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SMALL INTESTINE (D SACHAR, SECTION EDITOR)

Lactase Non-persistence and Lactose Intolerance

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Abstract
Purpose of Review To evaluate the clinical and nutritional significance of genetically determined lactase non-persistence and potential lactose and milk intolerance in 65–70% of the world's adult population.
Recent Findings Milk consumption is decreasing in the USA and is the lowest in countries with a high prevalence of lactase non-persistence. The dairy industry and Minnesota investigators have made efforts to minimize the influence of lactose intolerance on milk consumption. Some lactose intolerant individuals, without co-existent irritable bowel syndrome, are able to consume a glass of milk with a meal with no or minor symptoms. The high frequency of lactase persistence in offspring of Northern European countries and in some nomadic African tribes is due to mutations in the promoter of the lactase gene in association with survival advantage of milk drinking.
Summary Educational and commercial efforts to improve calcium and Vitamin D intake have focused on urging consumption of tolerable amounts of milk with a meal, use of lowered lactose-content foods including hard cheeses, yogurt, and lactose-hydrolyzed milk products.

Keywords Lactase non-persistence · Lactose intolerance · Lactase persistence · Evolution, positive selection · Milk drinking

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Introduction

The concept of healthy adults having isolated less than normal intestinal lactase levels became clear in 1963 after Auricchio, et al. and Dahlqvist et al. described healthy adults with low lactase levels and lactose and milk intolerance [1, 2]. The etiology and the clinical significance of hypolactasia were as not clear at the time.

Genetic Etiology

Our 1966 *Journal of the American Medical Association* (*JAMA*) paper suggesting that intestinal lactase activity was under genetic control was based on finding low lactase levels and lactose and milk intolerance in 70% of African Americans versus 5% in Whites. [3••]. This was the second most frequently cited *JAMA* gastroenterology paper in a 50-year-period, led by the 1932 Crohn, Ginzburg, and Oppenheimer paper describing regional ileitis [4]. Cuatrecasas and colleagues found a racial difference in hypolactasia that they attributed to lack of enzyme induction secondary to lack of lactose ingestion; they also mentioned the possibility of genetic control [5].

Low Lactase Levels as the Norm

We soon received a letter from Dr. Bekolari Ransome-Kuti, a prominent Nigerian physician, that "we had it all wrong, that low levels of lactase after weaning was the norm and that whites had a lactase excess" [6]. We confirmed Dr. Ransome-Kuti's prediction in an article in *Science in 1968,* as we demonstrated lactose intolerance in 19 of 20 healthy Asians and predicted that the bulk of the world's adult population, including 30 million individuals in the USA, are probably (potentially) intolerant to lactose in milk [7].

Current Status of Lactase Genetics

Now some 50 years later, it is clear that differences in lactase activity are due to a genetic polymorphism. There are three genotypes: homozygous lactase persistent (***LP***), homozygous lactase non-persistent (***LNP***), and heterozygotes. Intermediate enzyme activity in the heterozygotes implied that cis-acting allelic variations as a regulatory agent neighboring the lactase gene are responsible for the polymorphism [8••] Table 1.

As we had predicted, LNP is the most common phenotype in humans, estimated at 65–70% [9••]. LP is the mutation, presumably the result of strong positive selection, being common only in populations with a long history of pastoralism and milking. Lactase persistence is present in groups that herded cattle and drank milk prior to 1500 AD [10••, 11, 12••]. The genetic trait of LP is attributable to allelic variants in an enhancer region upstream of the lactase gene, LCT. As of 2015, five different functional alleles have been identified. There is marked diversity of the LP gene in various groups of African milk drinkers. The differences reflect the effects of parallel selection, the stochastic processes of the occurrence and spread of the mutations, and the depth of milk drinking tradition [13•].

The lactase gene (MCM6) spans approximately 50 kb in size and is located on chromosome 2. In 2002, Enattah et al. demonstrated that the C/T-13910 and G/A-22018 DNA variants, located 14 kb upstream to the gene encoding for the lactase enzyme were associated with reduced intestinal lactase activity [14••]. Mutation of the regulatory gene has been accepted as the cause of the hypolactasia. The CC genotype indicates LNP. The TT genotype is dominant and indicates LP and the heterozygote CT is associated with an intermediate lactase level of activity [15–17]. Heterozygote (CT) individuals had some evidence of lactose malabsorption with higher breath hydrogen levels and more bloating and flatulence after a 50-g lactose load than homozygous TT subjects [18•]. In adult patients with homozygous LP, enzyme levels at the jejunal brush border are ten times higher than in biopsies from LNP homozygotes. [19]. There are commercial kits for determining lactase genotypes but they have not been clinically practical and do not provide information on the amount of lactose tolerated by the subject with LNP [20•]. Recent investigations of the 13910 CJ genotype in children of European ancestry, studied in Boston, predicted LNP and LP allele development [21•]. In 2016, it was postulated that LNP is directed by DNA-variation-dependent epigenetic aging [22•]. Half levels of lactase activity are sufficient to digest significant amounts of lactose. The levels are not present in vast excess, so that under conditions of stress, heterozygotes may be more prone to become lactose intolerant. Examples of secondary lactose malabsorption include insults such as celiac disease, gastroenteritis, Giardiasis, colchicine therapy, Crohn's disease of the small bowel, and tropical sprue [23••, 24••] Table 2.

Historical Perspective

This is a marvelous tale of evolution, embodying a geographic or culture-historical hypothesis. Archeologists have traced the Neolithic culture development as the start of agriculture and possibly the domestication of dairy animals and cheese production to the areas of Iran and Syria at least 11,000–10,000 years ago. Others date the start of agriculture back 20,000 years. The Neolithic culture spread to Greece 8400 years ago and reached the Balkans 8000 years ago. By 7500 years ago, the gene for LP and the ability to drink milk in adulthood emerged in central Europe. Genotyping material from skeletons confirmed the presence of the lactase persistence (TT) gene. Well-developed dairy economy was established in central Europe by 6500 years ago [28••, 29••, 30•].

Lactase Persistence

Much of the recent genetic and anthropologic literature is focused on LP. This is most prevalent in northern Europe, with the highest frequency in Sweden and Denmark (>90%). The

Table 1 Downregulation of the lactase gene in lactase non-persistence

Polymorphism	Prevalence	Allelic variant	Lactase activity
Lactase persistence (Mutation, Dominant)	30%	T/T 13910	10 × > hypolactasia
Heterozygotes	(Admixture)	C/T 13910	Half activity
Lactase Non-persistent ("Normal," Recessive)	70%	C/C 13910	Inactive

Table 2 Definitions concerning lactose metabolism

Lactase deficiency: lowered levels of lactase activity in jejunal biopsies

Congenital lactase deficiency: extremely rare

Lactase non-persistence: adult hypolactasia 70% of world adult population

Secondary hypolactasia: damage to mucosal lactase (e.g. celiac, giardiasis, enteritis)

Lactose malabsorption: lowered blood glucose rise or increased breath hydrogen rise after oral lactose load, originally 50 g. Smaller amounts used clinically.

Lactose intolerance: originally described as symptoms that accompanied lactose malabsorption with a 50 g lactose tolerance test. Levitt et al. now use term for symptoms with 12 g of lactose that do not occur with a placebo. They also, confusingly, use the term for individuals who claim they are symptomatic with milk, even if they are not lactose malabsorbers [25•].

frequency decreases as one moves south and east (50% in Spain and Italy). A similar decline is seen, from north to south in India. LP is also frequent in some milk consuming nomads of the Afro-Arabian area (90%in Tutsi, 50% in Fulani) [30•]. There is a very low level of persistence in the Asiatic countries (1% in China). In the USA, there is LP in 70 to 80% of Whites of European or Scandinavian extraction, 30% of Mexicans, and 20% of African Americans. Conversely LNP is found in 70% of Ashkenazi Jews, 100% of pure bred American Indians, and in Eskimos of Asiatic origin but not of European ancestry. In Israel, the prevalence of the CC genotype, associated with hypolactasia, was 97% in Bedouin Arabs, 93% in Iraqi Jews, 83% among Ashkenazi Jews, and 82% among Moroccan Jews [26•]. Countries with a high prevalence of lactose malabsorption (LM) or of lactase non-persistence (LNP) are shown in Table 3 [26•, 27••].

Congenital lactose intolerance, which appears at the onset of nursing, is a rare disorder caused by severe mutations on both alleles of the lactase gene and occurs in either a compound heterozygous or homozygous pattern of inheritance. The gene patterns are different from those seen with adult lactase non-persistence [31•].

Table 3 Prevalence of lactose malabsorption or lactase non-persistence [8••, 9••, 26•, 27•]

Chinese (LNP)	100%	Egypt, general (LM)	73%
Vietnamese (LM)	100	Germany, general (LM)	70
Japanese (LM)	100	Hungary, general (LM)	56
Bantu, Uganda (LM)	100	Mexico, general (LM)	53
Peru, non-Caucasian (LM)	94	Northern Italy (LM)	52
Iraqi Jews (LNP)	93	Fulani (LNP)	50
Australian Aborigine (LM)	84	Greece, general (LM)	45
Nigeria Yorba (LM)	83	UK White (LNP)	22
Ashkenazi Jews (LNP)	83	Finland (LM)	17
Moroccan Jews (LNP)	82	US White, general (LM)	15
US Native American (LM)	81	Central Italy (LM)	15
Brazil, general (LM)	80	Irish (LNP)	14
Chile, general (LM)	80	Danes (LNP)	12
African American (LM)	75	Swedes (LNP)	10

Genetically Programmed down Regulation of Lactase Activity

Most animal species have a post weaning fall in lactase activity. In a homogeneous population of Australian Aboriginal children, there was diminished lactose digestion (3 g/k) at 6 months and a year, even though some of these infants were still nursing [32] (Breast milk has 8% lactose, cow's milk 5% lactose). This can be cited as evidence that the lactase in the non-persistent population is not inducible by lactose. In our 1967 study of African American children, teenagers and adults, there was a steady decrease in lactose tolerance with advancing age [33]. The age specific prevalence of lactose malabsorption in 409 healthy African American children, ages 13 months to 11 years, demonstrated a steady decrease in lactose digestion, as measured by peak blood glucose after a lactose load (2 g/k), with increasing age. Lactose malabsorption was present in 27% of those 1to 2-year-age group, 33% in the 5 to 6-year-age group and 74% in the 11 to 12-year-age group. There was no significant difference between high and low economic statuses of the parents. Lactose related symptoms did not appear until age 8, suggesting that the steady decline of available lactase reaches an identifiable clinical threshold in this population by 8 years of age. Milk intolerance was often noted in late childhood after age 8 and in early adolescence. Many remembered consuming large amounts of milk as children [34]. Thus, in practice, lactose intolerance may not be considered as a cause of abdominal pain in some teenaged patients who had been milk drinkers [35].

Other Populations

Similar results were seen in South African blacks with lactose malabsorption in 31% less than 5 years of age and in 80% of those over 10 [36]. In Sri Lanka (formerly Ceylon) lactose digestion was normal in infancy and young childhood, declining around age eight, being abnormal in 59% in the 10–14-year-age group [37]. Similar results were seen in southern India [38]. The Finns, who are about one-quarter Siberian (Asiatic) extraction, have the highest prevalence of lactase non-persistence among the Scandanavian countries.

Lactase Downregulation

Recent publications indicate that C/T-13910 is the main polymorphism and that the C allele is linked to a decline in lactase mRNA [17]. In an earlier study of lactase non-persistent white adults born in or near Naples, multifactorial events were

shown to be involved in down-regulation after weaning. By measuring lactase activity, lactase messenger RNA levels and in vitro lactase biosynthesis, it was concluded that both transcriptional and posttranscriptional factors cause the decline of intestinal lactase [39]. As stated, lactase activity is high in all fully mature human babies, then a genetic polymorphism, which acts in cis to the lactase gene, determines either high or low messenger RNA expression which is reflected in lactase persistence activity or lactase non-persistence [17].

Lactase Non-persistence as a Recessive Trait

In 1968 using an assumption of a 100% frequency of lactose intolerance in Africa in the area of mouth of the Niger River, where the majority of future African Americans were kidnapped, we calculated the mode of inheritance of low lactase levels in African Americans. We assumed a 30% European gene admixture in Baltimore African Americans in the 1960s. A Hardy Weinberg equation predicted an autosomal recessive inheritance of low lactase levels (lactase non-persistence). The predicted lactase levels in unaffected African Americans, most probably heterozygotes, was 5.67 U, in close agreement with the observed mean of 4.74 U, (range 2.2–8.5 U) The mean level in the unaffected whites was 7.8 U, presumably composed of homozygous lactase persistent and heterozygotes [40••].

Confirmation

Convincing confirmatory evidence of the recessive inheritance of lactase non-persistence came in 1974 from large family studies in Finland [41]. LP individuals were either heterozygous or homozygous for an allele that allows lactase to persist [9••]. Studies of lactose digestion in twins showed concordance in monozygous pairs [42]. Lactase persistence behaves as a dominant trait. Jarvela described three levels of lactase/sucrase ratio, those with hypolactasia (CC), those with intermediate levels or heterozygotes (CT), and those with lactase persistence (TT-1390) [17]. Studies in Ecuador trace the frequency of lactase persistence to the degree of European admixture in the population [43•].

Lactose Malabsorption

Lactose is hydrolyzed by intestinal lactase, a beta-galactosidase, to glucose and galactose which are actively absorbed by the sodium-dependent glucose carrier. Lactase persistence behaves as a dominant trait. Half levels of lactase activity are sufficient to digest significant amounts of lactose, such as 50 g, which is equivalent to the lactose in a quart of milk and is used in the standard lactose tolerance test. If the blood glucose rise is less than 20 mg/dl, this is considered evidence of lactose malabsorption. It is important to note that Suarez and his co-workers in Minnesota, the number two dairying state in the country, have tried to diminish the significance of lactose intolerance by using 12 g of lactose (equivalent to a glass of milk) as a test of lactose absorption. Thus, their estimates of lactose malabsorption are less than most other studies using 50 g of lactose [44]. Elevation of breath hydrogen, over 20 ppm, after a lactose load is also considered evidence of lactose malabsorption and is a commonly used, non-invasive test [45••].

Mechanism of Lactose Induced Symptoms

In subjects with lactase non-persistence, a 50-g-lactose load results in net secretion into the stomach, duodenum, and jejunum. The lactose test solution had been diluted fivefold when it reached the mid ileum [46]. Twelve and 24 g caused net fluid accumulation in the jejunum and ileum, whereas 6 g led to net secretion in the jejunum [47]. In the colon there was fermentation of the unabsorbed lactose into short chain fatty acids and interference with net absorption [46]. The carbon dioxide and hydrogen produced by the fermentation contribute to the bloating, frothy diarrhea, and flatulence.

Variables Influencing Lactose Tolerance

The symptoms resulting from lactose malabsorption are influenced by (1) the amount of the lactose load (8 oz milk = 12 g of lactose, ½ cup of ice cream = 4.9 g of lactose, 30 g of cheddar cheese = 0.02 g of lactose); (2) the rate of gastric emptying; (3) the ingestion of food with the lactose, especially meals with higher fat content or higher osmolality which slow gastric emptying (e.g., chocolate milk); (4) the residual lactase activity, being lower in heterozygotes; (5) the dilution of the lactose load by gastric and small bowel fluid; (6) the rate of contact with the mucosal surface; (7) the sensitivity of the small bowel to distension caused by fluid secretion in response to the osmotic load of unabsorbed lactose; (8) the ability of the colonic flora to ferment unabsorbed lactose, even as little as 5 g [48•]; (9) the individual sensitivity of the colon to distension with excess fluid with an increased osmolality, and (10) sensitivity to the gaseous distension. As stated, Bedine et al. found that the threshold for lactose-induced symptoms was doubled when the lactose was given with a meal, going from 12 to 24 grams [47]. Other factors include age, gender, individual sensitivities, eating habits, genetics, environment, food ideologies, and cultural patterns.

Threshold for Lactose-Induced Symptoms

We found that 54% of lactose intolerant adolescents developed cramps and/or bloating after drinking 8 oz (half pint) of milk while fasting [49]. Among 44 lactose intolerant adults, 8 oz (240 ml) of low-fat milk produced gaseousness or cramps in 59%. Subjects with co-existent IBS were excluded [50]. As

mentioned above, the threshold for lactose-induced symptoms was doubled when the lactose was given with a meal, going from 12 to 24 g [47]. Suarez and coworkers found that lactose intolerant adults (identified by self-definition or by use of 12 g breath hydrogen test) were able to consume a glass of low fat milk with a meal with only minor symptoms [44]. The use of milk with a meal delays gastric emptying and dilutes the lactose. In order to improve the consumption of calcium and Vitamin D, this study is being used to promote the consumption of a glass of milk with breakfast and dinner, especially in populations with a high prevalence of lactase non-persistence in adults, including African Americans [51••].

Lactose Intolerance

This term is used differently by various researchers. The amount of lactose as the challenge dose varies and the Minnesota group insists on a placebo control. This term, lactose intolerance, was initially applied to patients who develop abdominal distension, cramps, bloating, flatulence, sometimes vomiting and/or a laxative effect after a 50-g-lactose load, equivalent to the lactose in a quart of milk. If this is combined with evidence of lactose malabsorption, the specificity for lactase non-persistence is 96%. As a source of confusion, the Minnesota group and others define lactose intolerance as symptoms with a 12-g load taken as milk with a meal that is not present with a placebo [25•]. In addition, patients who recall a history of symptoms that they believe are related to dairy products, but are not lactose malabsorbers, are also imprecisely labeled as lactose intolerants [44]. These writers want their definition to be used to determine the prevalence of lactose issues in this country. Until then, they and the dairy industry want to continue to minimize the importance of lactose malabsorption and the use of lactose hydrolyzed milk [52••]. This campaign of using new definitions and selectively reviewing only controlled trial studies is reminiscent of the recently publicized effort by the sugar industry to discredit studies suggesting the health benefits in lowering of sugar intake [53••]. The absence of symptoms in a person with lactase non-persistence may not assure that the lactose was digested, and that the individual received the nutrient contents of the milk. In a small pediatric study, there was fat and nitrogen loss in the stool and decreased nitrogen retention on a lactose containing diet compared to a sucrose containing diet [24, 54-56]. The majority of lactose intolerant individuals have few or no symptoms with 90–100% lactose hydrolyzed milk [60].

Actual and Perceived Milk and Lactose Intolerance

Most lactase non-persistent (LNP) patients will notice bloating, flatulence, cramps, or a laxative effect 1 to 2 hours after drinking one or two glasses of skim milk on an empty stomach. Levitt and his colleagues noted symptoms in all subjects after two glasses of milk even with a meal [25•]. Some subjects have symptoms with milk and with a lactose load and are not lactose malabsorbers. This is discussed below in reference to milk intolerance and co-existent Irritable Bowel Syndrome (IBS). Having the perception that one is lactose intolerant actually impairs health-related quality of life. Symptom recall tends to be amplified by the patient. This is relevant because those who attribute their abdominal symptoms to lactose ingestion, tend to avoid dairy products, leading to lower calcium intake and potentially worsening post-menopausal osteoporosis [58].

Adaptation to Lactose Ingestion in Lactase Non-persistent Individuals

While lactase enzyme is not inducible by continued nursing or by lactose ingestion, excess undigested lactose is digested by colonic microflora. Diversity in the colonic microbiota plays a role in either utilizing unabsorbed sugars or in fermenting them with resultant symptom production. Regular dairy food consumption by lactase non-persistent individuals could lead to colonic adaptation by the microbiome, mimicking a prebiotic effect. The rationale for this approach is that colonic bacteria adapt to chronic lactose exposure with an increase in fecal beta galactosidase activity and decreased hydrogen production. This is thought to reflect the proliferation of lactose-fermenting organisms that do not produce hydrogen [25•].

This adaptation would allow lactase non-persistent people to consume more dairy foods, enhancing a favorable microbiome. In LNP subjects, 25 g of lactose twice a day for 2 weeks increased Bifidobacterium and lowered breath hydrogen levels. In other studies, lactobacilli increased in fecal slurries [59]. In one study by Hertzler and Saviano, adaptation to continued lactose ingestion dissipated in 72 h [60]. However, when 50 g of lactose, equivalent to a quart of milk, was used as the challenge, investigators could not demonstrate adaptation [61]. As another mode of adaptation, lactulose and other prebiotics have been used to assist lactose digestion and symptom control. There is an anecdote of a lactose intolerant individual who had adapted to prolonged ice cream intake at her place of employment, then losing this adaptation when given antibiotics for a urinary tract infection. Adaptation may be a useful strategy of therapy to assure calcium ingestion, as in pregnancy, for example [59].

Coexistence of Irritable Bowel Syndrome Lactose Intolerance

Patients with the IBS are seemingly more sensitive to unabsorbed lactose than non-IBS patients. In terms of the role of IBS and lactose intolerance in IBD patients, Bohner and Tuynman in 1969 studied 70 IBS patients who went on a

lactose-restricted diet, and there was a measurable decrease in symptoms in the 17 lactose malabsorbers while the lactose absorbers did not show similar improvement [62]. In Chinese patients, who were all LNP, malabsorption of 40 g of lactose was observed in both 93% of adult Chinese controls and in 92% of patients with diarrheal irritable bowel syndrome (IBS-D). The IBS-D patients had significantly more symptoms with 10, 20, and 40 g of lactose than the non-IBS patients. Elevated breath hydrogen levels were significantly associated with symptom score, suggesting that more undigested lactose got to the colon or there were microbiome differences in the small bowel or colon. The IBS-D patients also more frequently self-reported milk intolerance and consumed less dairy products. However, as in other studies, the self- reporting of lactose intolerance did not always correlate with hydrogen breath results [45••]. In another study of Chinese patients, all presumably having lactase non-persistence, breath hydrogen excretion after 20 g of lactose, fasting, was similar in 64 healthy controls and in 277 IBS patients (80.1% IBS-D; 4% IBS-C; and 12.6% IBS-Mixed). Lactose intolerance symptoms were significantly more prevalent in the IBS patients than in the healthy controls. This included bloating, diarrhea, pain, and borborygmi. Symptomatic subjects were more likely to have high hydrogen excretion levels, visceral hypersensitivity as measured by rectal barostat studies, or both. Visceral hypersensitivity in the IBS patients was related to the severity of bloating [63]. It is likely that these same factors are responsible for symptoms associated with other poorly absorbed, fermentable carbohydrates.

Thus, the evaluation and treatment of patients with functional complaints and bloating should not focus solely on lactose. This concept is involved in the use of the FODMAP multi-carbohydrate restricted diet with IBS patients. Since IBS occurs in at least 15% of the general population, it is important to consider the presence of IBS or other functional disorders when one is trying to determine the frequency and severity of lactose intolerance. This is a possible criticism of some of the studies that make up some of the controlled trials cited by the NIH consensus conference on lactose intolerance discussed below [51••]. A survey conducted in Spanish gastroenterologists concluded that they considered lactose intolerance a "minor" condition and tended to overlap it with IBS [64].

Influence of Lactose Intolerance on Dairy Consumption

Milk consumption in the USA is decreasing markedly. Americans, on average, drink 37% less milk today than they did in 1970, according to data from the USDA. Forty years ago, per capita consumption was nearly 1.5 cups per day; now it is nearer to 0.8. Whole milk consumption has tumbled by 78% from 1.1 cups per day to .24 cups. The greatest decrease in intake of fluid milk has been in teenagers (12 to 19), whose consumption decreased from 1977 to 2005 by 50%. They seem to choose flavored drinks over milk. Non-Hispanic Negroes consume less milk than any other group, even when corrected for economics [64, 65]. Obviously, numerous physical, social, and economic factors influence dairy food consumption and milk rejection. Lactase non-persistence and potential lactose intolerance, which is estimated to be present in 65 to 70% of the world's adult population, are considered factors in global milk drinking habits [23••]. In Fig. 1, countries with a high prevalence of LNP consume lower quantities of dairy foods [67••]. (Fig. 1)

In African American populations, the increasing prevalence of recognized lactose intolerance with age is accompanied, in both observed and reported studies, by a progressive decline in milk intake. As noted earlier, lactose induced symptoms do not usually appear in lactase non-persistent children until approximately 8 years of age. In 34 preschool (< 5 years old) lactose malabsorbing children (2 g per kilo), 87% were consuming 240 ml of milk per day, compared to 92% of the lactose absorbers [68]. School studies, at ages 9 to 12 of milk drinking in 312 African American and 221 white children showed that 20% of the African-American children consumed none or less than half of the half pint of whole milk given with their lunch. They were considered "non-milk drinkers." This was twice the rate of incomplete consumption in whites. In a sample of the African American "non-milk drinkers," 77% were malabsorbers of lactose (2 g/kg), and 87% had symptoms with the lactose load. In contrast, among the African American "milk drinkers," 35% had a flat lactose tolerance test. The African American mothers described the non-drinkers at school as not drinking milk at home, and conversely all the school milk drinkers, did drink milk at home. Seventy-nine percent of the mothers of non-milk drinkers described themselves as rejecting milk because of symptoms, not economics. Among the mothers of milk drinkers, 33% rejected milk because of symptoms [66]. There are parallel reports in children from other populations with a high prevalence of lactose maldigestion. A Swedish study confirmed the association of milk avoidance in adolescents with lactase non-persistence. Those with lactase persistence consumed significantly more milk and calcium [70].

Among adult hospitalized males, 39% of lactose intolerant subjects repeatedly rejected the 240 ml of low-fat (2%) milk served with their meals [50]. In Minnesota studies, 30% of adults classified as maldigesters reported not drinking milk when it was offered [25•]. In a 2000 survey linked to the census, African Americans were more likely to limit dairy food intake, to experience physical complaints, and to believe they were lactose intolerant [71]. In a study of adult Asian Indians, the frequency and quantity of milk intake were lower in subjects belonging to the lactase non-persistence genotype and lactose intolerant groups, especially females [72]. Interestingly, Asia has turned into the largest milk producer in 2013 with a 13-year average increase of 5.2%, largely from goats. Consumption is largely as cheeses and fermented products, such as yogurt [26••]. Presumably Asia

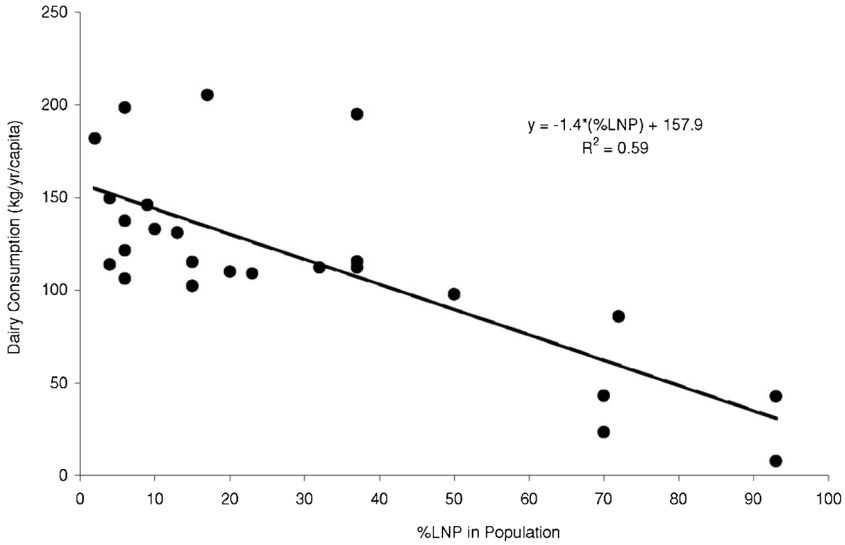

Fig. 1 Lactase non-persistent populations consume lower quantities of dairy foods. Dairy food consumption for each country is plotted against the percentage of the population that are lactase non-persistent (LNP). Twenty four countries are represented and national total dairy food consumption was assessed up to March 2007. Reprinted with permission from Shrier et al [67••] via Taylor and Francis Group

and other areas with a high prevalence of lactase non-persistence will be a market for lactose hydrolyzed products [57••]. Camel's milk, with relatively low lactose levels, in some countries, was acceptable to lactose intolerant individuals.

Lactose Digestion in Pregnancy

Despite the nutritional value of milk during pregnancy, lactase levels in some populations may be insufficient with resultant lactose maldigestion and possibly milk intolerance. In a Baltimore study, there was no change in lactose digestion of 240 ml of 1% fat milk taken fasting during pregnancy in a series of African American women at various stages of pregnancy and post-partum. The prevalence of lactose malabsorption (66–75%) was similar to that for non-pregnant African American women (80%). However, there were fewer symptoms reported by the lactose maldigesting pregnant women so the absence of symptoms did not represent a reliable guide to lactose digestion [73]. It is possible that there was adaptation of the colonic flora to modest lactose intake during pregnancy. Health care providers should discuss the pregnant woman's ability to tolerate milk with other foods and educate her to other food options, including providing sources of calcium such as hard cheeses, yogurt, or lactose hydrolyzed milk. Lactose hydrolyzed milk is currently available in the national Women and Infant Children (WIC) program.

Relationship of Lactose Metabolism to Disease

Theoretically, osteoporosis and fracture risk could be higher in white populations with a high prevalence of lactase non-persistence and decreased dairy consumption. This has also been shown in patients with cystic fibrosis, pancreatic insufficiency, and lactose malabsorption. Interestingly, the lactase non-persistent population of West Africa has a lower frequency of osteoporosis than lactase persistent East Africans. This is true in the African American population as well. Low vitamin D intake could be associated with rickets. There is a possibility that dairy foods have a protective role for some aspects of the metabolic syndrome and possibly colorectal cancer and other gastrointestinal malignancies [24••]. Although studies linking milk consumption to cardiovascular disease have been inconsistent, there has been a definite decrease in the consumption of whole milk compared to lower fat milks.

NIH Consensus Conference on Lactose Intolerance and Health

The 2010 NIH Consensus Conference was based largely on rigidly double-blinded placebo controlled studies performed and reviewed by the Minnesota group that trivialized the impact of lactose intolerance on patients and on milk consumption. The conclusions of the conference [52••] are listed below with our editorial comments in italics.

The conclusions of the Consensus conference were the following:

1. Lactose intolerance is a real and important clinical syndrome, but its true prevalence is not known.

    a. *Since they reserve the term "lactose intolerance" only for individuals with lactose malabsorption who have symptoms with a 12 g lactose load but not with a placebo, they claim the "true" prevalence of lactose intolerance in the United States is not known. Actually it is well recognized that at least 30 million adults in the United states and 70% of adults world-wide are lactase non-persistent and are potentially milk intolerant. The approach of the dairy industry-related research which is to minimize the importance of lactose intolerance is*

reminiscent of the recent sugar industry sponsored publication minimizing the role of sugar in obesity [53••].

2. The majority of people with lactose malabsorption do not have clinical lactose intolerance. Many individuals who think they are lactose intolerant are not lactose malabsorbers.

    a. *There are still millions of adolescents and adults world-wide who would be symptomatic with a glass of low fat milk while fasting.*

3. Many individuals with real or perceived lactose intolerance avoid dairy and ingest inadequate amounts of calcium and vitamin D, which may predispose them to decreased bone accrual, osteoporosis, and other adverse health outcomes. In most cases, individuals do not need to eliminate dairy consumption completely.

    a. *We agree but beg to disagree with the committee's attempt to dismiss the use of lactose hydrolyzed milk products as being proven by only some, but not all, controlled trials. The majority of results are positive. The market for lactose hydrolyzed milk products was over $2 billion in 2010, the year of the NIH conference*.

4. Evidence-based dietary approaches with and without dairy foods and supplementation strategies are needed to ensure appropriate consumption of calcium and other nutrients in lactose intolerant individuals.
5. Educational programs and behavioral approaches for individuals and their healthcare providers should be developed and validated to improve the nutrition and symptoms of individuals with lactose intolerance and dairy avoidance.

Dietary Implications of Lactose Malabsorption

1. Suspect lactose intolerance in the patient who is complaining of bloating, flatulence, cramps, or diarrhea who is consuming milk, ice cream, milk shakes on an empty stomach, soft cheeses, cordial liquors, whey products, frozen yogurt, or yogurt products with added milk or lactose. Also, suspect lactose intolerance in members of population groups with a high prevalence of lactase non-persistence, including Asian, African, African American, American Indian, Ashkenazi Jews, or Mediterranean peoples [74]. (See Table 1) Lactose intolerance may become evident when the individual is in an environment where milk is served with each meal, as in a hospital, college, or penal institution.
2. Consider secondary lactose intolerance in patients with celiac disease, tropical sprue, giardiasis, infectious enteritis, and small bowel Crohn's disease [24••]. The use of dairy foods in patients is confounded by the phenotype divide of lactase status in various populations [75•].
3. Reduce dietary lactose to amount that when taken with a meal will not cause symptoms but realize that some milk nutrients may be lost [54-56]. Consider the possibility of adaptation to small amounts of lactose consumed daily [56••].
4. Suggest low lactose products including yogurt, hard cheeses, and lactose-hydrolyzed milk and provide lactose digesting products such as beta-galactosidase enzyme (Lactaid, et al.) or bacterial or yeast products [76•]. A 43 g serving of mature-hard cheese contains less than 1 g of lactose compared to 11 to 13 g in a cup of milk [26••].
5. Dietary recommendations should be modified and respectful of those who do not drink milk.
6. Assure adequate calcium and nutritional intake and consider supplementation when needed, especially in individuals who are avoiding dairy products [77•].

Conclusion

As we predicted in 1968, 65–70% of the world's adult population have hypolactasia after childhood. The three phenotypes, lactase non-persistence, lactase persistence, and heterozygotes are under genetic control with lactase persistence being the mutation that is seemingly the result of generations of continued milk consumptions as an historic example of positive selection. Milk consumption is lower in countries with a high prevalence of lactase non-persistence. Educational efforts are being directed at encouraging individuals with lactase non-persistence to consume adequate amounts of calcium and Vitamin D either as forms of dairy foods with lowered lactose content, such as hard cheese, yogurt, and lactose hydrolyzed products, modest amounts of milk with meals which dilute the lactose and delay gastric emptying or as supplements of calcium and vitamin D.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This review contains published papers that presumably met journal standards for publication.

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