Choline intake and its dietary reference values in Korea and other countries: a review

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ABSTRACT

Choline is a water-soluble organic compound that is important for the normal functioning of the body. It is an essential dietary component as de novo synthesis by the human body is insufficient. Since the United States set the Adequate Intakes (AIs) for total choline as dietary reference values in 1998, Australia, China, and the European Union have also established the choline AIs. Although choline is clearly essential to life, the 2020 Dietary Reference Intakes for Koreans (KDRIs) has not established the values because very few studies have been done on choline intake in Koreans. Since choline intake levels differ by race and country, human studies on Koreans are essential to set KDRIs. Therefore, the present study was undertaken to provide basic data for developing choline KDRIs in the future by analyzing data on choline intake in Koreans to date and reference values of choline intake and dietary choline intake status by country and race.

Keywords: Choline intake; Dietary Reference Intakes; Koreans

INTRODUCTION

Choline belongs to the family of water-soluble quaternary ammonium compounds [1]. Synthesis of 2-Hydroxy-\(N,N,N\)-trimethylethan-1-aminium can be achieved de novo in the human body [2]. Choline is considered an essential nutrient in diets since the body produces insufficient quantities for physiological functions [3]. The United States Institute of Medicine (IOM) has officially recognized choline as an essential nutrient and set the Adequate Intakes (AIs) for total choline as dietary reference values since 1998 [4]. Choline AIs were also estimated by the Australian National Health and Medical Research Council (NHMRC) in 2006 [5], the Chinese Nutrition Society (CNS) in 2013 [6], and the European Food Safety Authority (EFSA) in 2016 [7].

Choline and its derivatives have several important functions in the human body, including maintaining the structural integrity of cell membranes and transmembrane signaling, cholinergic neurotransmission, lipid and cholesterol transport, and methyl-group donation in methylation [8-10]. Because of its varied roles in human metabolism, choline deficiency or
excess intake might be involved in diverse diseases such as non-alcoholic fatty liver disease [11,12], atherosclerosis [13,14], neurological disorders [15,16], and cancers [17-19].

In the endogenous pathway for choline biosynthesis, phosphatidylethanolamine is methylated by S-adenosylmethionine as a methyl donor [2]. Thus, dietary choline requirements are affected by the metabolic methyl-exchange relationship between choline and three nutrients: methionine, folate, and vitamin B12 [8]. The necessity of choline can be determined when these nutrients are in sufficient amounts to sustain normal physiological functions [8,20].

A reference for choline intake is required in Korea due to the increasing interest in choline and the availability of various choline supplements and choline-added foods. However, scientific databases for choline contents in Korean daily foods and choline intake data in Koreans are still lacking, despite numerous studies in the Western countries on choline essentiality and its association with diseases. A systematic literature review on choline was conducted for addition to the 2020 Dietary Reference Intakes for Koreans (KDRIs). However, the committee withheld the setting of choline Dietary Reference Intakes (DRIs) because there was an insufficient scientific basis for establishing its reference intake. The present study aims to provide basic data by analyzing reference values of choline intake and dietary choline intake status by country.

**REFERENCE VALUES OF CHOLINE INTAKE BY COUNTRY**

The U.S. Food and Nutrition Board of the IOM established the AIs for total choline in 1998 as part of the reference values set for nutrient intakes for healthy populations [4]. AIs were estimated due to insufficient data to derive the Estimated Average Requirements (EARs) for choline. Similarly, the Australian NHMRC [5], the CNS [6], and the EFSA [7] also estimated the reference intake for choline as AIs (Table 1).

Choline AIs of the IOM were estimated to be 125 mg/day for infants aged 0–6 months based on the volume of milk consumed and its total choline content [21,22], and at 150 mg/day for

| Table 1. DRI for choline (mg/d) | IOM, USA (1998) | NHMRC, Australia (2006) | EFSA, EU (2016) | CNS, China (2013) |
|--------------------------------|----------------|--------------------------|----------------|-----------------|
| Subject                        | AI     | UL | Subject | AI     | UL | Subject | AI | Subject | AI | Subject | AI | UL |
| Age                             |        |    | Age     |        |    | Age     |        | Age     |        | Age     |        |    |
| 0–6 mon                         | 125    | -  | 0–6 mon | 125    | -  | 0–6 mon | 120   | 0–5 mon | 120 | 0–5 mon | 120 | -  |
| 7–12 mon                        | 150    | -  | 7–12 mon| 150    | -  | 7–11 mon| 160   | 6–12 mon| 150 | 6–12 mon| 150 | -  |
| 1–3 yrs                         | 200    | 1,000 | 1–3 yrs | 200    | 1,000| 1–3 yrs | 140   | 1–3 yrs | 200 | 1–3 yrs | 200 | 1,000 |
| 4–8 yrs                         | 250    | 1,000| 4–8 yrs | 250    | 1,000| 4–6 yrs | 170   | 4–6 yrs | 250 | 4–6 yrs | 250 | 1,000 |
| 9–13 yrs                        | 375    | 2,000| 9–13 yrs| 375    | 2,000| 7–10 yrs| 250   | 7–10 yrs| 300 | 7–10 yrs| 300 | 1,500 |
| 14–18 yrs                       | 550    | 3,000| 14–18 yrs| 550   | 3,000| 11–14 yrs| 340  | 11–13 yrs| 400 | 11–13 yrs| 400 | 2,000 |
| ≥ 19 yrs                        | 550    | 3,500| ≥ 19 yrs| 550   | 3,500| 15–17 yrs| 400  | 14–17 yrs| 500 | 14–17 yrs| 500 | 2,500 |
| Adult                           |        |    | Adult   | 400    | 3,000| Adult   |        | Adult   | 500 | Adult   | 500 | 3,000 |
| Pregnant                        |        |    | Pregnant| 480    | -  | +20     | 3,000 |        |      |        |      |    |
| ≤ 18 yrs                        | -      | 3,000| ≤ 18 yrs| -      | 3,000| ≤ 18 yrs| -      | 3,000   | -  |       |      |    |
| 19–50 yrs                       | -      | 3,500| 19–50 yrs| -      | 3,500| 19–50 yrs| -      | 3,500   | -  |       |      |    |
| Breastfeeding                   |        |    | Breastfeeding| 520 |    | Breastfeeding | 3,000 |    |       |      |    |
| ≤ 18 yrs                        | -      | 3,000| ≤ 18 yrs| -      | 3,000| ≤ 18 yrs| -      | 3,000   | -  |       |      |    |
| 19–50 yrs                       | -      | 3,500| 19–50 yrs| -      | 3,500| 19–50 yrs| -      | 3,500   | -  |       |      |    |

IOM, Institute of Medicine; NHMRC, National Health and Medical Research Council; CNS, Chinese Nutrition Society; EFSA, European Food Safety Authority.

*Not possible to establish.
infants aged 7–12 mon by extrapolation from the early infancy body weight [23]. Similarly, the NHMRC set the AIs to be 125 mg/day for infants aged 0–6 mon [21,22] and 150 mg/day for infants aged 7–12 mon. The EFSA estimated the AI to be 160 mg/day for infants aged 7–11 mon by upwards extrapolation by allometric scaling from choline intake of exclusively breastfed infants aged 0–6 mon with AI of 120 mg/day [24]. AIs for children and adolescents of all 3 institutions (the IOM, the NHMRC, and the EFSA) were extrapolated using the body weights of adults and growth factors [25,26]. For children and adolescents, the AIs estimated by both the IOM and the NHMRC were the same, and were set according to gender. However, AIs of the EFSA were not established by gender.

For choline AIs, major difference was obtained in values for adults between the IOM and the NHMRC compared to the EFSA. The IOM and the NHMRC estimated choline AIs to be 550 mg/day for male adults and 425 mg/day for female adults based on the amount (7 mg/kg/day) that could prevent liver damage as assessed by measuring serum alanine aminotransferase levels [20]. The EFSA set a lower AI of 400 mg/day for both male and female adults based on the mean choline intake observed for healthy populations [27], which is also the amount needed to replete most of the depleted subjects with liver/muscle damage [12].

For pregnant women of all ages and any trimester, the IOM estimated the AI to be 450 mg/day based on fetal and placental choline accumulation [28,29], and the EFSA set the AI to be 480 mg/day using isometric scaling and the mean gestational increase in body weight [7]. In contrast, the NHMRC set different values by age group for pregnant women: 415 mg/day for ages 14–18 yrs and 440 mg/day for ages 19 yrs or older. The IOM set the AI to be 550 mg/day for lactating women of all ages, while the NHMRC set AIs to be 525 mg/day for ages 14–18 yrs and 550 mg/day for ages 19 years and above. AIs for lactating women set by the IOM, the NHMRC, and the EFSA were calculated as AIs for non-lactating adult women plus the choline amount secreted in mature milk during the first 6 mon.

Data used to set the Tolerable Upper Intake Levels (ULs) by the IOM and the NHMRC included a single case report of hypotension [30] and several studies involving cholinergic effects and body odor effects after large choline doses [31-34]. The IOM and the NHMRC considered 7.5 g/day of choline as the Lowest Observed Adverse Effect Level (LOAEL). After application of an uncertainty factor of 2 and rounding, the UL of 3.5 g choline/day for adults was established. There are no data to suggest that there is increased susceptibility during pregnancy or lactation; therefore, the ULs remained the same. No UL was established for infants, whereas the ULs for children and adolescents were derived from adult values by allometric scaling according to reference body weights [35,36]. The EFSA did not consider ULs for choline.

**INTAKE OF CHOLINE IN KOREANS**

In the assessment by Jeong et al. [35], dietary choline intake of the Korean population in 1998 and 2001 was estimated by gender and age using nationwide data on per capita food intakes obtained from the Korea National Health and Nutrition Examination Survey (KNHANES) (Fig. 1). The average dietary choline intake by Koreans was 623.0 mg/day (687.2 mg/day for men and 560.2 mg/day for women) in 1998, and 602.4 mg/day (659.1 mg/day for men and 551.0 mg/day for women) in 2001. Dietary choline intakes of men were overall higher than in women. The highest consumption of choline among all age groups was 712.0 mg/day in
adolescents aged 13–19 yrs in 1998, and 662.2 mg/day in adults aged 30–49 yrs in 2001. The choline database used in these results consisted of data from a total of 165 foods commonly eaten in Korea, selected using the dietary intake data of the 1998 and 2001 KNHANES, a population representative sample survey of Korea, and the 2002 and 2003 Dietary Intake and Risk Assessment of Contaminants in Korean Foods [37]. In addition, the Korea Ministry of Food and Drug Safety (MFDS)'s Food and Nutrition database contains levels of total choline and glycine betaine for processed foods.

Fig. 2 presents a comparison of choline intake by year of Koreans aged 20-29 yrs. The dietary choline intake of Korean adults (56 college students in Daejeon area) aged 20–30 years in 2002 was determined by Chung et al. [36]. They reported that men consumed 353.5–1,222.5 mg/day of choline and women consumed 213.1–722.3 mg/day. The mean choline intake was determined to be 658.2 ± 243.9 mg/day for men and 423.3 ± 133.6 mg/day for women.
women, indicating that choline intake in men was about 200 mg/day higher than in women. In a study of choline intake for 30 college students of the same age range in the same region in 2004, the mean intake of choline was 654.53 ± 353.68 mg for men and 473.99 ± 183.76 mg for women [38]. Compared with results for 1998 and 2001 [35], choline intakes in 2002 [36] and 2004 [38] were found to be similar for men but lower for women.

**INTAKE OF CHOLINE BY COUNTRY AND RACE**

A recent report [39] describes the dietary choline intake from surveys performed in China [40], Mexico [41], New Zealand [41], Taiwan [42], and 9 European countries [27] (Fig. 3). These data show that people in the northern European countries consume higher dietary choline than the population in the Mediterranean countries [27]. Total choline intakes of Japanese adults ranged from 445 mg/day to 513 mg/day for men and from 388 to 442 mg/day for women [43] (data not shown), which were similar to values obtained in northern European countries, but higher than the Chinese [40] and Taiwanese [42] intakes.

A cohort study has estimated dietary choline intakes among the ethnically diverse adults who participated in the Multiethnic Cohort (MEC) Study [44] (Fig. 4). The cohort consisted of adult men and women living in Hawaii and California, and comprised the following ethnic
compositions: African American, Latino, Japanese American, Native Hawaiian, Caucasian, and other ancestries [45]. The study reported that men consumed significantly higher amounts of total choline than women. However, total choline intakes of men and women had similar levels after adjusting for daily energy intake. Furthermore, the energy-adjusted total choline intakes varied significantly by race/ethnicity in both men and women, suggesting that choline intakes could differ by ethnic background.

CONCLUSION

Human studies on Koreans are essential to establish the KDRIs as previous studies have reported differences in the levels of choline intake by race and country. Additionally, an estimate of UL would require examining intakes from supplements, as well as a comprehensive and reliable database of choline content in foods. In order to prevent adverse effects on public health due to choline deficiency and excessive intake, the following studies need to be conducted: randomized controlled trial of choline intake in Korean subjects; observational studies on choline intake in Koreans (including studies on choline metabolism-related gene polymorphisms); examining the effects of dietary choline intake levels on health parameters (including measurements of plasma and tissue choline compounds and metabolites); quantifying the increase in choline requirement, in carriers of alleles requiring an increased need for choline; biomarkers of choline status; consequences of the epigenetic modifications of genes involved in hormonal and vascular physiology, and their expressions following alterations in choline intake during pregnancy; quantitative assessment of choline transfer from mother to the fetus; quantification of the incorporated choline compounds in the body or in different organs during fetal development.

REFERENCES

1. Ellingson DJ, Shippar JJ, Gilmore JM. Determination of free and total choline and carnitine in infant formula and adult/pediatric nutritional formula by liquid chromatography/tandem mass spectrometry (LC/MS/MS): single-laboratory validation, first action 2015.10. J AOAC Int 2016;99:204-9. PUBMED | CROSSREF
2. Bremer J, Greenberg D. Methyl transfering enzyme system of microsomes in the biosynthesis of lecithin (phosphatidylcholine). Biochim Biophys Acta 1961;46:205-16. CROSSREF
3. Zeisel SH, Klatt KC, Caudill MA. Choline. Adv Nutr 2018;9:58-60. PUBMED | CROSSREF
4. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, D.C.: National Academies Press; 1998. p.390-422.
5. Australian Government Department of Health and Ageing, New Zealand Ministry of Health; National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand: Including Recommended Dietary Intakes. Canberra: National Health and Medical Research Council; 2006.
6. Chinese Nutrition Society. Chinese Dietary Reference Intakes 2013. Beijing: China Science Publishing and Media Ltd.; 2013.
7. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Dietary reference values for choline. EFSA J 2016;14:4484. CROSSREF
8. Zeisel SH, Blusztajn JK. Choline and human nutrition. Annu Rev Nutr 1994;14:269-96. PUBMED | CROSSREF
9. Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. Annu Rev Nutr 2006;26:229-50.

PUBMED | CROSSREF

10. Stead LM, Brosnan JT, Brosnan ME, Vance DE, Jacobs RL. Is it time to reevaluate methyl balance in humans? Am J Clin Nutr 2006;83:5-10.

PUBMED | CROSSREF

11. Buchman AL, Dubin MD, Moukarzel AA, Jenden DJ, Roch M, Rice KM, Gornbein J, Ament ME. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. Hepatology 1995;22:1399-403.

PUBMED

12. Fischer LM, daCosta KA, Kwock L, Stewart PW, Lu TS, Stabler SP, Allen RH, Zeisel SH. Sex and menopausal status influence human dietary requirements for the nutrient choline. Am J Clin Nutr 2007;85:1275-85.

PUBMED | CROSSREF

13. Dalmeijer GW, Olthof MR, Verhoeef P, Bots ML, van der Schouw YT. Prospective study on dietary intakes of folate, betaine, and choline and cardiovascular disease risk in women. Eur J Clin Nutr 2008;62:386-94.

PUBMED | CROSSREF

14. Konstantinova SV, Tell GS, Vollset SE, Nygård O, Bleie Ø, Ueland PM. Divergent associations of plasma choline and betaine with components of metabolic syndrome in middle age and elderly men and women. J Nutr 2008;138:914-20.

PUBMED | CROSSREF

15. Bartus RT, Dean RL 3rd, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. Science 1982;217:408-14.

PUBMED | CROSSREF

16. Shaw GM, Carmichael SL, Yang W, Selvin S, Schaffer DM. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. Am J Epidemiol 2004;160:102-9.

PUBMED | CROSSREF

17. Xu X, Gammon MD, Zeisel SH, Lee YL, Wermur JG, Teitelbaum SL, Bradshaw PT, Neugut AI, Santella RM, Chen J. Choline metabolism and risk of breast cancer in a population-based study. FASEB J 2008;22:2045-52.

PUBMED | CROSSREF

18. Xu X, Gammon MD, Zeisel SH, Bradshaw PT, Wermur JG, Teitelbaum SL, Neugut AI, Santella RM, Chen J. High intakes of choline and betaine reduce breast cancer mortality in a population-based study. FASEB J 2009;23:4022-8.

PUBMED | CROSSREF

19. Lee JE, Giovannucci E, Fuchs CS, Willett WC, Zeisel SH, Cho E. Choline and betaine intake and the risk of colorectal cancer in men. Cancer Epidemiol Biomarkers Prev 2010;19:884-7.

PUBMED | CROSSREF

20. Zeisel SH, Da Costa KA, Franklin PD, Alexander EA, Lamont JT, Sheard NF, Beiser A. Choline, an essential nutrient for humans. FASEB J 1991;5:2093-8.

PUBMED | CROSSREF

21. Holmes-McNary MQ, Cheng WL, Mar MH, Fussell S, Zeisel SH. Choline and choline esters in human and rat milk and in infant formulas. Am J Clin Nutr 1996;64:572-6.

PUBMED | CROSSREF

22. Zeisel SH, Char D, Sheard NF. Choline, phosphatidylcholine and sphingomyelin in human and bovine milk and infant formulas. J Nutr 1986;116:90-8.

PUBMED | CROSSREF

23. National Center for Health Statistics (US). Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. Vital Health Stat 1 1994;(32):1-407.

PUBMED

24. WHO Multicentre Growth Reference Study Group. Breastfeeding in the WHO Multicentre Growth Reference Study. Acta Paediatr Suppl 2006;450:16-26.

PUBMED | CROSSREF

25. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. Science 1997;276:122-6.

PUBMED | CROSSREF

26. Kleiber M. Body size and metabolic rate. Physiol Rev 1947;27:511-41.

PUBMED | CROSSREF
27. Vennemann FB, Ioannidou S, Valsta LM, Dumas C, Ocké MC, Mensink GB, Lindtner O, Virtanen SM, Tlustos C, D’Addezio L, et al. Dietary intake and food sources of choline in European populations. Br J Nutr 2015;114:2046-55.

28. Widdowson EM, McCance RA. The effect of finite periods of undernutrition at different ages on the composition and subsequent development of the rat. Proc R Soc Lond B Biol Sci 1963;158:329-42.

29. Welsch F. Studies on accumulation and metabolic fate of (N-Me3h)choline in human term placenta fragments. Biochem Pharmacol 1976;25:1021-30.

30. Boyd WD, Graham-White J, Blackwood G, Glen I, McQueen J. Clinical effects of choline in Alzheimer senile dementia. Lancet 1977;2:711.

31. Gelenberg AJ, Doller-Wojcik JC, Growdon JH. Choline and lecithin in the treatment of tardive dyskinesia: preliminary results from a pilot study. Am J Psychiatry 1979;136:772-6.

32. Growdon JH, Cohen EL, Wurtman RJ. Huntington's disease: clinical and chemical effects of choline administration. Ann Neurol 1977a;1:418-22.

33. Growdon JH, Hirsch MJ, Wurtman RJ, Wiener W. Oral choline administration to patients with tardive dyskinesia. N Engl J Med 1977b;297:524-7.

34. Lawrence CM, Millac P, Stout GS, Ward JW. The use of choline chloride in ataxic disorders. J Neurol Neurosurg Psychiatry 1980;43:452-4.

35. Jeong HO, Kim CI, Lee HS, Chung YJ. Estimation of dietary choline intake of Korean by gender, age and region. Korean J Nutr 2005;38:320-6.

36. Chung YJ, Cho HI, Na JS. Dietary choline intake of Korean young adults. Korean J Nutr 2004;37:617.

37. Korea Food and Drug Administration. Korea Health Industry Development Institute. Dietary Intake and Risk Assessment of Contaminants in Korean Foods. Seoul: Korea Health Industry Development Institute; 2006.

38. Na JS, Cho HI, Lim JH, Yun HI, Sok DE, Lee JW, Byun MW, Chung YJ. Plasma choline concentration of some Korean young adults and correlation with dietary choline intake. Korean J Nutr 2006;39:115-20.

39. Wiedeman AM, Barr SI, Green TJ, Xu Z, Innis SM, Kitts DD. Dietary choline intake: current state of knowledge across the life cycle. Nutrients 2018;10:1513.

40. Yu D, Shu XO, Xiang YB, Li H, Yang G, Gao YT, Zheng W, Zhang X. Higher dietary choline intake is associated with lower risk of nonalcoholic fatty liver in normal-weight Chinese women. J Nutr 2014;144:2034-40.

41. López-Carrillo L, Gamboa-Loira B, Becerra W, Hernández-Alcaraz C, Hernández-Ramírez RU, Gandolfi AJ, Franco-Marina F, Cebrián ME. Dietary micronutrient intake and its relationship with arsenic metabolism in Mexican women. Environ Res 2016;151:445-50.

42. Cheng CP, Chen CH, Kuo CS, Kuo HT, Huang KT, Shen YL, Chang CH, Huang RF. Dietary choline and folate relationships with serum hepatic inflammatory injury markers in Taiwanese adults. Asia Pac J Clin Nutr 2017;26:642-9.

43. Nagata C, Wada K, Tamura T, Konishi K, Kawachi T, Tsuji M, Nakamura K. Choline and betaine intakes are not associated with cardiovascular disease mortality risk in Japanese men and women. J Nutr 2015;145:1787-92.

44. Yonemori KM, Lim U, Koga KR, Wilkens LR, Au D, Boushey CJ, Le Marchand L, Kolonel LN, Murphy SP. Dietary choline and betaine intakes vary in an adult multiethnic population. J Nutr 2013;143:894-9.

45. Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, Stram DO, Monroe KR, Earle ME, Nagamine FS. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 2000;151:346-57.