Review Article

# From 'lactose intolerance' to 'lactose nutrition'

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The concept of lactose intolerance has become embedded in Western medicine and developing economy medicine. It is based on evidence that intestinal lactase activity persists into later childhood and throughout life in only a minority of the world's population, notably northern European–derived populations. These people have the T single nucleotide polymorphism (SNP) of the rs49882359 allele (C/T), also known as C/T-13910, the MCM6 gene which positively influences the lactase LCT gene. Other lactase persistent (LP) populations are found in Africa and the Middle East with different genetic variants. These SNPs represent co-evolution with dairying since the agricultural revolution and nutrient-dependent ecological adaptation. That said, gastrointestinal symptoms considered due to small intestinal lactose malabsorption are poorly correlated with lactase non-persistence (LNP), the situation for most people. With LNP, colonic microbiome lactase enables lactose fermentation to occur so that none is found in faeces. Whether the short chain fatty acids (SCFAs) and gases (hydrogen, carbon dioxide and methane) produced cause symptoms is dose-dependent. Up to 25 g of lactose at any one time can usually be consumed by a LNP person, but its food and meal pattern context, the microbiomic characteristics, age and other factors may alter tolerance. Thus, the notion that lactose intolerance is a disorder or disease of LNP people is misplaced and has been one of cultural perspective. What actually matters is whether a particular dairy product as normally consumed give rise to symptoms. It is, therefore, proposed that lactose tolerance tests be replaced with dairy food tolerance tests.

**Key Words: Lactase persisters (LP), Lactase non-persisters (LNP), rs49882359 allele, gut microbiome, dairy food tolerance test (DFTT)**

## THE IMPERATIVE FOR RECONCEPTUALISATION OF LACTOSE IN HEALTH

Lactose intolerance, a concept that emerged in the 1960s, privileges the European view of health and milk-rich Western diets which have been de facto universal reference points. The term frames the inability to digest milk after infancy as a defect – intolerance – when in fact it is the natural state of more than two-thirds of the world's population, including most people in Asia. Young children almost universally produce lactase and can digest the lactose in their mother's milk. But as they mature, most switch off the lactase gene expression, as children are weaned. Only about 35% of the human population can digest lactose beyond the age of about seven or eight.[1]

Lactose intolerance has been a way of distinguishing the use and risks of dairy foods by people of different ethnicities for many years and considered to be a health problem if not a disease. This is intriguing given the universal exposure of us all to breast milk with its lactose content at the beginning of extra-uterine life, and consistent with a functional role for lactose. If such a role were to cease or change when breast feeding ceases, it would beg the question as to what that role or roles might be.

The emphasis on acute gastrointestinal symptoms presumed to occur in those who may not have an adequate persistence of lactase activity into childhood and beyond has been a preoccupation of dairy food nutrition. Yet what is observed may be within the bounds of physiology if lactose effects are dose-related or if the lactose-containing food in question itself has lactase activity sufficient to digest its lactose load which reaches the small intestine.[2,3] In any case, some lactose may survive into the large intestine and contribute to its physiology.

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In a Jakarta workshop held on 8th August 2015, the broader nutritional relevance of lactose, and the dairy foods which provide it, was canvassed. The background papers for this workshop are provided in this Special Issue of APJCN.[4-8]

## EVOLUTIONARY AND HISTORICAL CONSIDERATIONS

The advent of dairying culture following the agricultural revolution some 10,000 years ago, whether through migration, settlement, food shortage or local climatic conditions, was considered to be a key driver for lactase persistence (LP) beyond weaning (Table 1) . Based on a simulation model that has integrated genetic and archaelogical data, LP was estimated to have co-evolved with dairying around 7,500 years ago in Central Europe.[9] However, a low frequency of the T SNP (single nucleotide polymorphism ) of the rs4988235(C, T) alleles (also known as C/T-13910) that is responsible for LP/lactose tolerance in Bronze Age Europeans (around 2,900-2,400 BC) has now been reported, indicating a more recent positive selection onset.[12] These are the alleles of the MCM6 gene which positively influences the lactase LCT gene. Cattle and dairy consumption spread through Europe with the Neolithic transition, and finally reached Central and Western Europe after 5,500 BC, then Northern Europe after 4,100 BC.[10] A genetic basis for having or not having 'lactose intolerance' seemed likely. People whose ancestors had herded cattle were thought to have 'evolved' in some way over a relatively short time frame to make better use of milk and this became the accepted paradigm.[11,12]

The point of these observations is that lactase persistence is rather novel for humans and probably adaptive for particular circumstances whereas for most of our history as Homo sapiens, and particular circumstances. For most of the current global population, lactase non-persistence (LNP) is the norm and most of these people tolerate ≥9–12 g (equivalent to 200 mL or 1 glass of milk) and up to 25 g on any one occasion (Table 2).[13-15] Nowadays, trade, product innovation, health claims and food security challenge the dairy intake tolerance of the LNP without a clear understanding of lactose nutrition.

## CONTEMPORARY PERSPECTIVES

The difficulty in tackling lactose nutrition from both public health and clinical points of view is that its articulation has come from the lactase-persistent minorities who have had a vested, perhaps sometimes altruistic, point of view to provide or market dairy foods to the LNP majority**.** This cultural, socio-economic and 'scientific' medical bias has informed our expectations and interpretation of dairy-related health. As long ago as 1988, Scrimshaw and Murray showed that the acceptability of dairy foods among LNP individuals had little to do with their 'lactose intolerance'.[3]

The bias has been exaggerated because of the frequency of intestinal symptoms attributable to various socio-behavioural (anxiety states), food intake (eg laxative, sugary fructose drinks) or recurrent food-borne illnesses (viral or bacterial diarrhoeal) episodes. Associations come to be regarded as causal agents. Table 1 enumerates

**Table 1.** Definitions of lactose-related gut health terms

| Term | Abbreviation | Interpretation |
|---|---|---|
| Lactase persistent | LP | The dominant genetic trait in adults with continuous ability to digest lactose throughout adulthood |
| Lactase non persistent | LNP | The natural decline in intestinal lactase to <10 u/g of tissue which leaves adults with minimal ability to digest lactose |
| Lactase deficiency | LD | Reduction of intestinal lactase enzyme from either genetic (LNP) or any secondary causes due to diseases of the proximal small bowel mucosa |
| Lactose maldigestion | LM | Inability to digest lactose due to primary (LNP) or secondary causes resulting in undigested lactose reaching the colon |
| Lactose intolerance | LI | Symptoms resulting from the ingestion of lactose including flatus, gas, bloating, cramps, diarrhoea and rarely vomiting. Currently, symptoms must not be present when an inert placebo is exchanged for lactose |
| Lactose sensitivity | | Symptoms (with or without symptoms of LI) with systemic features like depression, headache, fatigue |
| Dairy food tolerance | DFT | Assessment of milk or dairy product containing lactose rather than lactose alone (as outlined in this paper for the DFT Test, DFTT) |

Source: modified from Szilagy, 2015.[57]

**Table 2.** Lactose and calcium content of common foods

| Dairy products | Calcium content (mg) | Lactose content (g) |
|---|---|---|
| Yogurt, plain, low fat, 1 cup | 448 | 8.4 |
| Milk, whole (3.25% fat), 1 cup | 276 | 12.8 |
| Milk, reduced fat, 1 cup | 285 | 12.2 |
| Ice cream, vanilla, 1/2 cup | 92 | 4.9 |
| Cheddar cheese, 30g | 204 | 0.07 |
| Swiss cheese, 30 g | 224 | 0.02 |
| Cottage cheese, creamed (small curd), 1 cup | 135 | 1.4 |

Source: modified from Gerbault et al, 2013.[43]

several terms and their definitions in the literature which have been advanced to capture the concept of lactose-related health .

## RELEVANT MEASUREMENT OF LACTOSE PHYSIOLOGY AND PATHOPHYSIOLOGY

Since we know that LNP is poorly associated with so-called 'lactose intolerance', and that amounts of lactose up to 12-24 g on a single occasion are tolerable by almost all people whatever their lactase status, and that we virtually never ingest pure lactose, a 'lactose tolerance test' is not what is required for present public health or clinical purposes. The questions that actually have to be addressed are whether, which and how much dairy product is tolerable. For this we need a 'dairy food tolerance test' which could have acute (several hours, perhaps as long as 24 hours) symptom evaluation and breath hydrogen as the end points (see below). Since the evidence is now that East Asian populations, at least, gain health advantage at no more than one serving of dairy a day, more than that need not to be tested, because it need not be more to be recommended. Moreover, from a practical point of view, smaller amounts spread out over the day will be more tolerable in any case.

## LACTOSE AS A NUTRIENT

The most obvious role of lactose in human milk is the provision of energy, since it provides about half of an infant's energy needs.[16] It is the principal breast milk carbohydrate at 7 g% with oligosaccharides of various types providing another 1.3 g%, a total of 8 g%, almost double that of cow's milk at about 4.8 g%.[16] The role of lactose as a potential prebiotic in LNP subjects is also plausible in accord with the functional relevance of such non-digestible carbohydrates[17] and merits its role as a nutrient in LNP people. In LP people, meeting energy needs will largely occur as a result of small intestinal lactose digestion and absorption through lactase activity (lactase phlorizin hydrolase, LPH) in the mucosal brush border membrane. Should lactose survive to the large intestine, then it enhances the fermentation of lactic acid bacteria like bifidobacteria.[18] The colonic microbiota, 80% of which may split lactose into glucose and galactose with (phospho-) β-galactosidases, hydrolyse and ferment the lactose which comes into the colon, giving rise to metabolites such as short chain fatty acids (SCFAs), mainly acetate, propionate and butyrate) and gases (H2, CO2, CH4).[16] These products, play a role in the pathophysiology of lactase non persistence.

SCFAs may provide energy locally to the microbiota and the colonocytes as well as systemically after their absorption into the portal circulation and transport to the liver (where they may have metabolic regulatory roles as well). Milk, probably on account of its lactose and oligosaccharide content, is bifidogenic which suggests that it may confer on an individual a more healthful intestinal microbiota.[4] Since gut bifidobacteria decline with age, milk saccharides may have a life-long role in countering immune-senescence.[19]

It is generally assumed that galactose produced on hydrolysis of lactose, may also serve as a substrate for cerebrosides, gangliosides, and mucoproteins with various neural and immunological roles (it forms part of the ABO blood group antigens). Galactose can be endogenously formed, as in breast tissue, and degraded; in excess, as galactosaemia, which can be toxic. More than through its probable bifidogenicity, lactose may itself be involved in promoting innate immunity.[20]

The failure to appreciate a unique role of lactose is leading to efforts to replace it in dairy products and even breast milk substitutes with oligosaccharides which are like those in milk and serve as prebiotics, as can lactose.[21]

The role of lactose in life-long human health may be inextricably linked to other dairy components, to its fermentation, to product formulation and to companion foods and food patterns. Its biological relevance may change with age as well, with key periods being infancy, growth and development, the reproductive years and later life. There is much interest in the contribution that dairy foods (and their lactose content) might play in the changing patterns of disease which we now experience.[5,7,22] These include obesity and sarcopenia,[23] diabetes,[24] cardiovascular disease,[23,25] immune dysfunction, bone health,[26] enteropathies and iinflammatory bowel disease,[27] central nervous system health (because of the gut-CNS neuroendocrine connections) and reproductive health as with uterine fibroids.[7,28]

## LACTASE PERSISTENCE AND ITS HEALTH OUTCOMES

From the biological point of view, it is attractive to classify people into lactase persisters (LP) and lactase non-persisters (LNP) since this is definable and assessable. The question is, though, to what extent this is more than of physiological interest in the public health and clinical domains. The answer seems to be that LP may allow greater lactose tolerance, but not usefully more than what most LNP can achieve with acceptable levels of dairy intake i.e. providing ≤25 g per day or even more if spread out across the day.[2,4,7,23,25,29-31]

The limits to lactose intake in LP have more to do with how little dairy is necessary for health gains (≤1 serve per day for all-cause and cardiovascular mortality,[23] and for colorectal cancer[32,33]) and how much increases the likelihood of adverse outcomes (e.g. fracture ≥1 serve per day[26]). Added to this are considerations of food affordability and sustainability where less rather than more is increasingly the issue.

## LACTASE NON-PERSISTENCE AND ITS HEALTH OUTCOMES

Among the longest-living populations are LNP in scattered North-East Asian villages in Japan, Western China and Kinmen Island so that this biological state is no obvious barrier to the best of health. As indicated above, LNP can tolerate modest amounts of lactose and dairy products, even gaining health advantage by doing so.[5,34,35]

The symptomatic differences between Chinese individuals are not so much related to 'lactose tolerance' as to the gut microbiota and its products of fermentation.[36] Survival of intact lactose to the large intestine provides scope for enhanced absorption of the divalent cation calcium.[37]

An advantage in being a LNP may be that it imposes a

physiological ceiling on lactose and, therefore, dairy excess. However, we almost never consume lactose in isolation so that the dietary context of any lactose consumed by LNP will be a further modulator of its physiology.[38] Dairy food processing, traditional or commercial, is inclined to a reduction in lactose exposure.[39,40]

## LACTOSE AND THE HUMAN MICROBIOME

The combined genomes and gene products of resident human microbes constitute the human microbiome.[41,42] The human genome which belongs to its eukaryotic cells, encodes not more than 20 enzymes for carbohydrate digestion, mostly sucrose, oligosaccharides, starch and lactose. However, to this must be added the metabolic capacity of the gut microbiome, particularly that in the large intestine, and especially when considering LNP people.

As indicated above, the trait of lactase persistence emerged about 7,500 years ago and became population-accentuated more recently among those who became Europeans or their descendants. It is a gene–culture co-evolution, where one phenomenon feeds off of the other.[43] Whatever its advantage, generations and many more people without this characteristic lived in parallel. For this reason, so-called lactose intolerance has been referred to as the "default" phenotype dependent on 'the ancestral or wild type' version of the human LCT (lactase-phlorizin hydrolase) gene.[44,45]

The LP allele appeared as a selective advantage. Bersaglieri considered that people with the mutation would have had more fertile offspring than those who lacked it and that the degree of selection was "among the strongest yet seen for any gene in the genome".[46] Over many generations, the advantage could have helped a population become dominant if "the population [had] a supply of fresh milk and [was] dairying".

Babu et al (2010) reported that the frequency and degree of lactose malabsorption is higher in southern than in northern Indian populations because of genetic differences in these populations as shown by the lactose tolerance test, lactose hydrogen breath test (HBT), and identification of lactase gene c/T-13910.[47] Did or does this matter?

Interestingly, 15 g lactose/d given to Japanese lactose malabsorbers increased the amount of lactobacilli, enterococci, and short-chain fatty acids and decreased clostridia and bacteroides in feces within 6 d. In addition, bacterial β-galactosidase is abundant in the colon.[48,49] Altogether, this suggests adaptive capacity for dietary lactose.

He et al (2005) reported that Bacteroides, Prevotella, Bifidobacterium, Atopobium group, Streptococcus/ Lactococcus and Lactobacillus/Enterococcus, Clostridium histolyticum/lituseburense group, Eubacterium low G + C2, Peptostreptococcus and the Ruminococcus group possess β-galactosidase activity which breaks down lactose to glucose and galactose.[48] Since the majority of the faecal microbiota is capable of hydrolyzing lactose, it is unlikely that lactose itself will present a large osmotic challenge to the colon, although its metabolites could, as suggested by the work of He and colleagues.[16,50]

## TRADITIONAL DAIRY FOODS AMONG LNP PEOPLE

As already indicated, LP is a recent human adaptation and its geographic distribution correlates with the importance of dairying in different human populations.[43] At the same time, if dairy products are fermented and consumed in small amounts, lactase status may not be relevant to the progress of dairying in a food culture.

This notion may be reflected in habitual consumption of traditional dairy foods in a particular culture. In Indonesia, for example, Dadih is consumed as a traditional food, served at weddings and given the title of respect "Datuk" in West Sumatra during the ethnic traditional "adat" ceremony. Dadih is consumed mostly by those of higher social status and served to honour guests. It may also reflect the milk consumption pattern in the community. Dadih and dahi are Indonesian and Indian yogurts, respectively, made from buffalo or cow milk and share the same root word. This may indicate a spread of dairy technology from India.[8]

## DAIRY FOODS AND HEALTH

### *Acute*

Beyond infancy, dairy foods are regarded as contributors to a more varied and nutritious diet, albeit non-essential. Nevertheless, in children they have commonly been a convenient way to improve child nutritional status, even where they have not been uniformly traditional foods, as in Indonesia.[8,51] In Chinese adults , calcium homeostasis is achieved at relatively low calcium intakes of ≤500 mg per day,[52] which may, of course, depend on a number of other factors like lactose as an enhancer of calcium absorption, on vitamin D status to increase calcium absorption or on low sodium intakes when less calcium is lost in the urine.

### *Medium to long-term*

The potential immune-protective roles of lactose have been underscored[20] as have its likely synergy with other milk and dietary factors to favour health.[7] This contrasts with the pre-occupation about 'lactose intolerance' and LNP.

### *Trade-offs and optimisation*

Apart from the mainly abdominal and gastrointestinal discomfort which may be experienced with what amounts to lactose 'overdose' or disordered colonic fermentation, there are few if any serious health consequences of lactose consumption in real life. One that has been explored is that of cariogenicity, although this is probably a problem dependent on associated oral hygiene.[53] Thus, on balance, LNP have more to gain than to lose by consumption of small amounts of dairy foods.

## DAIRY FOOD TOLERANCE TESTS

As will be clear, the problem of which people actually complain is gastrointestinal disturbance after milk or dairy product consumption, but with attribution to lactose because of what is known about LNP in the complainant's family or community. Whether a particular dairy product might account for the complaint should be evaluated with that product and at normal serving size. It is a

moot point whether it is necessary to evaluate larger serving size other than for patient education. Most 'lactose tolerance tests' (LTT) are with pure lactose, at the upper limit of what is an acceptable intake from food. It is, therefore, proposed that, for clinical purposes, 'Dairy Food Tolerance' (DFT) tests replace LTT.

The proposed DFT should establish whether a patient experiences the reported symptoms with a dairy product(s) of concern in an amount which can be regarded as usual for the person's food culture and standardize the DFT against a reference UHT full fat liquid milk (250 mL) by taking account of age and gender in the evaluations.[6,19] Documentation of the background diet will be useful for interpretative purposes.

Foods to be evaluated in the proposed DFT may vary, but would be expected to include local and traditional dairy foods, yogurts, assorted milks (by fat content, sugar content, flavoured or not), cheeses, bread and baked goods, processed breakfast cereals, mixes for pancakes, biscuits, cookies, instant potatoes, soups, breakfast drinks, butter, salad dressings, candies and other snacks containing small amount of lactose, namely low lactose foods.

***Serving size, distribution & meal/dietary patterns***

This should be in accord with local practice.

***Demographic considerations***

Ethno-cultural studies can inform more detailed enquiry, including those to do with lactase polymorphisms, and aid the understanding of a patient's complaint.[54-56]

It may be relevant to have an algorithm which, where findings are negative, could proceed to other tolerance tests e.g. with fructose (this may be a differential diagnosis). If probiotic dairy foods are used, they can be tested as well since they may increase colonic lactase capacity.[57]

## CONCLUSIONS

- Breast-fed infants derive a major part of their energy intake from lactose, which may also play a role in innate immunity and contribute galactose to neurometabolism.
- Lactose may be consumed as a dairy food component in modest amounts, up to 12-24 g per day, preferably in small amounts across the day, in those 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 microbiota if it is not digested in the small intestine.
- Lactose may enhance divalent cation absorption.
- Lactose may enhance innate gut immunity not only in early, but also 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).

## AUTHOR DISCLOSURES

Dr Widjaja Lukito is currently the President of Indonesian Danone Institute Foundation. Drs Safarina G Malik and Ingrid S Surono are Scientific Members of the Indonesian Danone Institute Foundation. Prof Mark L Wahlqvist has no conflict of interest with this paper.

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Review Article

# From 'lactose intolerance' to 'lactose nutrition'

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# 從"乳糖不耐"到"乳糖營養"

乳糖不耐症的概念建構在西方及開發中經濟體的醫學。其證據為佔全球少數的北歐衍生族群，其腸道乳糖酶活性續存至兒童晚期及整個生命週期。這些人擁有 rs49882359 等位基因（C/T）的 T 單核甘酸多型性（SNP），又被稱為 C/T-13910，其 MCM6 基因正向影響乳糖酶 LCT 基因。其他在非洲及中東的乳糖酶續存族群，他們有不同的基因變異。這些 SNPs 代表自農業革命及營養依賴的生態適應與乳品業的共同演化。意即，多數人因為小腸乳糖吸收不良產生的腸胃道症狀與其是否為乳糖酶非續存（LNP）關係不大。LNP 者，大腸菌相的乳糖酶能夠發酵乳醣，所以糞便中並無乳糖存在。短鏈脂肪酸（SCFAs）及氣體（氫氣、二氧化碳及甲烷）是否引起症狀，端看其劑量。一個 LNP 者，在任何時間均可消化最多 25 公克的乳糖。食物或餐點內容、腸道菌相的特性、年齡及其他因素，才是影響其耐受性原因。因此，LNP 者的乳糖不耐是一種失調或是疾病的主張是一種錯置及文化觀點。真正重要的是常被攝取的乳製品是否會引起症狀。也就是說，建議以乳製品耐受性測試取代乳糖不耐症測試。

**關鍵字：乳糖酶持續者（LP）、乳糖酶非持續者（LNP）、rs49882359 等位基因、腸道微生物、乳製品耐受性測驗（DFTT）**