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

TABLE 1 Dietary reference intake values for choline[1]

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

[1] AI, Adequate Intake; UL, Tolerable Upper Limit.
[2] Source of intake should be food and formula only. Data obtained from the Institute of Medicine (9).

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).

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

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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 Warrier (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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References

1. Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. Annu Rev Nutr 2006;26:229–50.
2. Zeisel SH. Importance of methyl donors during reproduction. Am J Clin Nutr 2009;89:673S–7S.
3. Jiang X, Yan J, West AA, Perry CA, Malysheva OV, Devapatla S, Pressman E, Vermeylen F, Caudill MA. Maternal choline intake alters the epigenetic state of fetal cortisol-regulating genes in humans. FASEB J 2012;26:3563–74.
4. Kempson SA, Montrose MH. Osmotic regulation of renal betaine transport: transcription and beyond. Pflugers Arch 2004;449:227–34.
5. Fischer LM, daCosta K, Kwock L, Stewart P, Lu T-S, Stabler S, Allen R, Zeisel S. Sex and menopausal status influence human dietary requirements for the nutrient choline. Am J Clin Nutr 2007;85:1275–85.
6. Resseguie ME, da Costa KA, Galanko JA, Patel M, Davis IJ, Zeisel SH. Aberrant estrogen regulation of PEMT results in choline deficiency-associated liver dysfunction. J Biol Chem 2011;286:1649–58.
7. Ganz AB, Klatt KC, Caudill MA. Common genetic variants alter metabolism and influence dietary choline requirements. Nutrients 2017;9:837.
8. Coles CD, Kable JA, Keen CL, Jones KL, Wertelecki W, Granovska IV, Pashtepa AO, Chambers CD, Cifasd. Dose and timing of prenatal alcohol exposure and maternal nutritional supplements: developmental effects on 6-month-old infants. Matern Child Health J 2015;19:2605–14.
9. Institute of Medicine, National Academy of Sciences USA. Choline. Dietary reference intakes for folate, thiamin, riboflavin, niacin, vitamin B12, panthothenic acid, biotin, and choline. Washington D.C.: National Academy Press, 1998:390–422.
10. Zeisel SH, Mar MH, Howe JC, Holden JM. Concentrations of choline-containing compounds and betaine in common foods. J Nutr 2003;133:1302–7.
11. Wallace TC, Fulgoni VL 3rd. Assessment of total choline intakes in the United States. J Am Coll Nutr 2016;35:108–12.
12. Wang Y, Surzenko N, Friday WB, Zeisel SH. Maternal dietary intake of choline in mice regulates development of the cerebral cortex in the offspring. FASEB J 2016;30:1566–78.
13. Chan J, Deng L, Mikael LG, Yan J, Pickell L, Wu Q, Caudill MA, Rozen R. Low dietary choline and low dietary riboflavin during pregnancy influence reproductive outcomes and heart development in mice. Am J Clin Nutr 2010;91:1035–43.
14. Meck WH, Williams CL, Cermak JM, Blusztajn JK. Developmental periods of choline sensitivity provide an ontogenetic mechanism for regulating memory capacity and age-related dementia. Front Integr Neurosci 2007;1:7.
15. Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, Leonard S, Stevens KE, Freedman R. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. Am J Psychiatry 2013;170:290–8.
16. Buchman AL, Ament ME, Sohel M, Dubin M, Jenden DJ, Roch M, Pownall H, Farley W, Awal M, Ahn C. Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: proof of a human choline requirement: a placebo-controlled trial. J Parenter Enteral Nutr 2001;25:260–8.

17. Schall JI, Mascarenhas MR, Maqbool A, Dougherty KA, Elci O, Wang DJ, Altes TA, Hommel KA, Shaw W, Moore J, et al. Choline supplementation with a structured lipid in children with cystic fibrosis: a randomized placebo-controlled trial. J Pediatr Gastroenterol Nutr 2016;62:618–26.
18. Innis SM, Davidson AG, Chen A, Dyer R, Melnyk S, James SJ. Increased plasma homocysteine and S-adenosylhomocysteine and decreased methionine is associated with altered phosphatidylcholine and phosphatidylethanolamine in cystic fibrosis. J Pediatr 2003;143:351–6.
19. Kohlmeier M, da Costa KA, Fischer LM, Zeisel SH. Genetic variation of folate-mediated one-carbon transfer pathway predicts susceptibility to choline deficiency in humans. Proc Natl Acad Sci U S A 2005;102:16025–30.
20. da Costa KA, Corbin KD, Niculescu MD, Galanko JA, Zeisel SH. Identification of new genetic polymorphisms that alter the dietary requirement for choline and vary in their distribution across ethnic and racial groups. FASEB J 2014;28:2970–8.
21. Ganz AB, Cohen VV, Swersky CC, Stover J, Vitiello GA, Lovesky J, Chuang JC, Shields K, Fomin VG, Lopez YS, et al. Genetic variation in choline-metabolizing enzymes alters choline metabolism in young women consuming choline intakes meeting current recommendations. Int J Mol Sci 2017;18:252.
22. Jiang X, Bar HY, Yan J, Jones S, Brannon PM, West AA, Perry CA, Ganti A, Pressman E, Devapatla S, et al. A higher maternal choline intake among third-trimester pregnant women lowers placental and circulating concentrations of the antiangiogenic factor fms-like tyrosine kinase-1 (sFLT1). FASEB J 2013;27:1245–53.
23. Jiang X, Jones S, Andrew BY, Ganti A, Malysheva OV, Giallourou N, Brannon PM, Roberson MS, Caudill MA. Choline inadequacy impairs trophoblast function and vascularization in cultured human placental trophoblasts. J Cell Physiol 2014;229: 1016–27.
24. King JH, Kwan STC, Yan J, Klatt KC, Jiang X, Roberson MS, Caudill MA. Maternal choline supplementation alters fetal growth patterns in a mouse model of placental insufficiency. Nutrients 2017;9:765.
25. Kwan STC, King JH, Yan J, Jiang X, Wei E, Fomin VG, Roberson MS, Caudill MA. Maternal choline supplementation during murine pregnancy modulates placental markers of inflammation, apoptosis and vascularization in a fetal sex-dependent manner. Placenta 2017;53:57–65.
26. Davenport C, Yan J, Taesuwan S, Shields K, West AA, Jiang X, Perry CA, Malysheva OV, Stabler SP, Allen RH, et al. Choline intakes exceeding recommendations during human lactation improve breast milk choline content by increasing PEMT pathway metabolites. J Nutr Biochem 2015;26:903–11.
27. Fischer LM, da Costa KA, Galanko J, Sha W, Stephenson B, Vick J, Zeisel SH. Choline intake and genetic polymorphisms influence choline metabolite concentrations in human breast milk and plasma. Am J Clin Nutr 2010;92:336–46.
28. Dellschaft NS, Richard C, Lewis ED, Goruk S, Jacobs RL, Curtis JM, Field CJ. The dietary form of choline during lactation affects maternal immune function in rats. Eur J Nutr 2017 Jun 30. doi: 10.1007/s00394-017-1493-0. [Epub ahead of print].
29. Lewis ED, Richard C, Goruk S, Wadge E, Curtis JM, Jacobs RL, Field CJ. Feeding a mixture of choline forms during lactation improves offspring growth and maternal lymphocyte response to ex vivo immune challenges. Nutrients 2017;9713.
30. Detopoulou P, Panagiotakos DB, Antonopoulou S, Pitsavos C, Stefanadis C. Dietary choline and betaine intakes in relation to concentrations of inflammatory markers in healthy adults: the ATTICA study. Am J Clin Nutr 2008;87:424–30.
31. Gao X, Wang Y, Randell E, Pedram P, Yi Y, Gulliver W, Sun G. Higher dietary choline and betaine intakes are associated with better body composition in the adult population of Newfoundland, Canada. PLoS One 2016;11:e0155403.
32. Richman EL, Kenfield SA, Stampfer MJ, Giovannucci EL, Zeisel SH, Willett WC, Chan JM. Choline intake and risk of lethal prostate cancer: incidence and survival. Am J Clin Nutr 2012;96:855–63.
33. Cho E, Willett WC, Colditz GA, Fuchs CS, Wu K, Chan AT, Zeisel SH, Giovannucci EL. Dietary choline and betaine and the risk of distal colorectal adenoma in women. J Natl Cancer Inst 2007;99:1224–31.
34. Zeisel SH, Warrier M. Trimethylamine N-oxide, the microbiome, and heart and kidney disease. Annu Rev Nutr 2017;37:157–81.
35. Cho CE, Caudill MA. Trimethylamine-N-oxide: friend, foe, or simply caught in the cross-fire? Trends Endocrinol Metab 2017;28:121–30.