

Choline

Nutrient

Choline has several important functions. These are as follows: 1) it is a source of the methyl groups needed to make the primary methyl donor *S*-adenosylmethionine, 2) it is a part of the neurotransmitter acetylcholine, and 3) it is a component of the major phospholipids in membranes [phosphatidylcholine (PC) and sphingomyelin] (1). PC is a main constituent of VLDLs and is required for their secretion and the export of fat from the liver (1). Choline is also important for normal fetal development (2, 3). Betaine, formed from the oxidation of choline, is an important osmolyte in the kidney glomerulus and helps with the reabsorption of water from the kidney tubule (4). The choline moiety can be produced endogenously through the phosphatidylethanolamine *N*-methyltransferase (PEMT) pathway, whereby PC is formed from phosphatidylethanolamine (mainly in the liver). Despite this capacity to form choline in the liver, most people need to consume choline in their diets (5), though premenopausal women need to eat less choline unless they have common genetic polymorphisms affecting estrogen-induced PEMT expression (6, 7).

Deficiencies

Healthy humans with normal folate and vitamin B-12 status who were fed a choline-deficient diet developed fatty liver disease, liver damage [elevated plasma alanine (or aspartate) transaminase] or muscle damage (elevated creatine phosphokinase), which resolved when choline was restored to the diet (5). Prolonged inadequate intake of choline may predispose individuals to nonalcoholic fatty liver disease and cognitive decline (1, 5, 9, 19). In rodent models, pregnancy depletes liver stores of choline metabolites and the maternal dietary choline intake influences brain development in the fetus (12) and the prevalence of heart defects in the mother (13). Notably, supplementing the maternal diet with additional choline has a long-lasting beneficial effect on offspring cognition in multiple animal models (14). Limited evidence has characterized choline needs during human pregnancy. Women fed controlled diets containing the current Adequate Intake (AI) recommendation for pregnancy exhibited reductions in circulating one-carbon metabolites. Several randomized controlled trials have shown a beneficial effect of maternal choline supplementation on offspring neurocognitive outcome (8, 15).

Dietary Recommendations

In 1998, the US Institute of Medicine's Food and Nutrition Board established the AI and Tolerable Upper Limit (UL) for

Abbreviations used: AI, Adequate Intake; PC, phosphatidylcholine; TMAO, trimethylamine *N*-oxide; UL, Tolerable Upper Limit.

TABLE 1 Dietary reference intake values for choline¹

Population	Age	AI, mg/d	UL, mg/d
Infants	0–6 mo	125 (18 mg/kg)	Not possible to establish ²
	6–12 mo	150	Not possible to establish ²
Children	1–3 y	200	1000
	4–8 y	250	1000
	9–13 y	375	2000
Males	14–18 y	550	3000
	≥19 y	550	3500
Females	14–18 y	400	3000
	≥19 y	425	3500
Pregnancy	All ages	450	Age-appropriate UL
Lactation	All ages	550	Age-appropriate UL

¹AI, Adequate Intake; UL, Tolerable Upper Limit.

²Source of intake should be food and formula only. Data obtained from the Institute of Medicine (9).

choline (Table 1) (9). The AI for infants is estimated from the calculated intake from human breast milk.

Dietary 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 ≥10% of the daily requirement per serving (10). There is a wide variation in choline intake in the diet, with nationally representative data showing that only 11% of adult Americans achieve the AI for choline (11).

Foods also contain the choline metabolite betaine (10), which cannot be converted to choline but can be used as a methyl donor, thereby sparing some choline requirements (10). Plant-derived food sources can be a rich source of betaine (named after beets), with grain products being particularly good sources. Many prepackaged foods add lecithin (i.e., phosphatidylcholine) and thus contribute to total dietary choline intakes. Few commercially available multivitamin supplements, including prenatal vitamins, include choline; those that do contain only small quantities (25–50 mg).

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 (9).

Clinical Uses

Hepatic complications associated with total parenteral nutrition, which include fatty infiltration of the liver and hepatocellular damage, have been reported by many clinical groups. Some of this liver disease associated with total parenteral nutrition is related to choline deficiency and is prevented with supplemental choline or phosphatidylcholine (16). Specific medical conditions, such as cystic fibrosis, increase daily choline losses and likely increase choline needs (17, 18).

Recent Research

Common genetic variants in choline and folate metabolic enzymes influence the risk of choline inadequacy and the metabolic fate of dietary choline across different life stages and nutrient intakes (7, 19, 20). Single nucleotide polymorphisms, such as rs12325817 and rs4646343 in the *PEMT* gene and rs2236225 in the *MTHFD1* gene, influence the risk of choline deficiency and the partitioning of choline towards oxidation or phosphatidylcholine production (19, 21).

Emerging evidence has highlighted a role for maternal choline supplementation in promoting placental health (22–25) and in reducing placental production of corticotropin-releasing hormone via epigenetic mechanisms (3). In addition to choline's role during pregnancy, emerging research demonstrates that higher choline intakes during lactation improve breast milk choline content (26, 27) and that the form of choline in the maternal diet influences the development of the offspring's immune system (28, 29).

Higher self-reported dietary choline intakes have been linked to lower concentrations of proinflammatory markers (30), a less metabolically deleterious distribution of body fat (31), and a lower risk of developing lung and breast cancer. However, diets high in choline have also been associated with an increased risk for prostate cancer progression (32) and for colorectal adenomas (33).

Recent interest has focused on the gut microbiome-derived choline metabolite trimethylamine *N*-oxide (TMAO) and its role in diabetes, chronic kidney disease, and cardiovascular disease [reviewed by Zeisel and Warriar (34) and Cho and Caudill (35)]. Numerous animal models have suggested that high TMAO levels are prothrombotic or proatherogenic, contribute to obesity and impaired glucose intolerance, and induce renal damage. Whether TMAO is a causal factor involved in the development or progression of chronic diseases in humans requires further randomized controlled trial evidence. Research to understand how common food sources interact with the gut microbiome to influence plasma TMAO responses is ongoing.

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