

Review Article

Lactose nutrition in lactase nonpersisters

Mark L Wahlqvist BMedSc, MD, FRACP FAFPHM FAIFST FACN FTSE^{1,2,3}

¹Monash Asia Institute, Monash University, Melbourne, Australia

²Fuli Institute of Food Science and Nutrition, Zhejiang University, Hangzhou, Zhejiang, China

³Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan

Lactose handling by the human gut by most people, beyond being breast-fed, has been considered a disorder rather than physiological. A non-human mammalian milk source is novel for the majority. During the first 6 months of life, when neonates and infants are best breast-fed, lactose along with other macronutrients, provides energy, but may have other functions as well. At birth, babies are endowed with their mother's vaginal microbiome, but not if they are born by Caesarean section. How much maternal milk lactose survives the infant's small intestine and is processed by this unique gut microbiome and to what end is still uncertain, but no lactose or galactose appears in the faeces. Once intestinal lactase activity declines in most infants, lactose may enhance innate immunity through the cathelicidin antimicrobial peptide (CAMP), which is best achieved by lactose synergy with other colonic fermentation metabolites such as butyrate. It is of interest whether this lactose function or a variant of it persists. It might not be evident when lactase is persistent, as it is in most people of northern European ancestry. Population genomics indicate that lactase persistence became prevalent only about 3000-1000 BC, the Bronze Age of Eurasia. Gastrointestinal symptoms (GIS) in lactase nonpersisters who consume dairy foods are partly dose dependent and not usually evident with single lactose intakes ≤ 25 g per day. Spreading intake across the day reduces the risk as can various dietary patterns. Nevertheless, individual differences in GIS lactose sensitivity may merit public health and clinical consideration.

Key Words: lactase persisters, lactose nutrition, lactose intolerance, cathelicidin antimicrobial peptide (CAMP), innate immunity

LACTOSE NUTRITION AND POPULATION GENOMICS

For most of the world's peoples, intestinal lactase activity is present during the first few months of life when it is in our survival interests to be breast fed. Population genomics indicate that lactase persistence became more prevalent in a North European minority only about 3000-1000BC, the Bronze Age of Eurasia.¹

LACTOSE NUTRITION, GROWTH AND DEVELOPMENT AND FOOD CULTURE

At birth and for the first few months of life, as long as we are breast fed, lactose forms an inevitable part of our diet and determinant of our nutritional status.^{2,3} From initial colostrum intake to the mature breast milk ingestion period, lactose ingestion increases. Initially, this lactose is digested in the small intestine with an uncertain 'spillover' into the large intestine. The gut microbiome to which any lactose presents is partly determined by the birth, vaginal or 'Caesarean', canal, probably with life-long health implications.⁴ For most of the world's population, except for mainly those of European ancestry, after a few months, small intestinal lactase (a beta-galactosidase) activity declines and any ingested lactose is instead fermented in the colon.⁵ Neither the disaccharide lactose nor its constituent monosaccharide galactose are found in the faeces in early life and probably not later.⁶ The products of colonic lactose fermentation after hydrolysis to glucose

and galactose are the intermediates lactate, formate and succinate and then the short chain fatty acids (SCFA) acetate, propionate and butyrate along with the gases hydrogen, carbon dioxide and methane.⁷

The extent to which lactose is available for colonic lactose fermentation will depend on whether small intestinal brush border lactase activity persists in one form or another, the ingested lactose load, the distribution of lactose intake across the day, associated food and nutrient properties (chemical and physico-chemical) and intake, intestinal microbiota and gut motility. Prior infection, use of antibiotics and underlying disease and associated treatment also need to be taken into account.

It is likely that, in lactase nonpersisters, adaptation to at least low intakes of lactose also takes place, dependent on the prevailing food culture and the place of dairy foods in it.⁵ For example, in North East Asia, where dairy has not been a traditional part of the diet, exposures have in-

Corresponding Author: Prof Mark L Wahlqvist, Fuli Institute of Food Science and Nutrition, Room D437 Agriculture, Biological and Environmental Building, Zijingan Campus, Zhejiang University, 833 Yuhantang Road, West Lake District, Hangzhou City, Zhejiang Province, China 310058.
Tel/Fax: +86-571-8898-2463
Email: mark.wahlqvist@gmail.com
Manuscript accepted 07 December 2015.
doi: 10.6133/apjcn.2015.24.s1.04

creased in recent times and some adaptation may have occurred. This may have applied to post World War 2 Taiwan and Japan where dairy intakes were encouraged during food shortage, reconstruction and economic recovery. By now, not only liquid milk from reconstituted dry milk powder containing lactose, but also fresh milk and fermented dairy products are increasingly common place in Japan and Taiwan.

Older people in Asia are accustomed to use of milk powder which may still contain lactose.^{8,9} Although lactose digestion and absorption may decrease with age in European populations and be asymptomatic, for ageing lactase nonpersisters the question will be more one of change in the colonic functions of non-digested lactose which might be microbiomic, in innate immunity or in some other role (see below).^{6,10}

A potential risk is emerging for the millions of lactase nonpersisters in the proliferation of dairy products based on fractionated products which separate whey protein as a so-called value added product for its immune, possible weight management and other properties, leaving a relatively lactose-dense remainder for the socio-economically disadvantaged. Efforts are being made to export such products from the USA to China. As will be seen, the synergy of dairy components for health is becoming clear as are the problems and dubious efficacy of peculiar components in their own right. An example is dairy calcium for calcium homeostasis and bone health in lactase nonpersisters who achieve it on lower calcium intakes if other nutritional factors (like vitamin D and phytonutrients from fruits and vegetables) are taken into account.^{11,12}

LIMITED LACTOSE ABSORPTION AS PHYSIOLOGY

Lactase nonpersisters are generally regarded as 'abnormal' when gut symptoms appear at higher doses which are mostly reported with single intakes ≥ 25 g/day.⁵

Traditionally, if these people consumed dairy foods, they would have been fermented or cheeses with little or no lactose content – as in Mongolia with horse milk or western China with goat or sheep milk. At most, the products provided small amounts of 12-24 g/day spread out through the day.

But lactose intakes are increasing in NE and SE Asia as dairy intakes increase from beverages (eg sweetened drinks, milk coffees and teas) and at breakfast with the potential to exceed these amounts. One 200-250 ml milk beverage may contain 12-15 g lactose. That said, there is not a close link between lactase status and gastrointestinal symptoms.⁵

In a study of Chinese, regarded as lactase nonpersisters, with and without symptoms considered attributable to lactose intolerance, when challenged with 25 g of lactose, there was no detectable difference in lactose hydrolysis, but there was in the production of SCFA (short chain fatty acid) metabolites and of gases (hydrogen, carbon dioxide and methane).⁷ This leaves a wide range of lactose intakes, especially in the 'lactose tolerant', to have an asymptomatic and presumably physiological exposure of the colon to lactose.

Considerable attention has been given to the adverse

consequences of lactose-free diets by way of restricted dairy food consumption and associated nutrient deficiencies.¹³ Reports focus on bone health, osteoporosis and fracture for which the peculiar role of dairy is controversial. Nevertheless, high dairy consumers in northern Europe have higher fracture rates than the lower dairy consumers in southern Europe.¹² Lactase nonpersisters in Asia have generally lower fracture rates than lactase persistent Europeans.¹⁴

The question in relation to health advantage is whether lactose which survives the small intestine may have physiological relevance in the colon. There are at least 2 ways in which this may be important. The first is that lactose may enhance divalent cation like calcium uptake.¹⁵ The second is as an immune-stimulant through its role as a substrate for a favourable gut microbiome^{16,17} and its direct cellular (colonocyte and phagocyte) effects on the generation of anti-microbial peptides.⁴

LACTOSE FERMENTATION DEPENDENCY ON LIMITED LACTOSE ABSORPTION WITH COLONIC 'SPILLOVER'

Lactose fermentation metabolites are intermediate (lactate, formate, succinate) and end products SCFAs (butyrate, propionate and acetate) and gases (H₂, CO₂, CH₄).⁷

They may provide some benefits (immune, hepatic regulation, central nervous system (CNS) substrates, colonocyte differentiation), but may also account for gastrointestinal (GI) symptoms.⁷

LACTOSE FERMENTATION AND COLONIC MICROBIOTA

It is generally understood that lactose is bifidogenic, but its potential ongoing role to provide this function in non-lactase persisters is usually neglected.¹⁶⁻¹⁸ Lactose may still be present in fermented dairy products like yogurt and reach the colon albeit subject to probiotic lactase.^{16,19,20} A greater understanding of the effects and consequences of lactose fermentation for the gut microbiota awaits enterotype characterisation and evidence of perturbation.

Three enterotypes appear to characterise the basic gut microflora although much of it can be changed by diet within days: Prevotella, Bacteroides and Ruminococcus. Prevotella is associated with agrarian plant and carbohydrate-based diets containing simple sugars, which might include lactose. Bacteroides is associated with more animal-based diets.²¹

Efforts to replace lactose in breast milk substitutes and dairy products with oligosaccharides like those in milk overlook the unique health roles which lactose may play.²² Lactose not only may serve as a prebiotic, as can oligosaccharides, but also stimulate innate immunity.⁶ The latter role may depend on its ability to induce the colonic epithelial cell gene for antimicrobial peptides (AMP) such as cathelicidin, also present in monocytes and macrophages. Of particular interest, this effect is synergistic with the short chain fatty acid (SCFA) butyrate.

HEALTH IMPLICATIONS

There are several potential health implications for lactose nutrition although these may be more to do with it as an

indicator for dairy intake or as a nutritional factor in synergy with other food intake and behavioural factors^{13,17,18}

- Cardiovascular Disease (CVD)
- Diabetes
- Immune function
- Bone health
- Enteropathies e.g. Coeliac disease
- Inflammatory bowel disease
- Body compositional e.g. obesity, sarcopenia
- Central Nervous System health (because of the gut-CNS neuroendocrine connections)
- Uterine fibroids

Most of the health focus of lactase non-persistence has been on the problems of either gastrointestinal symptoms or the potential adverse consequences of lower calcium intakes with dairy avoidance. It is now clear that the gastrointestinal symptoms are partly dose-dependent and can be minimised by the consumption of small dairy servings and the overall dietary pattern. They are also related to colonic fermentation.⁷

The contribution of low or no dairy intake to osteoporosis and fracture in lactase nonpersisters is questionable because such people can have satisfactory bone health on 400-500 mg calcium per day¹¹ where diets are plentiful in plant foods such as soy^{23,24} fruits and vegetables²⁵ and where vitamin D nutrition is adequate through sunlight exposure and diet and people are physically active.^{11,26} Indeed, in pregnant African women supplemented with calcium, post-partum bone health is worse than in the non-supplemented controls.²⁷ In lactase persistent Swedish women, increased calcium intake largely from dairy, is associated with no less or actually more fracture.²⁸

ARE LACTOSE-FREE FOODS NECESSARY?

It is liquid or reconstituted powdered milk which presents the greatest lactose load beyond the period of breast feeding. This usually comes from bovine mammals, but may come from ovine, equine or other animals. Mostly, milk is fermented before consumption and ingested as yogurt, cheese or similar commodities which have less lactose.²⁰ School milk and food aid programs in the 20th century increased liquid milk consumption. This may be evolving further with the greater consumption of liquid meals and milk-based beverages like sugary drinks, milk teas and coffees like latte.

There is, therefore, a case to be made for and against lactose-free foods:

Cons

- Lactase non-persistence is physiological
- It should be possible to minimise GI symptoms by attention to possible predisposing risk factors (e.g. maternal, birth, antibiotic usage), food & product type, dietary pattern, dose and spacing.
- There may be health disadvantage in a lactose free diet (e.g. immune dysfunction, colonic health)

Pros

Possible population bimodality of lactose tolerance with the less tolerant (more GI symptomatic) being within the apparent physiological range of intake of ≤ 25 g/day.

PUBLIC HEALTH AND CLINICAL PRACTICE POLICY FOR LACTOSE NUTRITION

- Avoid terminology that would imply that lactase non-persistence is a disorder or disease
- Encourage all people to consume dairy products in small amounts and in conjunction with other nutritious foods
- Provide information which would allow the recognition and mitigation of GI symptoms possibly attributable to lactose, but not to preclude other explanations.
- Develop a greater interest in the potential health advantages of lactose nutrition

CONCLUSIONS

- Lactose may be consumed in modest amounts, up to 12-24 g/day, preferably in small amounts across the day, in those in whom lactase persistence is not physiological, without clinical symptoms.
- Lactose-free or lactase-supplemented foods are not necessary for those in whom lactase activity is not persistent beyond infancy
- Lactose may favourably alter the colonic microbiome if it is not digested in the small intestine
- Lactose may enhance innate gut immunity in early (and possibly later) life through synergistic action with other carbohydrates or SCFA (e.g. butyrate)

Lactose avoidance may result in unnecessary dairy food avoidance in those who would be advantaged by a regular intake of small quantities (less than 1 serve per day).^{29,30-33}

AUTHOR DISCLOSURES

The author has no conflict of interest in regard to this paper.

REFERENCES

1. Allentoft ME, Sikora M, Sjogren KG, Rasmussen S, Rasmussen M, Stenderup J et al. Population genomics of Bronze Age Eurasia. *Nature*. 2015;522:167-72. doi: 10.1038/nature14507.
2. American Academy of Family Physicians. Breastfeeding, family physicians supporting (position paper). [cited 2015/7/30]; Available from: <http://www.aafp.org/about/policies/all/breastfeeding-support.html>.
3. World Health Organization, UNICEF. Innocenti Declaration on the Protection, Promotion, and Support of Breastfeeding [cited 2015/7/30]; Available from: <http://www.unicef.org/programme/breastfeeding/innocenti.htm>.
4. Goedert JJ, Hua X, Yu G, Shi J. Diversity and composition of the adult fecal microbiome associated with history of cesarean birth or appendectomy: Analysis of the American Gut Project. *EBioMedicine*. 2014;1:167-72. doi: 10.1016/j.ebiom.2014.11.004.
5. Wilt TJ, Shaukat A, Shamliyan T, Taylor BC, MacDonald R, Tacklind J et al. Lactose Intolerance and Health. No. 192 (Prepared by the Minnesota Evidence-based Practice Center under Contract No. HHS 290-2007-10064-I.). Rockville, MD: Agency for Healthcare Research and Quality; February 2010. AHRQ Publication No. 10-E004.
6. Cederlund A, Kai-Larsen Y, Printz G, Yoshio H, Alvelius G, Lagercrantz H et al. Lactose in human breast milk an inducer of innate immunity with implications for a role in intestinal homeostasis. *PLoS One*. 2013;8:e53876. doi: 10.1371/journal.pone.0053876.

7. He T, Priebe MG, Harmsen HJ, Stellaard F, Sun X, Welling GW, Vonk RJ. Colonic fermentation may play a role in lactose intolerance in humans. *J Nutr.* 2006;136:58-63. doi:
8. Huang LY, Wahlqvist ML, Huang YC, Lee MS. Optimal dairy intake is predicated on total, cardiovascular, and stroke mortalities in a Taiwanese cohort. *J Am Coll Nutr.* 2014;33:426-36. doi: 10.1080/07315724.2013.875328.
9. Wu SJ, Chang YH, Wei IL, Kao MD, Lin YC, Pan WH. Intake levels and major food sources of energy and nutrients in the Taiwanese elderly. *Asia Pac J Clin Nutr.* 2005;14:211-20.
10. Di Stefano M, Veneto G, Malservisi S, Strocchi A, Corazza GR. Lactose malabsorption and intolerance in the elderly. *Scand J Gastroenterol.* 2001;36:1274-8.
11. WHO. Population nutrient intake goals for preventing diet-related chronic diseases: recommendations for the prevention of osteoporosis Section [cited 2015/7/30]; Available from: http://www.who.int/dietphysicalactivity/publications/trs916/en/gsfao_osteo.pdf.
12. Fang AP, Li KL, Shi HY, He JJ, Li H. Calcium metabolism in healthy Chinese adults with habitual dietary calcium intakes: a systematic review and meta-analysis. *Asia Pac J Clin Nutr.* doi: : 10.6133/apjcn.092015.30.
13. Widodo Y, Sandjaja S, Sumedi E, Khouw I, Deurenberg P. The effect of socio-demographic variables and dairy use on the intake essential macro- and micronutrients in 0.5-12-year-old Indonesian children. *Asia Pac J Clin Nutr.* doi: 10.6133/apjcn.2016.25.2.09.
14. Litwic A, Edwards M, Cooper C, Dennison E. Geographic differences in fractures among women. *Womens Health (Lond Engl).* 2012;8:673-84. doi: 10.2217/wh.12.54.
15. Kwak HS, Lee WJ, Lee MR. Revisiting lactose as an enhancer of calcium absorption. *International Dairy Journal.* 2012;22:147-51. doi: 10.1016/j.idairyj.2011.09.002.
16. Savaiano DA. Lactose digestion from yogurt: mechanism and relevance. *Am J Clin Nutr.* 2014;99(5 Suppl):1251s-5s. doi: 10.3945/ajcn.113.073023.
17. Venema K. Intestinal fermentation of lactose and prebiotic lactose derivatives, including human milk oligosaccharides. *International Dairy Journal.* 2012;22:123-40. doi: 10.1016/j.idairyj.2011.10.011.
18. Gänzle M, Bryans J, Jelen P, Smithers G. Nutrition and health aspects of lactose and its derivatives: State of the science. *International Dairy Journal.* 2012;22:87. doi: 10.1016/j.idairyj.2011.11.001.
19. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the substantiation of health claims related to live yoghurt cultures and improved lactose digestion (ID 1143, 2976) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA Journal.* 2010;10:1763. doi: 10.2903/j.efsa.2010.1763.
20. Adolffson O, Meydani SN, Russell RM. Yogurt and gut function. *Am J Clin Nutr.* 2004;80:245-56. doi:
21. Wikipedia. Gut flora [cited 2015/7/30]; Available from: https://en.wikipedia.org/wiki/Gut_flora.
22. Zivkovic AM, Barile D. Bovine milk as a source of functional oligosaccharides for improving human health. *Adv Nutr.* 2011;2:284-9. doi: 10.3945/an.111.000455.
23. Taku K, Melby MK, Takebayashi J, Mizuno S, Ishimi Y, Omori T, Watanabe S. Effect of soy isoflavone extract supplements on bone mineral density in menopausal women: meta-analysis of randomized controlled trials. *Asia Pac J Clin Nutr.* 2010;19:33-42.
24. Yamori Y, Miura A, Taira K. Implications from and for food cultures for cardiovascular diseases: Japanese food, particularly Okinawan diets. *Asia Pac J Clin Nutr.* 2001;10:144-5.
25. Wattanapenpaiboon N, Lukito W, Wahlqvist ML, Strauss BJ. Dietary carotenoid intake as a predictor of bone mineral density. *Asia Pac J Clin Nutr.* 2003;12:467-73. doi:
26. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. *Am J Clin Nutr.* 2003;77:504-11.
27. Jarjou LM, Laskey MA, Sawo Y, Goldberg GR, Cole TJ, Prentice A. Effect of calcium supplementation in pregnancy on maternal bone outcomes in women with a low calcium intake. *Am J Clin Nutr.* 2010;92:450-7. doi: 10.3945/ajcn.2010.29217.
28. Warendsjo E, Byberg L, Melhus H, Gedeberg R, Mallmin H, Wolk A, Michaelsson K. Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. *BMJ.* 2011;342:d1473. doi: 10.1136/bmj.d1473.
29. Lukito K, Malik SG, Surono IS, Wahlqvist ML. From 'lactose intolerance' to 'lactose nutrition'. *Asia Pac J Clin Nutr.* 2015;24(Suppl 1):S1-S8. doi: 10.6133/apjcn.2015.24.s1.01.
30. Vandenplas Y. Lactose intolerance. *Asia Pac J Clin Nutr.* 2015;24(Suppl 1):S9-S13. doi: 10.6133/apjcn.2015.24.s1.02.
31. Lee MS, Wahlqvist ML, Peng CJ. Dairy foods and health in Asians: Taiwanese considerations. *Asia Pac J Clin Nutr.* 2015;24(Suppl 1):S14-S20. doi: 10.6133/apjcn.2015.24.s1.03.
32. Hegar B, Widodo A. Lactose intolerance in Indonesian children. *Asia Pac J Clin Nutr.* 2015;24(Suppl 1):S31-S40. doi: 10.6133/apjcn.2015.24.s1.06.
33. Surono IS. Traditional Indonesian dairy foods. *Asia Pac J Clin Nutr.* 2015;24(Suppl 1):S26-S30. doi: 10.6133/apjcn.2015.24.s1.05.

Review Article

Lactose nutrition in lactase nonpersisters

Mark L Wahlqvist BMedSc, MD, FRACP FAFPHM FAIFST FACN FTSE^{1,2,3}

¹Monash Asia Institute, Monash University, Melbourne, Australia

²Fuli Institute of Food Science and Nutrition, Zhejiang University, Hangzhou, Zhejiang, China

³Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan

乳糖酶非續存者的乳糖營養

多數人在斷奶後，如果他們的腸道無法消化乳糖，會被認為是一種失調，而非生理反應。非人類的哺乳類乳源，對多數的人而言是新奇的食物。以母乳哺育新生兒及嬰兒是最佳的，在前六個月的生命時期，乳糖及其他巨量營養素，除了提供能量之外，可能還有其他功能。出生時，自然產嬰兒從產道，獲得母親的菌相，如果是剖腹產則無。有多少的母乳乳糖，可以通過嬰兒的腸子而不被消化，再被這種獨特腸道菌相作用，及其最後的作用，仍不確定。但可以確定的是糞便中並沒有乳糖或半乳糖。大部分的嬰兒，一旦小腸乳糖酶活性下降，乳糖可透過 cathelicidin 抗菌肽促進先天免疫。當乳糖與腸道發酵代謝產物，如丁酸，一起作用時，其結果最佳。這到底是乳糖的功能，或是它持續的一種變異，是一個有趣的問題。大多數乳糖酶續存的北歐血統的人，上述現象就不明顯。族群基因學指出，乳糖酶續存在公元前 3000-1000 年才出現在青銅時代的歐亞大陸。乳糖非續存者攝取乳製品的腸胃道症狀（GIS）雖為部分劑量依賴，但每日單次攝取小於等於 25 公克乳糖並不會有症狀。將攝取量分散在一天之內，如不同的飲食型態，可以降低風險。然而，乳糖敏感性的 GIS 個體差異，可能值得公共衛生及臨床考量。

關鍵字：乳糖酶續存者、乳糖營養、乳糖不耐症、cathelicidin 抗菌肽（CAMP）、先天免疫