2001) examined the relationship between consumption of drinks sweetened with sugars and childhood obesity. They concluded that for each additional serving of the drinks consumed, the

odds of becoming obese increased by 60 percent. Drinks sweetened with sugars, such as soft drinks, have been suggested to promote obesity because compensation at subsequent meals for energy consumed in the form of a liquid could be less complete than for energy consumed as solid food (Mattes, 1996).

Published reports disagree about whether a direct link exists between the trend toward increased intakes of sugars and increased rates of obesity. The lack of association in some studies may be partially due to the pervasive problem of underreporting food intake, which is known to occur with dietary surveys (Johnson, 2000). Underreporting is more prevalent and severe by obese adolescents and adults than by their lean counterparts (Johnson, 2000). In addition, foods high in added sugars are selectively underreported (Krebs-Smith et al., 2000). Thus, it can be difficult to make conclusions about associations between sugars intake and BMI by using self-reported data.

Based on the above data, it appears that the effects of increased intakes of total sugars on energy intake are mixed, and the increased intake of added sugars are most often associated with increased energy intake. There is no clear and consistent association between increased intake of added sugars and BMI. Therefore, the above data cannot be used to set a UL for either added or total sugars.

GI. Although there have been several short-term studies on the relationship between dietary GI and hunger, satiety, and energy intake at single meals, many of the studies are confounded by differences between test diets in variables other than GI (Roberts, 2000b). Among relatively controlled studies (Guss et al., 1994; Holt and Brand Miller, 1995; Ludwig et al., 1999; Rodin, 1991; Spitzer and Rodin, 1987), voluntary energy intake was 29 percent higher following consumption of high GI test meals or preloads compared to those of low GI, as summarized in Figure 6-4 (Roberts, 2000b). These data strongly suggest an effect of GI on short-term energy intake, but there are currently little data on the effect of GI on energy intake from longer-term clinical trials. Such data are necessary before the effects of the GI of carbohydrate-containing foods on energy regulation can be appropriately evaluated because the effects of GI on energy intake might become smaller over time. Obtaining data from clinical trials is especially important because although one nonblinded study reported greater weight loss success in obese patients treated with a low GI diet compared with a conventional low fat diet (Spieth et al., 2000), the two epidemiological studies reporting BMI in their evaluations of the relationship between GI and development of chronic diseases observed no significant association between GI and BMI (Liu et al., 2000; Salmerón et al., 1997a, 1997b).

TABLE 6-10 Sugar and Energy Intake

Reference	Design and Study	Sugar Intake (% of Energy)
Total sugar		
Gibson, 1993	2,705 boys and girls Department of Health Survey of British School Children	 < 20.7 20.7–25.2 > 25.2
Nicklas et al., 1996	568 boys and girls, 10 y Bogalusa Heart Study	18.0 22.0 26.4 31.2
Farris et al., 1998	568 boys and girls, 10 y Bogalusa Heart Study	16.1 23.5 28.2 35.6
Added sugar		
Lewis et al., 1992	Nationwide Food Consumption Survey (1977–1978)	
Gibson, 1996a	1,087 men and 1,110 women Dietary and Nutritional Survey of British Adults	 < 10 10–13 14–16 17–20 > 20
Gibson, 1997	1,675 boys and girls, 1.5–4.5 y U.K. National Diet and Nutrition Survey of Children	 < 12 12–16 16–20 20–25 > 25
Bowman, 1999	Continuing Survey of Food Intakes by Individuals (1994–1996)	< 10 10–18 > 18

a,b,c Different lettered superscripts within each study indicate that values were significantly different.

Energy Intake (kcal)

Boys		Girls	
10–11 y	14–15 y	10–11 y	14–15 y
1,954[a]	2,401[a]	1,753[a]	1,819[a]
2,095[b]	2,526[b]	1,838[b]	1,961[b]
2,066[b]	2,549[b]	1,871[b]	1,901[a,b]

2,291
2,245
2,274
2,016

2,249
2,286
2,144
2,061

High consumers of added sugars had greater energy intakes than consumers of moderate and low added sugars

Men	Women
2,219[a]	1,438[a]
2,430[b]	1,681[b]
2,455[b,c]	1,738[b]
2,549[b,c]	1,773[b]
2,596[c]	1,774[b]

Boys	Girls
1,129[a]	1,097[a]
1,168[a,b]	1,102[a]
1,187[a,b]	1,139[a]
1,188[a,b]	1,115[a]
1,217[b]	1,116[a]

1,860[a]
2,040[b]
2,049[b]

TABLE 6-11 Interventional and Epidemiological Data on Sugar Intake and Body Mass Index (BMI)

Reference	Study Design	Sugar Intake (% of energy)
Total sugars		
Dunnigan et al., 1970	9 men and women, 4-wk crossover	31% sucrose sucrose-free
Fehily et al., 1984	493 men, 45–59 y 7-d weighed dietary record	
Dreon et al., 1988	155 obese men, 30–59 y 7-d dietary record	13.7 ± 8.4 g/1,000 kcal
Miller et al., 1990	107 men and 109 women, 18–71 y 24-h recall and 2-d dietary questionnaire	
Gibson, 1993	2,705 boys and girls Department of Health Survey of British School Children	< 20.7 20.7–25.2 < 25.2
Bolton-Smith and Woodward, 1994b	11,626 men and women, 25–64 y Scottish Heart Health and MONICA studies	Quintile 1 2 3 4 5
Gibson, 1996b	1,087 men and 1,110 women, 16–64 y Dietary and Nutritional Survey of British Adults	Quintile 1 2 3 4 5

BMI (kg)
62.4
63.8
Significant negative association between sucrose intake and BMI
Significant negative correlation between sucrose intake and BMI
Significant negative correlation between sugar intake and percentage of body fat for women; no association for men

Boys		Girls	
10–11 y	14–15 y	10–11 y	14–15 y
18.6[a]	20.2[a]	18.2[a]	21.2[a]
17.9[a,b]	20.0[a,b]	18.1[a]	20.2[b]
17.5[b]	19.2[b]	17.9[a]	19.8[b]

Men	Women
27.0	26.5
26.4	26.0
26.0	25.5
25.5	25.1
24.7	24.4

Significant negative correlation between sugar intake and BMI

Men	Women
24.9	25.4
25.3	24.7
25.2	24.5
24.8	23.8
24.4	24.4

Weak negative association between sugar intake and BMI

continued

TABLE 6-11 Continued

Reference	Study Design	Sugar Intake (% of energy)
Added sugars		
Lewis et al., 1992	Nationwide Food Consumption Survey (1977–1978)	
Bolton-Smith and Woodward, 1994b	11,626 men and women, 25–64 y Scottish Heart Health and MONICA studies	Quintile 1 2 3 4 5
Gibson, 1996a	1,087 men and 1,110 women, 16–64 y Dietary and Nutritional Survey of British Adults	< 10 10–13 14–16 17–20 > 20
Ludwig et al., 2001	Planet Health intervention and evaluation project	

[a,b,c,d] Different lettered superscripts within each study indicate that values were significantly different.

Physical Activity

Although consumption of high GI test foods increases glucose oxidation and suppresses the availability of free fatty acids (Ritz et al., 1991), for factors that would be predicted to have an adverse effect on the capacity for endurance exercise there are conflicting reports on whether consumption of high GI diets prior to exercise results in measurably adverse exercise performance. Some studies report a negative effect of consumption of high GI carbohydrates prior to exercise compared with consumption of low GI carbohydrates (DeMarco et al., 1999; Gleeson et al., 1986; Okano et al., 1988; Thomas et al., 1991), while other studies report no effect on exercise performance (Chryssanthopoulos et al., 1994; Décombaz et al., 1985; Febbraio et al., 2000; Hargreaves et al., 1987; Sparks et al., 1998). It is possible that the level and duration of exercise and amount of test food have critical influences on the results obtained in such studies. Since the

BMI (kg)	
High consumers of added sugars tended to weigh less than moderate consumers	
Men	Women
27.2	26.5
26.4	25.8
26.1	25.6
25.4	25.4
24.5	24.1
Significant negative correlation between added sugar intake and BMI	
Men	Women
25.9[a]	26.0[a]
25.5[a,b]	24.9[a,b]
24.8[b,c]	24.2[b]
24.4[c,d]	24.1[b]
24.1[c,d]	23.8[b]
Significant negative correlation between added sugar intake and BMI	
For each additional serving of sugar-sweetened drink consumed, BMI and frequency of obesity increased; baseline consumption of sugar-sweetened drinks was independently associated with change in BMI	

available studies are in considerable conflict, the potential for GI to impact exercise performance at submaximal levels of exercise seems limited.

Lung Cancer

One case-control study in Uruguay (463 cases and 465 controls) suggested that foods rich in sugars, total sucrose intake, sucrose-to-dietary fiber ratio, and GI were associated with increased risk of lung cancer (De Stefani et al., 1998).

Breast Cancer

The data examining sugars intake and breast cancer have been inconsistent (World Cancer Research Fund/American Institute for Cancer

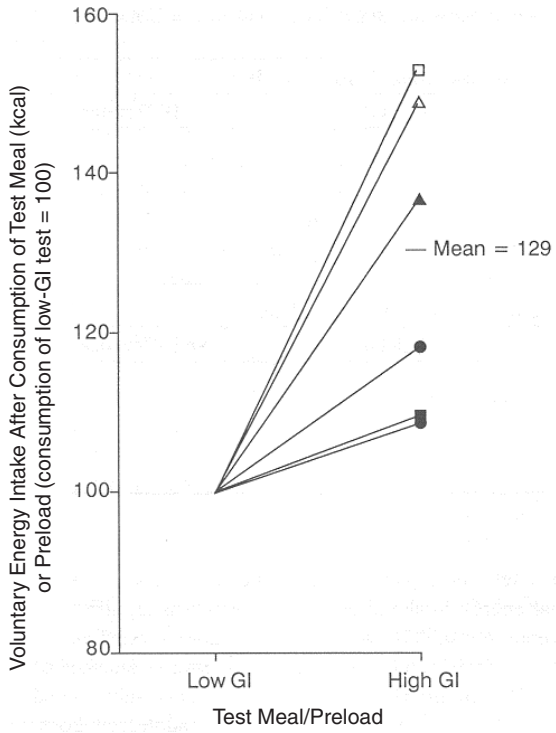

FIGURE 6-4 Summary of data from crossover studies examining the effects of the glycemic index (GI) of test meals or preloads on subsequent energy intake. Δ from Spitzer and Rodin (1987), ▲ from Rodin (1991), ■ from Guss et al. (1994), • from Holt and Brand Miller (1995), □ from Ludwig et al. (1999). All published studies that used pairs of diets differing in GI that contained physiologic amounts of energy, were isocaloric, and were approximately matched for all factors are summarized (i.e., data from 10% sugar solutions in Guss et al. [1994] and the high and medium GI meals only in Ludwig et al. [1999]). Where energy intake was assessed at more than one time point, data from the longest period were used. Reprinted, with permission, from Roberts (2000b). Copyright 2000 by the International Life Sciences Institute.

Research, 1997) and therefore are insufficient to determine a role of sugars in breast cancer (Burley, 1998). There are indications that insulin resistance and insulin-like growth factors may play a role in the development of breast cancer (Bruning et al., 1992; Kazer, 1995).

Prostate Cancer

The Health Professionals Follow-Up Study (n = 47,781 men) demonstrated a reduced risk of advanced prostate cancer associated with increased fructose intakes. Both fruit intake and nonfruit sources of fructose predicted reduced risk of advanced prostate cancer (Giovannucci et al., 1998), but evidence to suggest a role of sugars in prostate cancer is lacking (Burley, 1998).

Colorectal Cancer

The World Cancer Research Fund and American Institute for Cancer Research (1997) reviewed the literature linking foods, nutrients, and dietary patterns with the risk of human cancers worldwide. Data from five case-control studies showed an increase in colorectal polyps and colorectal cancer risk across intakes of sugars and foods rich in sugars (Benito et al., 1990; Macquart-Moulin et al., 1986, 1987; Miller et al., 1983; Tuyns et al., 1988). The subgroups studied showed an elevated risk for those consuming 30 g or more per day compared with those eating less than 10 g/d. Others have concluded that high consumption of fruits and vegetables, as well as the avoidance of foods containing highly refined sugars, are likely to reduce the risk of colon cancer (Giovannucci and Willett, 1994). In many of the studies, sugars increased the risk of colorectal cancer while fiber and starch had the opposite effect. One investigator suggested that the positive association between high sugars consumption and colorectal cancer reflects a global dietary habit that is generally associated with an increased risk of colorectal cancer and may not indicate a biological effect of sugars on colon carcinogenesis (Macquart-Moulin et al., 1987). Burley (1997) concluded from a review of the available literature that there was insufficient evidence to conclude whether sugars had a role in colon cancer.

Concerning a possible relationship between GI and colon cancer, two groups recently reported a case-control study suggesting increased risk of colon cancer among individuals consuming a high versus a low GI diet (Franceschi et al., 2001; Slattery et al., 1997). However, data from other types of investigations are currently unavailable.

Summary

GI

There is a significant body of data suggesting that more slowly absorbed starchy foods that are less processed, or have been processed in traditional ways, may have health advantages over those that are rapidly

digested and absorbed. These foods have been classified as having a low GI and reduce the glycemic load of the diet. Not all studies of low GI or low glycemic load diets have resulted in beneficial effects. However, none have shown negative effects. At a time when populations are increasingly obese, inactive, and prone to insulin resistance, there are theoretical reasons that dietary interventions that reduce insulin demand may have advantages. In this section of the population, it is likely that more slowly absorbed carbohydrate foods and low glycemic load diets will have the greatest advantage.

Dietary GI and glycemic load have relatively predicable effects on circulating glucose, hemoglobin A_{1c}, insulin, triacylglycerol, HDL cholesterol, and urinary C-peptide concentrations, particularly in individuals with diabetes and hyperlipidemia. Although the data are lacking in healthy individuals, on theoretical grounds, these effects would be expected to result in reduced risks of type 2 diabetes and cardiovascular disease in individuals consuming low GI versus high GI carbohydrates. However, the results of epidemiological studies are not always consistent, perhaps because of the difficulty of predicting dietary GI precisely from the relatively simple dietary assessment tools used in some studies. Thus, although there may be beneficial metabolic and disease prevention effects of consuming a greater proportion of carbohydrate from low GI sources, further studies are needed before general recommendations on this issue can be made for the general healthy population.

Further research is especially needed because recommendations to reduce the GI of carbohydrate consumed by the general healthy population would have a significant impact on recommended food sources. Currently, recommended healthy carbohydrate sources with a high GI include whole wheat breads, some breakfast cereals, and potatoes. A recommendation to replace bread and potatoes in the U.S. diet with foods of lower GI would involve major changes in current dietary patterns, and thus substantial evidence of significant beneficial effects of GI is needed. Another important practical issue in considering recommendations on GI is that dietary fiber somewhat decreases GI and may have a beneficial role in several chronic diseases, including the prevention of cardiovascular disease (see Chapter 7). Currently, the median intake of *Dietary Fiber* is only about half the Adequate Intake (AI) for *Total Fiber* (see Appendix Table E-4 and Chapter 7), and the question of whether lowering the GI has measurable beneficial effects on chronic diseases among individuals consuming recommended fiber intakes has received little attention (Luscombe et al., 1999).

Concerning obesity, there is limited evidence suggesting an effect of GI on short-term energy intake. Data from long-term clinical trials on the effects on energy intake are lacking and further studies are needed in this area.

In summary, a UL based on GI is not made at the present time because, although several lines of evidence suggest adverse effects of high GI carbohydrates, it is difficult to eliminate other contributing factors, and the critical mass of evidence necessary for recommending substantial dietary change is not available. Furthermore, it should be noted that sugars have a lower GI than starch yet are rapidly absorbed. However, the principle of slowing carbohydrate absorption, which may underpin the positive findings made in relation to GI, is a potentially important principal with respect to the beneficial health effects of carbohydrate. Further research in this area is needed.

Sugars

Based on the data available on dental caries, behavior, cancer, risk of obesity, and risk of hyperlipidemia, there is insufficient evidence to set a UL for total or added sugars. Although a UL is not set for sugars, a maximal intake level of 25 percent or less of energy from added sugars is suggested based on the decreased intake of some micronutrients of American subpopulations exceeding this level (see Chapter 11 and Appendix J). Because not all micronutrients and other nutrients such as fiber were not examined, the association between added sugars and these nutrients it is not known. While it is recognized that hypertriglyceridemia can occur with increasing intakes of total (intrinsic plus added) sugars, total sugars intake can be limited by minimizing the intake of added sugars and consuming naturally occurring sugars present in nutrient-rich milk, dairy products, and fruits.

Intake Assessment

Median intakes of added sugars were highest in young adults, particularly adolescent males (35.7 tsp or 143 g), and progressively declined with age (Appendix Table D-1). At the 95th percentile of intake, added sugars intakes were as high as 52 tsp (208 g or 832 kcal) for men aged 19 to 50 years.

RESEARCH RECOMMENDATIONS

- There is a need for more research to elucidate the metabolic and long-term health differences resulting from the ingestion of high versus low glycemic index carbohydrates using larger, diverse sample sizes and whole-food diets.
- There is a need for research to determine if the energy density approach to weight reduction is effective in the long-term.

- Experimental studies are needed to determine whether there is a metabolic effect of sugars in enhancing energy expenditure or in suppressing fat intake at a fixed level of energy.
- Research is needed to determine the effect of low glycemic index foods and low glycemic-load diets on serum lipids and other risk factors for chronic disease and complications, especially in high-risk groups.

REFERENCES

Albrink MJ, Ullrich IH. 1986. Interaction of dietary sucrose and fiber on serum lipids in healthy young men fed high carbohydrate diets. *Am J Clin Nutr* 43:419–428.

Allen JC, Keller RP, Archer P, Neville MC. 1991. Studies in human lactation: Milk composition and daily secretion rates of macronutrients in the first year of lactation. *Am J Clin Nutr* 54:69–80.

Amiel SA, Caprio S, Sherwin RS, Plewe G, Haymond MW, Tamborlane WV. 1991. Insulin resistance of puberty: A defect restricted to peripheral glucose metabolism. *J Clin Endocrinol Metab* 72:277–282.

Anderson DM, Williams FH, Merkatz RB, Schulman PK, Kerr DS, Pittard WB. 1983. Length of gestation and nutritional composition of human milk. *Am J Clin Nutr* 37:810–814.

Anderson GH, Atkinson SA, Bryan MH. 1981. Energy and macronutrient content of human milk during early lactation from mothers giving birth prematurely and at term. *Am J Clin Nutr* 34:258–265.

Archer SL, Liu K, Dyer AR, Ruth KJ, Jacobs DR, Van Horn L, Hilner JE, Savage PJ. 1998. Relationship between changes in dietary sucrose and high density lipoprotein cholesterol: The CARDIA Study. *Ann Epidemiol* 8:433–438.

Aronow WS, Ahn C. 1998. Risk factors for new coronary events in older African-American men and women. *Am J Cardiol* 82:902–904.

Arslanian S, Kalhan S. 1992. Effects of growth hormone releasing hormone on insulin action and insulin secretion in a hypopituitary patient evaluated by the clamp technique. *Acta Endocrinol* 127:93–96.

Assel B, Rossi K, Kalhan S. 1993. Glucose metabolism during fasting through human pregnancy: Comparison of tracer method with respiratory calorimetry. *Am J Physiol* 265:E351–E356.

Azar GJ, Bloom WL. 1963. Similarities of carbohydrate deficiency and fasting. II. Ketones, nonesterified fatty acids, and nitrogen excretion. *Arch Intern Med* 112:338–343.

Bell JD, Margen S, Calloway DH. 1969. Ketosis, weight loss, uric acid, and nitrogen balance in obese women fed single nutrients at low caloric levels. *Metabolism* 18:193–208.

Benito R, Obrador A, Stiggelbout A, Bosch FX, Mulet M, Muñoz N, Kaldor J. 1990. A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer* 45:69–76.

Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA, Kipnis DM. 1977. Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. *Diabetes* 26:1016–1023.

Bloom WL, Azar GJ. 1963. Similarities of carbohydrate deficiency and fasting. I. Weight loss, electrolyte excretion, and fatigue. *Arch Intern Med* 112:333–337.

Bolton-Smith C, Woodward M. 1994a. Coronary heart disease: Prevalence and dietary sugars in Scotland. *J Epidemiol Community Health* 48:119–122.

Bolton-Smith C, Woodward M. 1994b. Dietary composition and fat to sugar ratios in relation to obesity. *Int J Obes Relat Metab Disord* 18:820–828.

Bolton-Smith C, Woodward M, Smith WCS, Tunstall-Pedoe H. 1991. Dietary and non-dietary predictors of serum total and HDL-cholesterol in men and women: Results from the Scottish Heart Health Study. *Int J Epidemiol* 20:95–104.

Bossetti BM, Kocher LM, Moranz JF, Falko JM. 1984. The effects of physiologic amounts of simple sugars on lipoprotein, glucose, and insulin levels in normal subjects. *Diabetes Care* 7:309–312.

Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. 1995. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: Probable benefits of increasing folic acid intakes. *J Am Med Assoc* 274:1049–1057.

Bowman SA. 1999. Diets of individuals based on energy intakes from added sugars. *Fam Econ Nutr Rev* 12:31–38.

Brand JC, Colagiuri S, Crossman S, Allen A, Roberts DCK, Truswell AS. 1991. Low-glycemic index foods improve long-term glycemic control in NIDDM. *Diabetes Care* 14:95–101.

Brito MN, Brito NA, Migliorini RH. 1992. Thermogenic capacity of brown adipose tissue is reduced in rats fed a high protein, carbohydrate-free diet. *J Nutr* 122:2081–2086.

Britten P, Basiotis PP, Davis CA, Anand R. 2000. Is intake of added sugars associated with diet quality? Online. *Nutrition Insights* No 21. USDA Center for Nutrition Policy and Promotion. Available at http://www.usda.gov/cnpp/insights.htm. Accessed June 8, 2001.

Brooks GA, Mercier J. 1994. Balance of carbohydrate and lipid utilization during exercise: The "crossover" concept. *J Appl Physiol* 76:2253–2261.

Brosnan JT. 1999. Comments on metabolic needs for glucose and the role of gluconeogenesis. *Eur J Clin Nutr* 53:S107–S111.

Bruning PF, Bonfrèr JMG, van Noord PAH, Hart AAM, de Jong-Bakker M, Nooijen WJ. 1992. Insulin resistance and breast-cancer risk. *Int J Cancer* 52:511–516.

Burley VJ. 1997. Sugar consumption and cancers of the digestive tract. *Eur J Cancer Prev* 6:422–434.

Burley VJ. 1998. Sugar consumption and human cancer in sites other than the digestive tract. *Eur J Cancer Prev* 7:253–277.

Burt RL, Davidson IWF. 1974. Insulin half-life and utilization in normal pregnancy. *Obstet Gynecol* 43:161–170.

Buyken AE, Toeller M, Heitkamp G, Karamanos B, Rottiers R, Muggeo M, Fuller JH. 2001. Glycemic index in the diet of European outpatients with type 1 diabetes: Relations to glycated hemoglobin and serum lipids. *Am J Clin Nutr* 73:574–581.

Cahill GF. 1970. Starvation in man. *N Engl J Med* 282:668–675.

Cahill GF, Owen OE, Morgan AP. 1968. The consumption of fuels during prolonged starvation. *Adv Enzyme Reg* 6:143–150.

Cahill GF, Aoki TT, Ruderman NB. 1973. Ketosis. *Trans Am Clin Climatol Assoc* 84:184–202.

Calloway DH. 1971. Dietary components that yield energy. *Environ Biol Med* 1:175–186.

Carlson MG, Snead WL, Campbell PJ. 1994. Fuel and energy metabolism in fasting humans. *Am J Clin Nutr* 60:29–36.

Chandramouli V, Ekberg K, Schumann WC, Kalhan SC, Wahren J, Landau BR. 1997. Quantifying gluconeogenesis during fasting. *Am J Physiol* 273:E1209–E1215.
Chew I, Brand JC, Thornburn AW, Truswell AS. 1988. Application of glycemic index to mixed meals. *Am J Clin Nutr* 47:53–56.
Chryssanthopoulos C, Hennessy LCM, Williams C. 1994. The influence of pre-exercise glucose ingestion on endurance running capacity. *Br J Sports Med* 28:105–109.
Chugani HT. 1993. Positron emission tomography scanning: Applications in newborns. *Clin Perinatol* 20:395–409.
Chugani HT, Phelps ME. 1986. Maturational changes in cerebral function in infants determined by ^{18}FDG positron emission tomography. *Science* 231:840–843.
Chugani HT, Phelps ME, Mazziotta JC. 1987. Positron emission tomography study of human brain functional development. *Ann Neurol* 22:487–497.
Cohen JC, Schall R. 1988. Reassessing the effects of simple carbohydrates on the serum triglyceride responses to fat meals. *Am J Clin Nutr* 48:1031–1034.
Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. 1992. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 55:1018–1023.
Collier GR, Wolever TMS, Wong GS, Josse RG. 1986. Prediction of glycemic response to mixed meals in noninsulin-dependent diabetic subjects. *Am J Clin Nutr* 44:349–352.
Collier GR, Giudici S, Kalmusky J, Wolever TMS, Helman G, Wesson V, Ehrlich RM, Jenkins DJA. 1988. Low glycaemic index starchy foods improve glucose control and lower serum cholesterol in diabetic children. *Diabetes Nutr Metab* 1:11–19.
Condon JR, Nassim JR, Millard FJC, Hilbe A, Stainthorpe EM. 1970. Calcium and phosphorus metabolism in relation to lactose tolerance. *Lancet* 1:1027–1029.
Coppa GV, Gabrielli O, Pierani P, Catassi C, Carlucci A, Giorgi PL. 1993. Changes in carbohydrate composition in human milk over 4 months of lactation. *Pediatrics* 91:637–641.
Cott A. 1977. Treatment of learning disabilities. In: Williams RJ, Kalita DK, eds. *A Physician's Handbook on Orthomolecular Medicine*. New York: Pergamon Press. Pp. 90–94.
Coulston AM, Hollenbeck CB, Liu GC, Williams RA, Starich GH, Mazzaferri EL, Reaven GM. 1984. Effect of source of dietary carbohydrate on plasma glucose, insulin, and gastric inhibitory polypeptide responses to test meals in subjects with noninsulin-dependent diabetes mellitus. *Am J Clin Nutr* 40:965–970.
Cousins L, Rigg L, Hollingsworth D, Brink G, Aurand J, Yen SSC. 1980. The 24-hour excursion and diurnal rhythm of glucose, insulin, and C-peptide in normal pregnancy. *Am J Obstet Gynecol* 136:483–488.
Cowett RM, Susa JB, Kahn CB, Giletti B, Oh W, Schwartz R. 1983. Glucose kinetics in nondiabetic and diabetic women during the third trimester of pregnancy. *Am J Obstet Gynecol* 146:773–780.
Crapo PA, Kolterman OG. 1984. The metabolic effects of 2-week fructose feeding in normal subjects. *Am J Clin Nutr* 39:525–534.
Décombaz J, Sartori D, Arnaud M-J, Thélin A-L, Schürch P, Howald H. 1985. Oxidation and metabolic effects of fructose or glucose ingested before exercise. *Int J Sports Med* 6:282–286.
DeFronzo RA, Bonadonna RC, Ferrannini E. 1992. Pathogenesis of NIDDM. A balanced overview. *Diabetes Care* 15:318–368.

Dekaban AS, Sadowsky D. 1978. Changes in brain weights during the span of human life: Relation of brain weights to body heights and body weights. *Ann Neurol* 4:345–356.

DeMarco HM, Sucher KP, Cisar CJ, Butterfield GE. 1999. Pre-exercise carbohydrate meals: Application of glycemic index. *Med Sci Sports Exerc* 31:164–170.

Denne SC, Kalhan SC. 1986. Glucose carbon recycling and oxidation in human newborns. *Am J Physiol* 251:E71–E77.

De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Ronco A, Carzoglio JC. 1998. Dietary sugar and lung cancer: A case-control study in Uruguay. *Nutr Cancer* 31:132–137.

Dewey KG, Lönnerdal B. 1983. Milk and nutrient intake of breast-fed infants from 1 to 6 months: Relation to growth and fatness. *J Pediatr Gastroenterol Nutr* 2:497–506.

Dewey KG, Finley DA, Lönnerdal B. 1984. Breast milk volume and composition during late lactation (7–20 months). *J Pediatr Gastroenterol Nutr* 3:713–720.

Díez-Sampedro A, Eskandari S, Wright EM, Hirayama BA. 2001. Na^+-to-sugar stoichiometry of SGLT3. *Am J Physiol Renal Physiol* 280:F278–F282.

Dobbing J, Sands J. 1973. Quantitative growth and development of human brain. *Arch Dis Child* 48:757–767.

Dreon DM, Frey-Hewitt B, Ellsworth N, Williams PT, Terry RB, Wood PD. 1988. Dietary fat:carbohydrate ratio and obesity in middle-aged men. *Am J Clin Nutr* 47:995–1000.

Du Bois EF. 1928. The control of protein in the diet. *J Am Diet Assoc* 4:53–76.

Dunnigan MG, Fyfe T, McKiddie MT, Crosbie SM. 1970. The effects of isocaloric exchange of dietary starch and sucrose on glucose tolerance, plasma insulin and serum lipids in man. *Clin Sci* 38:1–9.

Edmond J, Austad N, Robbins RA, Bergstrom JD. 1985. Ketone body metabolism in the neonate: Development and effect of diet. *Fed Proc* 44:2359–2364.

Egger J, Carter CM, Graham PJ, Gumley D, Soothill JF. 1985. Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome. *Lancet* 1:540–545.

Ercan N, Gannon MC, Nuttall FQ. 1994. Effect of added fat on the plasma glucose and insulin response to ingested potato given in various combinations as two meals in normal individuals. *Diabetes Care* 17:1453–1459.

Ernst N, Fisher M, Smith W, Gordon T, Rifkind BM, Little JA, Mishkel MA, Williams OD. 1980. The association of plasma high-density lipoprotein cholesterol with dietary intake and alcohol consumption. The Lipid Research Clinics Program Prevalence Study. *Circulation* 62:IV41–IV52.

FAO/WHO (Food and Agriculture Organization/World Health Organization). 1998. *Carbohydrates in Human Nutrition.* Rome: FAO.

Farris RP, Nicklas TA, Myers L, Berenson GS. 1998. Nutrient intake and food group consumption of 10-year-olds by sugar intake level: The Bogalusa Heart Study. *J Am Coll Nutr* 17:579–585.

Febbraio MA, Keenan J, Angus DJ, Campbell SE, Garnham AP. 2000. Preexercise carbohydrate ingestion, glucose kinetics, and muscle glycogen use: Effect of the glycemic index. *J Appl Physiol* 89:1845–1851.

Fehily AM, Phillips KM, Yarnell JWG. 1984. Diet, smoking, social class, and body mass index in the Caerphilly Heart Disease Study. *Am J Clin Nutr* 40:827–833.

Felig P. 1973. The glucose-alanine cycle. *Metabolism* 22:179–207.

Ferris AM, Dotts MA, Clark RM, Ezrin M, Jensen RG. 1988. Macronutrients in human milk at 2, 12, and 16 weeks postpartum. *J Am Diet Assoc* 88:694–697.

Fitzsimons D, Dwyer JT, Palmer C, Boyd LD. 1998. Nutrition and oral health guidelines for pregnant women, infants, and children. *J Am Diet Assoc* 98:182–189.

Fomon SJ, Thomas LN, Filer LJ, Anderson TA, Nelson SE. 1976. Influence of fat and carbohydrate content of diet on food intake and growth of male infants. *Acta Paediatr Scand* 65:136–144.

Fontvieille AM, Acosta M, Rizkalla SW, Bornet F, David P, Letanoux M, Tchobroutsky G, Slama G. 1988. A moderate switch from high to low glycaemic-index foods for 3 weeks improves the metabolic control of type I (IDDM) diabetic subjects. *Diabetes Nutr Metab* 1:139–143.

Fontvieille AM, Rizkalla SW, Penfornis A, Acosta M, Bornet FRJ, Slama G. 1992. The use of low glycaemic index foods improves metabolic control of diabetic patients over five weeks. *Diabet Med* 9:444–450.

Ford ES, Liu S. 2001. Glycemic index and serum high-density lipoprotein cholesterol concentration among US adults. *Arch Intern Med* 161:572–576.

Forshee RA, Storey ML. 2001. The role of added sugars in the diet quality of children and adolescents. *J Am Coll Nutr* 20:32–43.

Forsum E, Kabir N, Sadurskis A, Westerterp K. 1992. Total energy expenditure of healthy Swedish women during pregnancy and lactation. *Am J Clin Nutr* 56:334–342.

Foster-Powell K, Brand Miller J. 1995. International tables of glycemic index. *Am J Clin Nutr* 62:871S–890S.

Franceschi S, Dal Maso L, Augustin L, Negri E, Parpinel M, Boyle P, Jenkins DJA, La Vecchia C. 2001. Dietary glycemic load and colorectal cancer risk. *Ann Oncol* 12:173–178.

Frost G, Wilding J, Beecham J. 1994. Dietary advice based on the glycaemic index improves dietary profile and metabolic control in type 2 diabetic patients. *Diabet Med* 11:397–401.

Frost G, Leeds A, Trew G, Margara R, Dornhorst A. 1998. Insulin sensitivity in women at risk of coronary heart disease and the effect of a low glycemic diet. *Metabolism* 47:1245–1251.

Frost G, Leeds AA, Doré CJ, Madeiros S, Brading S, Dornhorst A. 1999. Glycaemic index as a determinant of serum HDL-cholesterol concentration. *Lancet* 353:1045–1048.

Gamble JL. 1946. Physiological information gained from studies on the life raft ration. *Harvey Lect* 42:247–273.

Gannon MC, Nuttall FQ. 1987. Factors affecting interpretation of postprandial glucose and insulin areas. *Diabetes Care* 10:759–763.

Gannon MC, Nuttall FQ. 1999. Protein and diabetes. In: Franz MJ, Bantle JP, eds. *American Diabetes Association Guide to Medical Nutrition Therapy for Diabetes.* Alexandria, VA: American Diabetes Association. Pp. 107–125.

Gannon MC, Niewoehner CB, Nuttall FQ. 1985. Effect of insulin administration on cardiac glycogen synthase and synthase phosphatase activity in rats fed diets high in protein, fat or carbohydrate. *J Nutr* 115:243–251.

Gannon MC, Nuttall FQ, Westphal SA, Seaquist ER. 1993. The effect of fat and carbohydrate on plasma glucose, insulin, C-peptide, and triglycerides in normal male subjects. *J Am Coll Nutr* 12:36–41.

Gibbons A. 1998. Solving the brain's energy crisis. *Science* 280:1345–1347.

Gibney M, Sigman-Grant M, Stanton JL, Keast DR. 1995. Consumption of sugars. *Am J Clin Nutr* 62:178S–194S.

Gibson SA. 1993. Consumption and sources of sugars in the diets of British schoolchildren: Are high-sugar diets nutritionally inferior? *J Hum Nutr Diet* 6:355–371.

Gibson SA. 1996a. Are diets high in non-milk extrinsic sugars conducive to obesity? An analysis from the Dietary and Nutritional Survey of British Adults. *J Hum Nutr Diet* 9:283–292.

Gibson SA. 1996b. Are high-fat, high-sugar foods and diets conducive to obesity? *Int J Food Sci Nutr* 47:405–415.

Gibson SA. 1997. Non-milk extrinsic sugars in the diets of pre-school children: Association with intakes of micronutrients, energy, fat and NSP. *Br J Nutr* 78:367–378.

Giovannucci E, Willett WC. 1994. Dietary factors and risk of colon cancer. *Ann Med* 26:443–452.

Giovannucci E, Rimm EB, Wolk A, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. 1998. Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res* 58:442–447.

Gleeson M, Maughan RJ, Greenhaff PL. 1986. Comparison of the effects of pre-exercise feeding of glucose, glycerol and placebo on endurance and fuel homeostasis in man. *Eur J Appl Physiol* 55:645–653.

Glinsmann WH, Irausquin H, Park YK. 1986. Evaluation of health aspects of sugars contained in carbohydrate sweeteners. Report of Sugars Task Force. *J Nutr* 116:S1–S216.

Goldberg GR, Prentice AM, Coward WA, Davies HL, Murgatroyd PR, Wensing C, Black AE, Harding M, Sawyer M. 1993. Longitudinal assessment of energy expenditure in pregnancy by the doubly labeled water method. *Am J Clin Nutr* 57:494–505.

Gottstein U, Held K. 1979. Effects of aging on cerebral circulation and metabolism in man. *Acta Neurologica Scand* 60:54–55.

Groop LC, Eriksson JG. 1992. The etiology and pathogenesis of non-insulin-dependent diabetes. *Ann Med* 24:483–489.

Gulliford MC, Bicknell EJ, Scarpello JH. 1989. Differential effect of protein and fat ingestion on blood glucose responses to high- and low-glycemic-index carbohydrates in noninsulin-dependent diabetic subjects. *Am J Clin Nutr* 50:773–777.

Guss JL, Kissileff HR, Pi-Sunyer FX. 1994. Effects of glucose and fructose solutions on food intake and gastric emptying in nonobese women. *Am J Physiol* 267:R1537–R1544.

Guthrie JF, Morton JF. 2000. Food sources of added sweeteners in the diets of Americans. *J Am Diet Assoc* 100:43–48, 51.

Haffner SM, Fong D, Hazuda HP, Pugh JA, Patterson JK. 1988a. Hyperinsulinemia, upper body adiposity, and cardiovascular risk factors in non-diabetics. *Metabolism* 37:338–345.

Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. 1988b. Increased insulin concentrations in nondiabetic offspring of diabetic parents. *N Engl J Med* 319:1297–1301.

Haffner SM, Stern MP, Mitchell BD, Hazuda HP, Patterson JK. 1990. Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. *Diabetes* 39:283–288.

Hallfrisch J. 1990. Metabolic effects of dietary fructose. *FASEB J* 4:2652–2660.

Hallfrisch J, Reiser S, Prather ES. 1983. Blood lipid distribution of hyperinsulinemic men consuming three levels of fructose. *Am J Clin Nutr* 37:740–748.

Hanson PG, Johnson RE, Zaharko DS. 1965. Correlation between ketone body and free fatty acid concentrations in the plasma during early starvation in man. *Metabolism* 14:1037–1040.

Hargreaves M, Costill DL, Fink WJ, King DS, Fielding RA. 1987. Effect of pre-exercise carbohydrate feedings on endurance cycling performance. *Med Sci Sports Exerc* 19:33–36.

Harnack L, Stang J, Story M. 1999. Soft drink consumption among US children and adolescents: Nutritional consequences. *J Am Diet Assoc* 99:436–441.

Hatazawa J, Brooks RA, Di Chiro G, Bacharach SL. 1987. Glucose utilization rate versus brain size in humans. *Neurology* 37:583–588.

Hay WW. 1994. Placental supply of energy and protein substrates to the fetus. *Acta Paediatr Suppl* 405:13–19.

Hayford JT, Danney MM, Wiebe D, Roberts S, Thompson RG. 1979. Triglyceride integrated concentrations: Effect of variation of source and amount of dietary carbohydrate. *Am J Clin Nutr* 32:1670–1678.

Heinbecker P. 1928. Studies on the metabolism of Eskimos. *J Biol Chem* 80:461–475.

Hellerstein MK. 1999. De novo lipogenesis in humans: Metabolic and regulatory aspects. *Eur J Clin Nutr* 53:S53–S65.

Holbrook WP, Árnadóttir IB, Takazoe E, Birkhed D, Frostell G. 1995. Longitudinal study of caries, cariogenic bacteria and diet in children just before and after starting school. *Eur J Oral Sci* 103:42–45.

Hollenbeck CB, Coulston AM, Reaven GM. 1986. Glycemic effects of carbohydrates: A different perspective. *Diabetes Care* 9:641–647.

Holt SH, Brand Miller J. 1995. Increased insulin responses to ingested foods are associated with lessened satiety. *Appetite* 24:43–54.

Holt SHA, Brand Miller JC, Petocz P. 1997. An insulin index of foods: The insulin demand generated by 1000-kJ portions of common foods. *Am J Clin Nutr* 66:1264–1276.

Homko CJ, Sivan E, Reece EA, Boden G. 1999. Fuel metabolism during pregnancy. *Semin Reprod Endocrinol* 17:119–125.

Hoover HC, Grant JP, Gorschboth C, Ketcham AS. 1975. Nitrogen-sparing intravenous fluids in postoperative patients. *N Engl J Med* 293:172–175.

Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. 2001. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345:790–797.

Hultman E, Harris RC, Spriet LL. 1999. Diet in work and exercise performance. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*, 9th ed. Baltimore, MD: Williams and Wilkins. Pp. 761–782.

Indar-Brown K, Norenberg C, Madar Z. 1992. Glycemic and insulinemic responses after ingestion of ethnic foods by NIDDM and healthy subjects. *Am J Clin Nutr* 55:89–95.

IOM (Institute of Medicine). 1991. *Nutrition During Lactation*. Washington, DC: National Academy Press.

Janney NW. 1915. The metabolic relationship of the proteins to glucose. *J Biol Chem* 20:321–350.

Järvi AE, Karlström BE, Granfeldt YE, Björk IME, Vessby BOH, Asp N-GL. 1995. The influence of food structure on postprandial metabolism in patients with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 61:837–842.

Järvi AE, Karlström BE, Granfeldt YE, Björck IE, Asp N-GL, Vessby BOH. 1999. Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients. *Diabetes Care* 22:10–18.

Jenkins DJA, Wolever TMS, Taylor RH, Barker H, Fielden H, Baldwin JM, Bowling AC, Newman HC, Jenkins AL, Goff DV. 1981. Glycemic index of foods: A physiological basis for carbohydrate exchange. *Am J Clin Nutr* 34:362–366.

Jenkins DJA, Wolever TMS, Kalmusky J, Giudici S, Giordano C, Wong GS, Bird JN, Patten R, Hall M, Buckley G, Little JA. 1985. Low glycemic index carbohydrate foods in the management of hyperlipidemia. *Am J Clin Nutr* 42:604–617.

Jenkins DJA, Wolever TMS, Collier GR, Ocana A, Rao AV, Buckley G, Lam Y, Mayer A, Thompson LU. 1987a. Metabolic effects of a low-glycemic-index diet. *Am J Clin Nutr* 46:968–975.

Jenkins DJA, Wolever TMS, Kalmusky J, Guidici S, Girodano C, Patten R, Wong GS, Bird J, Hall M, Buckley G, Csima A, Little JA. 1987b. Low-glycemic index diet in hyperlipidemia: Use of traditional starchy foods. *Am J Clin Nutr* 46:66–71.

Jenkins DJA, Wolever TMS, Buckley G, Lam KY, Giudici S, Kalmusky J, Jenkins AL, Patten RL, Bird J, Wong GS, Josse RG. 1988a. Low-glycemic-index starchy food in the diabetic diet. *Am J Clin Nutr* 48:248–254.

Jenkins DJA, Wolever TMS, Jenkins AL. 1988b. Starchy foods and glycemic index. *Diabetes Care* 11:149–159.

Jenkins DJA, Jenkins AL, Wolever TM, Vuksan V, Brighenti F, Testolin G. 1990. Fiber and physiological and potentially therapeutic effects of slowing carbohydrate absorption. *Adv Exp Med Biol* 270:129–134.

Johnson RK. 2000. What are people really eating and why does it matter? *Nutr Today* 35:40–46.

Kahn SE, Prigeon RL, Schwartz RS, Fujimoto WY, Knopp RH, Brunzell JD, Porte D. 2001. Obesity, body fat distribution, insulin sensitivity and islet β-cell function as explanations for metabolic diversity. *J Nutr* 131:354S–360S.

Kalhan SC, Kiliç İ. 1999. Carbohydrate as nutrient in the infant and child: Range of acceptable intake. *Eur J Clin Nutr* 53:S94–S100.

Kalhan SC, D'Angelo LJ, Savin SM, Adam PAJ. 1979. Glucose production in pregnant women at term gestation. Sources of glucose for human fetus. *J Clin Invest* 63:388–394.

Kalhan SC, Oliven A, King KC, Lucero C. 1986. Role of glucose in the regulation of endogenous glucose production in the human newborn. *Pediatr Res* 20:49–52.

Kalhan S, Rossi K, Gruca L, Burkett E, O'Brien A. 1997. Glucose turnover and gluconeogenesis in human pregnancy. *J Clin Invest* 100:1775–1781.

Kalsbeek H, Verrips GH. 1994. Consumption of sweet snacks and caries experience of primary school children. *Caries Res* 28:477–483.

Kant AK. 2000. Consumption of energy-dense, nutrient-poor foods by adult Americans: Nutritional and health implications. The Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr* 72:929–936.

Kaufmann NA, Poznanski R, Blondheim SH, Stein Y. 1966. Effect of fructose, glucose, sucrose and starch on serum lipids in carbohydrate induced hypertriglyceridemia and in normal subjects. *Israel J Med Sci* 2:715–726.

Kazer RR. 1995. Insulin resistance, insulin-like growth factor I and breast cancer: A hypothesis. *Int J Cancer* 62:403–406.

Kennedy C, Sokoloff L. 1957. An adaptation of the nitrous oxide method to the study of the cerebral circulation in children: Normal values for cerebral blood flow and cerebral metabolic rate in childhood. *J Clin Invest* 36:1130–1137.

Kety SS. 1957. The general metabolism of the brain in vivo. In: Richter D, ed. *Metabolism of the Nervous System.* London: Pergamon Press. Pp. 221–237.

Kiens B, Richter EA. 1996. Types of carbohydrate in an ordinary diet affect insulin action and muscle substrates in humans. *Am J Clin Nutr* 63:47–53.

King KC, Tserng K-Y, Kalhan SC. 1982. Regulation of glucose production in newborn infants of diabetic mothers. *Pediatr Res* 16:608–612.

Knopp RH, Saudek CD, Arky RA, O'Sullivan JB. 1973. Two phases of adipose tissue metabolism in pregnancy: Maternal adaptations for fetal growth. *Endocrinology* 92:984–988.

Kopp-Hoolihan LE, van Loan MD, Wong WW, King JC. 1999. Longitudinal assessment of energy balance in well-nourished, pregnant women. *Am J Clin Nutr* 69:697–704.

Krebs-Smith SM, Graubard BI, Kahle LL, Subar AF, Cleveland LE, Ballard-Barbash R. 2000. Low energy reporters vs. others: A comparison of reported food intakes. *Eur J Clin Nutr* 54:281–287.

Krezowski PA, Nuttall FQ, Gannon MC, Bartosh NH. 1986. The effect of protein ingestion on the metabolic response to oral glucose in normal individuals. *Am J Clin Nutr* 44:847–856.

Kushi LK, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R, Kevaney J. 1985. Diet and 20-year mortality from coronary heart disease. The Ireland–Boston Diet–Heart Study. *N Engl J Med* 312:811–888.

Laine DC, Thomas W, Levitt MD, Bantle JP. 1987. Comparison of predictive capabilities of diabetic exchange lists and glycemic index of foods. *Diabetes Care* 10:387–394.

Lammi-Keefe CJ, Ferris AM, Jensen RG. 1990. Changes in human milk at 0600, 1000, 1400, 1800, and 2200 h. *J Pediatr Gastroenterol Nutr* 11:83–88.

Landau BR, Wahren J, Chandramouli V, Schumann WC, Ekberg K, Kalhan SC. 1996. Contributions of gluconeogenesis to glucose production in the fasted state. *J Clin Invest* 98:378–385.

Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJR, Gibbs JM, Wise RJS, Hatazawa J, Herold S, Beaney RP, Brooks DJ, Spinks T, Rhodes C, Frackowiak RSJ, Jones T. 1990. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain* 113:27–47.

Levin RJ. 1999. Carbohydrates. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*, 9th ed. Baltimore, MD: Williams and Wilkins. Pp. 49–65.

Lewis CJ, Park YK, Dexter PB, Yetley EA. 1992. Nutrient intakes and body weights of persons consuming high and moderate levels of added sugars. *J Am Diet Assoc* 92:708–713.

Liljeberg HGM, Åkerberg AKE, Björck IME. 1999. Effect of the glycemic index and content of indigestible carbohydrates of cereal-based breakfast meals on glucose tolerance at lunch in healthy subjects. *Am J Clin Nutr* 69:647–655.

Lingstrom P, van Houte J, Kashket S. 2000. Food starches and dental caries. *Crit Rev Oral Biol Med* 11:366–380.

Liu K, Stamler J, Trevisan M, Moss D. 1982. Dietary lipids, sugar, fiber, and mortality from coronary heart disease. Bivariate analysis of international data. *Arteriosclerosis* 2:221–227.

Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE. 2000. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* 71:1455–1461.

Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. 2001. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr* 73:560–566.

Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. 1999. High glycemic index foods, overeating, and obesity. *Pediatrics* 103:E26.

Ludwig DS, Peterson KE, Gortmaker SL. 2001. Relation between consumption of sugar-sweetened drinks and childhood obesity: A prospective, observational analysis. *Lancet* 357:505–508.

Luscombe ND, Noakes M, Clifton PM. 1999. Diets high and low in glycemic index versus high monounsaturated fat diets: Effects on glucose and lipid metabolism in NIDDM. *Eur J Clin Nutr* 53:473–478.

Mackrell DJ, Sokal JE. 1969. Antagonism between the effects of insulin and glucagon on the isolated liver. *Diabetes* 18:724–732.

Macquart-Moulin G, Riboli E, Cornée J, Charnay B, Berthezène P, Day N. 1986. Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer* 38:183–191.

Macquart-Moulin G, Riboli E, Cornée J, Kaaks R, Berthezène P. 1987. Colorectal polyps and diet: A case-control study in Marseilles. *Int J Cancer* 40:179–188.

Mann JI, Truswell AS. 1972. Effects of isocaloric exchange of dietary sucrose and starch on fasting serum lipids, postprandial insulin secretion and alimentary lipaemia in human subjects. *Br J Nutr* 27:395–405.

Mann JI, Watermeyer GS, Manning EB, Randles J, Truswell AS. 1973. Effects on serum lipids of different dietary fats associated with a high sucrose diet. *Clin Sci* 44:601–604.

Marckmann P, Raben A, Astrup A. 2000. Ad libitum intake of low-fat diets rich in either starchy foods or sucrose: Effects on blood lipids, factor VII coagulant activity, and fibrinogen. *Metabolism* 49:731–735.

Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. 1992. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: Results of a 25-year follow-up study. *Lancet* 340:925–929.

Mascarenhas AK. 1998. Oral hygiene as a risk indicator of enamel and dentin caries. *Community Dent Oral Epidemiol* 26:331–339.

Mattes RD. 1996. Dietary compensation by humans for supplemental energy provided as ethanol or carbohydrate in fluids. *Physiol Behav* 59:179–187.

Maxwell JD, McKiddie MT, Ferguson A, Buchanan KD. 1970. Plasma insulin response to oral carbohydrate in patients with glucose and lactose malabsorption. *Gut* 11:962–965.

McDonagh MS, Whiting PF, Wilson PM, Sutton AJ, Chestnutt I, Cooper J, Misso K, Bradley M, Treasure E, Kleijnen J. 2000. Systemic review of water fluoridation. *Br Med J* 321:855–859.

McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. 1984. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. *Am J Epidemiol* 119:667–676.

Mehta S, Kalsi HK, Nain CK, Menkes JH. 1977. Energy metabolism of brain in human protein-calorie malnutrition. *Pediatr Res* 11:290–293.

Meyer KA, Kushi LH, Jacobs DR, Slavin J, Sellers TA, Folsom AR. 2000. Carbohydrates, dietary fiber, and incident of type 2 diabetes in older women. *Am J Clin Nutr* 71:921–930.

Miller AB, Howe GR, Jain M, Craib KJP, Harrison L. 1983. Food items and food groups as risk factors in a case-control study of diet and colorectal cancer. *Int J Cancer* 32:155–161.

Miller SL, Wolfe RR. 1999. Physical exercise as a modulator of adaptation to low and high carbohydrate and low and high fat intakes. *Eur J Clin Nutr* 53:S112–S119.

Miller WC, Lindeman AK, Wallace J, Niederpruem M. 1990. Diet composition, energy intake, and exercise in relation to body fat in men and women. *Am J Clin Nutr* 52:426–430.

Miller WC, Niederpruem MG, Wallace JP, Lindman AK. 1994. Dietary fat, sugar, and fiber predict body fat content. *J Am Diet Assoc* 94:612–615.

Morris KL, Zemel MB. 1999. Glycemic index, cardiovascular disease, and obesity. *Nutr Rev* 57:273–276.

Neville MC, Keller RP, Seacat J, Casey CE, Allen JC, Archer P. 1984. Studies on human lactation. I. Within-feed and between-breast variation in selected components of human milk. *Am J Clin Nutr* 40:635–646.

Newburg DS, Neubauer SH. 1995. Carbohydrates in milks: Analysis, quantities, and significance. In: Jensen RG, ed. *Handbook of Milk Composition*. New York: Academic Press. Pp. 273–349.

Nicklas TA, Myers L, Farris RP, Srinivasan SR, Berenson GS. 1996. Nutritional quality of a high carbohydrate diet as consumed by children: The Bogalusa Heart Study. *J Nutr* 126:1382–1388.

Nommsen LA, Lovelady CA, Heinig MJ, Lönnerdal B, Dewey KG. 1991. Determinants of energy, protein, lipid, and lactose concentrations in human milk during the first 12 mo of lactation: The DARLING Study. *Am J Clin Nutr* 53:457–465.

Nordli DR, Koenigsberger D, Schroeder J, deVivo DC. 1992. Ketogenic diets. In: Resor SR, Kutt H, eds. *The Medical Treatment of Epilepsy*. New York: Marcel Dekker. Pp. 455–472.

Nuttall FQ, Gannon MC. 1981. Sucrose and disease. *Diabetes Care* 4:305–310.

Nuttall FQ, Mooradian AD, Gannon MC, Billington C, Krezowski P. 1984. Effect of protein ingestion on the glucose and insulin response to a standardized oral glucose load. *Diabetes Care* 7:465–470.

Nuttall FQ, Gannon MC, Burmeister LA, Lane JT, Pyzdrowski KL. 1992. The metabolic response to various doses of fructose in type II diabetic subjects. *Metabolism* 41:510–517.

Okano G, Takeda H, Morita I, Katoh M, Mu Z, Miyake S. 1988. Effect of preexercise fructose ingestion on endurance performance in fed men. *Med Sci Sports Exerc* 20:105–109.

Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill GF. 1967. Brain metabolism during fasting. *J Clin Invest* 46:1589–1595.

Owen OE, Smalley KJ, D'Alessio DA, Mozzoli MA, Dawson EK. 1998. Protein, fat, and carbohydrate requirements during starvation: Anaplerosis and cataplerosis. *Am J Clin Nutr* 68:12–34.

Papas AS, Joshi A, Palmer CA, Giunta JL, Dwyer JT. 1995. Relationship of diet to root caries. *Am J Clin Nutr* 61:423S–429S.

Park YK, Yetley EA. 1993. Intakes and food sources of fructose in the United States. *Am J Clin Nutr* 58:737S–747S.

Parks EJ, Hellerstein MK. 2000. Carbohydrate-induced hypertriacylglycerolemia: Historical perspective and review of biological mechanisms. *Am J Clin Nutr* 71:412–433.

Patel D, Kalhan S. 1992. Glycerol metabolism and triglyceride-fatty acid cycling in the human newborn: Effect of maternal diabetes and intrauterine growth retardation. *Pediatr Res* 31:52–58.

Patel MS, Johnson CA, Rajan R, Owen OE. 1975. The metabolism of ketone bodies in developing human brain: Development of ketone-body-utilizing enzymes and ketone bodies as precursors for lipid synthesis. *J Neurochem* 25:905–908.

Phelps RL, Metzger BE, Freinkel N. 1981. Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol, and individual amino acids in late normal pregnancy. *Am J Obstet Gynecol* 140:730–736.

Raguso CA, Pereira P, Young VR. 1999. A tracer investigation of obligatory oxidative amino acid losses in healthy, young adults. *Am J Clin Nutr* 70:474–483.

Rath R, Masˇek J, Kujalová V, Slabochová Z. 1974. Effect of a high sugar intake on some metabolic and regulatory indicators in young men. *Nahrung* 18:343–353.

Reaven GM. 1999. Insulin resistance: A chicken that has come to roost. *Ann N Y Acad Sci* 892:45–57.

Reinmuth OM, Scheinberg P, Bourne B. 1965. Total cerebral blood flow and metabolism. *Arch Neurol* 12:49–66.

Reiser S, Hallfrisch J. 1987. *Metabolic Effects of Dietary Fructose.* Boca Raton, FL: CRC Press.

Reiser S, Hallfrisch J, Michaelis OE, Lazar FL, Martin RE, Prather ES. 1979a. Isocaloric exchange of dietary starch and sucrose in humans. I. Effects on levels of fasting blood lipids. *Am J Clin Nutr* 32:1659–1669.

Reiser S, Handler HB, Gardner LB, Hallfrisch JG, Michaelis OE, Prather ES. 1979b. Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. *Am J Clin Nutr* 32:2206–2216.

Reiser S, Powell AS, Scholfield DJ, Panda P, Ellwood KC, Canary JJ. 1989. Blood lipids, lipoproteins, apoproteins, and uric acid in men fed diets containing fructose or high-amylose cornstarch. *Am J Clin Nutr* 49:832–839.

Renner R, Elcombe AM. 1964. Factors affecting the utilization of "carbohydrate-free" diets by the chick. II. Level of glycerol. *J Nutr* 84:327–330.

Ritz P, Krempf M, Cloarec D, Champ M, Charbonnel B. 1991. Comparative continuous-indirect-calorimetry study of two carbohydrates with different glycemic indices. *Am J Clin Nutr* 54:855–859.

Robert J-J, Cummins JC, Wolfe RR, Durkot M, Matthews DE, Zhao XH, Bier DM, Young VR. 1982. Quantitative aspects of glucose production and metabolism in healthy elderly subjects. *Diabetes* 31:203–211.

Roberts SB. 2000a. A review of age-related changes in energy regulation and suggested mechanisms. *Mech Ageing Dev* 116:157–167.

Roberts SB. 2000b. High-glycemic index foods, hunger, and obesity: Is there a connection? *Nutr Rev* 58:163–169.

Roche HM. 1999. Dietary carbohydrates and triacylglycerol metabolism. *Proc Nutr Soc* 58:201–207.

Rodin J. 1991. Effects of pure sugar vs. mixed starch fructose loads on food intake. *Appetite* 17:213–219.

Rossetti L, Giaccari A, DeFronzo RA. 1990. Glucose toxicity. *Diabetes Care* 13:610–630.

Rudolf MCJ, Sherwin RS. 1983. Maternal ketosis and its effects on the fetus. *Clin Endocrinol Metab* 12:413–428.

Ryan EA, O'Sullivan MJ, Skyler JS. 1985. Insulin action during pregnancy. Studies with the euglycemic clamp technique. *Diabetes* 34:380–389.

Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC. 1997a. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 20:545–550.

Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. 1997b. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *J Am Med Assoc* 277:472–477.

Sapir DG, Owen OE, Cheng JT, Ginsberg R, Boden G, Walker WG. 1972. The effect of carbohydrates on ammonium and ketoacid excretion during starvation. *J Clin Invest* 51:2093–2102.

Saris WH, Astrup A, Prentice AM, Zunft HJ, Formiguera X, Verboeket-van de Venne WP, Raben A, Poppitt SD, Seppelt B, Johnston S, Vasilaras TH, Keogh GF. 2000. Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs. complex carbohydrates on body weight and blood lipids: The CARMEN study. *Int J Obes Relat Metab Disord* 24:1310–1318.

Sawaya AL, Fuss PJ, Dallal GE, Tsay R, McCrory MA, Young V, Roberts SB. 2001. Meal palatability, substrate oxidation and blood glucose in young and older men. *Physiol Behav* 72:5–12.

Scheinberg P, Stead EA. 1949. The cerebral blood flow in male subjects as measured by the nitrous oxide technique. Normal values for blood flow, oxygen utilization, glucose utilization, and peripheral resistance, with observations on the effect of tiliting and anxiety. *J Clin Invest* 28:1163–1171.

Settergren G, Lindblad BS, Persson B. 1976. Cerebral blood flow and exchange of oxygen, glucose, ketone bodies, lactate, pyruvate and amino acids in infants. *Acta Paediatr Scand* 65:343–353.

Settergren G, Lindblad BS, Persson B. 1980. Cerebral blood flow and exchange of oxygen, glucose, ketone bodies, lactate, pyruvate and amino acids in anesthetized children. *Acta Paediatr Scand* 69:457–465.

Shannon WR. 1922. Neuropathologic manifestations in infants and children as a result of anaphylactic reaction to foods contained in their diet. *Am J Dis Child* 24:89–94.

Shaw JH. 1987. Causes and control of dental caries. *N Engl J Med* 317:996–1004.

Slattery ML, Benson J, Berry TD, Duncan D, Edwards SL, Caan BJ, Potter JD. 1997. Dietary sugar and colon cancer. *Cancer Epidemiol Biomarkers Prev* 6:677–685.

Smith JB, Niven BE, Mann JI. 1996. The effect of reduced extrinsic sucrose intake on plasma triglyceride levels. *Eur J Clin Nutr* 50:498–504.

Sokoloff L. 1973. Metabolism of ketone bodies by the brain. *Annu Rev Med* 24:271–280.

Sokoloff L, Fitzgerald GG, Kaufman EE. 1977. Cerebral nutrition and energy metabolism. In: Wurtman RJ, Wurtman JJ, eds. *Nutrition and the Brain.* New York: Raven Press. Pp. 87–139.

Sparks JW, Girard JR, Battaglia FC. 1980. An estimate of the caloric requirements of the human fetus. *Biol Neonate* 38:113–119.

Sparks MJ, Selig SS, Febbraio MA. 1998. Pre-exercise carbohydrate ingestion: Effect of the glycemic index on endurance exercise performance. *Med Sci Sports Exerc* 30:844–849.

Speer F. 1954. The allergenic tension-fatigue syndrome. *Pediatr Clin North Am* 1:1029–1037.

Spieth LE, Harnish JD, Lenders CM, Raezer LB, Pereira MA, Hangen SJ, Ludwig DS. 2000. A low-glycemic index diet in the treatment of pediatric obesity. *Arch Pediatr Adolesc Med* 154:947–951.

Spitzer L, Rodin J. 1987. Effects of fructose and glucose preloads on subsequent food intake. *Appetite* 8:135–145.
Streja DA, Steiner G, Marliss EB, Vranic M. 1977. Turnover and recycling of glucose in man during prolonged fasting. *Metabolism* 26:1089–1098.
Sunehag AL, Haymond MW, Schanler RJ, Reeds PJ, Bier DM. 1999. Gluconeogenesis in very low birth weight infants receiving total parenteral nutrition. *Diabetes* 48:791–800.
Surwit RS, Feinglos MN, McCaskill CC, Clay SL, Babyak MA, Brownlow BS, Plaisted CS, Lin P-H. 1997. Metabolic and behavioral effects of a high-sucrose diet during weight loss. *Am J Clin Nutr* 65:908–915.
Swanson JE, Laine DC, Thomas W, Bantle JP. 1992. Metabolic effects of dietary fructose in healthy subjects. *Am J Clin Nutr* 55:851–856.
Swink TD, Vining EPG, Freeman JM. 1997. The ketogenic diet: 1997. *Adv Pediatr* 44:297–329.
Thomas DE, Brotherhood JR, Brand JC. 1991. Carbohydrate feeding before exercise: Effect of glycemic index. *Int J Sports Med* 12:180–186.
Tillotson JL, Grandits GA, Bartsch GE, Stamler J. 1997. Relation of dietary carbohydrates to blood lipids in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *Am J Clin Nutr* 65:314S–326S.
Troiano RP, Briefel RR, Carroll MD, Bialostosky K. 2000. Energy and fat intakes of children and adolescents in the United States: Data from the National Health and Nutrition Examination Surveys. *Am J Clin Nutr* 72:1343S–1353S.
Tuyns AJ, Kaaks R, Haelterman M. 1988. Colorectal cancer and the consumption of foods: A case-control study in Belgium. *Nutr Cancer* 11:189–204.
USDA (U.S. Department of Agriculture). 1996. *The Food Guide Pyramid.* Home and Garden Bulletin No. 252. Washington, DC: U.S. Government Printing Office.
USDA/HHS (U.S. Department of Agriculture/U.S. Department of Health and Human Services). 2000. *Nutrition and Your Health: Dietary Guidelines for Americans.* Home and Garden Bulletin No. 232. Washington, DC: U.S. Government Printing Office.
van Dam RM, Visscher AWJ, Feskens EJM, Verhoef P, Kromhout D. 2000. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: The Zutphen Elderly Study. *Eur J Clin Nutr* 54:726–731.
Vining EPG. 1999. Clinical efficacy of the ketogenic diet. *Epilepsy Res* 37:181–190.
Walker ARP, Cleaton-Jones PE. 1992. Sugar intake and dental caries. *Br Dent J* 172:7.
Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. 1990. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med* 113:909–915.
Welsh S, Davis C, Shaw A. 1992. Development of the Food Guide Pyramid. *Nutr Today* 27:12–23.
Westphal SA, Gannon MC, Nuttall FQ. 1990. Metabolic response to glucose ingested with various amounts of protein. *Am J Clin Nutr* 52:267–272.
White JW, Wolraich M. 1995. Effect of sugar on behavior and mental performance. *Am J Clin Nutr* 62:242S–249S.
Wolever TMS. 1990. Relationship between dietary fiber content and composition in foods and the glycemic index. *Am J Clin Nutr* 51:72–75.
Wolever TMS, Jenkins DJA. 1986. The use of the glycemic index in predicting the blood glucose response to mixed meals. *Am J Clin Nutr* 43:167–172.

Wolever TMS, Nuttal FQ, Lee R, Wong GS, Josse RG, Csima A, Jenkins DJA. 1985. Prediction of the relative blood glucose response of mixed meals using the white bread glycemic index. *Diabetes Care* 8:418–428.

Wolever TMS, Jenkins DJA, Josse RG, Wong GS, Lee R. 1987. The glycemic index: Similarity of values derived in insulin-dependent and non-insulin-dependent diabetic patients. *J Am Coll Nutr* 6:295–305.

Wolever TMS, Jenkins DJA, Ocana AM, Rao VA, Collier GR. 1988. Second-meal effect: Low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. *Am J Clin Nutr* 48:1041–1047.

Wolever TMS, Jenkins DJA, Vuksan V, Josse RG, Wong GS, Jenkins AL. 1990. Glycemic index of foods in individual subjects. *Diabetes Care* 13:126–132.

Wolever TMS, Jenkins DJA, Jenkins AL, Josse RG. 1991. The glycemic index: Methodology and clinical implications. *Am J Clin Nutr* 54:846–854.

Wolever TMS, Jenkins DJA, Vuksan V, Jenkins AL, Buckley GC, Wong GS, Josse RG. 1992a. Beneficial effect of a low glycaemic index diet in type 2 diabetes. *Diabet Med* 9:451–458.

Wolever TMS, Jenkins DJA, Vuksan V, Jenkins AL, Wong GS, Josse RG. 1992b. Beneficial effect of low-glycemic index diet in overweight NIDDM subjects. *Diabetes Care* 15:562–564.

Wolraich ML, Wilson DB, White JW. 1995. The effect of sugar on behavior or cognition in children. A meta-analysis. *J Am Med Assoc* 274:1617–1621.

World Cancer Research Fund/American Institute for Cancer Research. 1997. *Food, Nutrition and the Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research.

Yamaura H, Ito M, Kubota K, Matsuzawa T. 1980. Brain atrophy during aging: A quantitative study with computed tomography. *J Gerontol* 35:492–498.

Yudkin J, Eisa O, Kang SS, Meraji S, Bruckdorfer KR. 1986. Dietary sucrose affects plasma HDL cholesterol concentration in young men. *Ann Nutr Metab* 30:261–266.

Ziegler EE, Fomon SJ. 1983. Lactose enhances mineral absorption in infancy. *J Pediatr Gastroenterol Nutr* 2:288–294.