Choline[1,2]

Choline has several important functions. It is a source of methyl groups needed to make the primary methyl donor, *S*-adenosylmethionine; a part of the neurotransmitter acetylcholine; and a component of the predominant phospholipids in membranes (phosphatidylcholine and sphingomyelin) (1). The choline derivative, phosphatidylcholine, is a main constituent of VLDL and is required for VLDL secretion and the export of fat from liver (2). Betaine, formed from choline, is an important osmolyte in the kidney glomerulus and helps with the reabsorption of water from the kidney tubule (3). The choline moiety can be produced endogenously when phosphatidylcholine is formed from phosphatidylethanolamine, mainly in the liver. Despite this capacity to form choline in liver, most men and postmenopausal women need to consume choline in their diets (4); the gene for the enzyme catalyzing this biosynthesis is induced by estrogen (5) and some young nonpregnant women may not need to eat choline (4). Genetic polymorphisms in genes of choline metabolism increase the dietary requirement for choline and almost one-half of young women have a gene polymorphism that makes choline biosynthesis unresponsive to estrogen, making these women's dietary choline requirement similar to men's.

Deficiencies: Healthy humans with normal folate and vitamin B-12 status who were fed a choline-deficient diet developed fatty liver, liver damage [elevated plasma alanine (or aspartate) transaminase] or developed muscle damage (elevated creatine phosphokinase) that resolved when choline was restored to the diet (4,6). Elevations in markers of DNA damage (7) and alterations in lymphocyte gene expression (8) were also observed in choline deficiency. During pregnancy, women in the lowest quartile of dietary choline intake had a higher risk of having a baby with a neural tube defect (NTD)[3] or cleft palate (9,10). In rodent models, maternal dietary choline influences brain development in the fetus (11,12) and increases the prevalence of heart defects (13).

Diet recommendations: In 1998, the U.S. Institute of Medicine's Food and Nutrition Board established an Adequate Intake (AI) and a Tolerable Upper Limit (UL) for choline (14). The AI is 425 and 550 mg/d for women and men, respectively, with more recommended during pregnancy and lactation. The AI for infants is estimated from the calculated intake from human breast milk.

Food sources: Choline and esters of choline are widely distributed in food; however, animal products generally contain more choline per unit weight than plants. Eggs, beef, chicken, fish, and milk as well as select plant foods like cruciferous vegetables and certain beans are particularly good sources of choline providing at least 10% of the daily requirement per serving (15–18). Humans consuming an ad libitum diet ingest between 150 and 600 mg choline/d as free choline and choline esters (10,19–23). In the 2005 NHANES study, only a small portion of Americans in all age groups ate diets that met the recommended intake for choline (24). Foods also contain the choline metabolite betaine (17), which cannot be converted to choline but can be used as a methyl donor, thereby sparing some choline requirements (25,26). Plant-derived foods can be a rich source of betaine (named after beets), with grain products being particularly good sources.

Clinical uses: Hepatic complications associated with total parenteral nutrition (TPN), which include fatty infiltration of the liver and hepatocellular damage, have been reported by many clinical groups. Frequently, TPN must be terminated because of the severity of the associated liver disease. Amino acid-glucose solutions used in TPN of humans contain no choline. The lipid emulsions used to deliver extra calories and essential fatty acids during parenteral nutrition contain choline in the form of phosphatidylcholine (20% emulsion contains 13.2 mmol/L). Some of the liver disease associated with TPN is related to choline deficiency and is prevented with supplemental choline or phosphatidylcholine (27–31). Thus, choline is an essential nutrient during long-term TPN.

Toxicity: The UL for choline was derived from the lowest observed adverse effect level (hypotension) in humans and is 3.5 g/d for an adult (14).

Recent research: Genetic variation likely underlies these differences in dietary requirements for choline. As discussed earlier, several metabolic pathways influence how much choline is required from diet, and single nucleotide polymorphisms in specific genes influence the efficiency of these pathways. Specifically, some polymorphisms in the folate pathways limit the availability of methyltetrahydrofolate and thereby increase the use of choline as a methyl donor, polymorphisms in the *PEMT* gene alter endogenous synthesis of choline, and polymorphisms in other genes of choline metabolism influence dietary requirements by changing the utilization of choline moiety (32,33).

In men, intakes exceeding the choline AI are needed to optimize homocysteine disposal after a methionine load as well as the removal of fat from liver (34). A choline intake exceeding current dietary recommendations was also shown to preserve markers of cellular methylation and attenuate DNA damage in a genetic subgroup of folate-compromised men (35).

Epidemiological studies have linked low dietary choline intake to higher concentrations of proinflammatory markers (36,37) as well as to increased risk of breast cancer (14) and to having a baby with a NTD (7). Elevated NTD risk was also associated with lower concentrations of serum total choline in a folate-fortified population (38). Additionally, genetic variants in choline metabolizing enzymes are associated with excess risk of NTD (39) and altered risk of breast cancer (40).

A recent study in a mouse model of Down Syndrome reported improvements in cognitive function and emotion regulation in

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Table 1. Dietary Reference Intake values for choline

Population	Age	AI	UL
AI for infants	0–6 mo	125 mg/d, 18 mg/kg	Not possible to establish[1]
	6–12 mo	150 mg/d	
AI for children	1–3 y	200 mg/d	1000 mg/d
	4–8 y	250 mg/d	1000 mg/d
	9–13 y	375 mg/d	2000 mg/d
AI for males	14–18 y	550 mg/d	3000 mg/d
	≥19 y	550 mg/d	3500 mg/d
AI for females	14–18 y	400 mg/d	3000 mg/d
	≥19 y	425 mg/d	3500 mg/d
AI for pregnancy	All ages	450 mg/d	Age-appropriate UL
AI for lactation	All ages	550 mg/d	Age-appropriate UL

[1]Source of intake should be food and formula only. From (14).

mice born to mothers supplemented with choline during the perinatal period (41). This work expands upon earlier work in rodents showing that extra exposure to choline during the perinatal period yielded long lasting beneficial effects on memory, learning and attention (42).

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[3]Abbreviations used: AI, Adequate Intake; NTD, neural tube defect; TPN, total parenteral nutrition; UL, Tolerable Upper Limit.

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