REVIEW ARTICLE

LACTOSE INTOLERANCE IN INFANTS, CHILDREN, AND ADOLESCENTS

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Abstract

Significant changes in our knowledge and approach towards lactose intolerance over the past quarter century has inspired us to present an updated review of lactose intolerance in infants children and adolescents. Differences between primary, secondary, congenital and developmental lactase deficiency are discussed. Children with suspected lactose intolerance can be assessed clinically by dietary lactose elimination or by tests including non invasive hydrogen breath testing or invasive intestinal biopsy determination of lactase (and other disaccharidases) concentration. Treatment consists of use of lactase treated dairy products or oral lactase, supplementation, limitation of lactose containing foods or dairy products. Dairy food is an important source of calcium for bone mineral health and of other nutrients that facilitate growth in children and adolescents. If dairy products are eliminated, other dietary sources of calcium or calcium supplements need to be provided.

Keywords: abdominal pain, breath tests, calcium, dietary, dairy products, diarrhea, flatulence, lactase, malabsorption

Introduction

American Academy of Pediatrics committee on nutrition presented a revised statement updating initial statements of 1978 (1) incorporating changes from 1990 supplements (2) and current state of art regarding lactose intolerance with updated recommendations regarding dietary calcium (3).

Lactose, a disaccharide that comprises monosaccharides, glucose and galactose, is the primary carbohydrate found extensively in human milk and most standard cow milk based formulas. Lactose is manufactured in mammary epithelial cells from glucose by a reaction involving α- lactalbumin (4). Lactose is specific nutrient for infancy supplying 40% of baby's energy needs, facilitates calcium and iron absorption, promotes healthy gastrointestinal tract (GIT) microflora, provides galactose which is incorporated as galactolipids into tissues of central nervous system. (5) Absorption of lactose requires lactase activity in small intestinal brush border to split the bond linking the 2 monosaccharides. A β. galactosidase termed 'lactase phlorizin hydrolase' (lactase) accounts for most of lactase activity in the intestinal mucosa. (6) Lactase is found in small intestines and localized to the tip of villi, a factor of clinical importance when considering the effect of diarrhoeal illness on the ability to tolerate milk.

Milk intolerance may be attributed to either lactose or protein content. Lactose intolerance can occur among infants and young children with acute diarrheal disease, although the clinical significance of this is limited except in more severely affected children. Symptoms of lactose intolerance are relatively common among older children and adolescents; however associated intestinal injury is infrequently seen. Lactose intolerance is a distinct entity from cow milk-protein sensitivity, which involves immune system, and causes varying degree of injury to intestinal mucosal surface. Cow milk protein intolerance is reported in 2% to 5% of infants within first 1-3 months of life, typically resolves by 1 yrs of age. (7,8)

Pediatricians and other pediatric care providers should maintain, awareness of the benefits and controversies related to consumption of dietary milk products and milk based infant formula. Lactose content of the milk often influences the ultimate decision about the use or continuation of milk in diet. Milk and dairy product avoidance has a negative effect on calcium and vitamin D intake in infants, children and adolescents. Other nutrients such as protein make dairy products an important source of nutrition for growing children.

Definitions

- Lactose intolerance is a clinical syndrome of 1 or more of the following; abdominal pain, diarrhea, nausea, flatulence and /or bloating after the ingestion of lactose or lactose containing food substances. Symptoms vary from individual to individual, depending on the amount of lactose consumed, degree of lactase deficiency and the form of food in which lactose is ingested.
- Primary lactase deficiency is attributable to relative or absolute absence of lactase that develops in childhood at various ages in different racial groups and is the most common cause of lactose malabsorption and lactose intolerance. Primary lactase deficiency is also referred to as adult type of hypolactasia, lactase non persistence or hereditary lactase deficiency.
- Secondary lactase deficiency results from small bowel injury such as acute gastroenteritis, persistent diarrhea, small bowel overgrowth, cancer chemotherapy and can present at any age but is more common in infancy.
- Congenital lactase deficiency is extremely rare. Survival is not possible without access to lactose free human milk substitute.
- Developmental lactase deficiency is relative lactase deficiency observed among preterm infants of less than 34 weeks gestation.

Primary Lactase Deficiency

Lactase activity begins to decrease in a genetically programmed fashion so that by adulthood it is low in many ethnic groups (9), highest prevalence being seen in Far East. Approximately 70% of world's population has primary lactase deficiency. (10,11) The percentage varies according to ethnicity and is related to use of dairy products in diet resulting in genetic selection of individuals with the ability to digest lactose (Table1). In populations with predominance of dairy foods in diet as few as 2% of population has primary lactase deficiency. In contrast prevalence of primary lactase deficiency is 50-80% in Hispanic people, 60 to 80% in

black and Ashkenazi Jewish people and almost 100% in Asian and American Indian people. (12-14) Age of onset and prevalence differs among various population. Ethnic group with higher prevalence have an earlier decrease of lactase activity. Approximately 20% of Hispanic, Asian and black children younger than 5 yrs of age have evidence of lactase deficiency and lactose malabsorption (15) whereas white children typically do not develop symptoms of lactose intolerance until after 4 or 5 yrs of age. Molecular studies of lactase have correlated genetic polymorphism of messenger RNA expression with persistence of lactase activity, demonstrating early loss (at 1-2 yrs of age) in Thai children and late (10-20 yrs of age) loss of activity in Finnish children. (14,16) Clinical signs of lactose intolerance at an earlier age than is typical for a specific ethnic group may warrant an evaluation for an underlying cause, because primary lactase deficiency would otherwise be unusual at such a young age. Typically onset of primary lactase deficiency is subtle and progressive over many years although it may be acute. Most lactase deficient individuals experience onset of symptoms in late adolescence and adulthood.

Dietary history is an unreliable means to confirm or exclude the diagnosis of lactose intolerance because clinical symptoms are prone to subjectivity. (17) One glass of milk or a scoop of ice cream may be tolerated even in lactose intolerant adult whereas an additional glass of milk or other milk products may produce symptoms. Because of variation of dairy intake in each individual's diet and in amount of lactose contained in different products symptoms may vary and be modified by diet and milk containing foods.

Table 1: Prevalence of Acquired Primary Lactase Deficiency (68)

Examples of groups among whom lactase deficiency predominates (60-100% lactase deficient)
Near East and Mediterranean: Arabs, Ashkenazi Jews, Greek Cypriots, Southern Italians
Asia: Thais, Indonesians, Chinese, Koreans
Africa: South Nigerians, Hausa, Bantu
North and South America: black Americans, Latinas, Eskimos, Canadian and American Indians, Chami Indians
Examples of groups among whom lactase persistence predominates (2-30% lactase deficient)
North Europeans
Africa: Hima, Tussi, Nomadic Fulani
India: individuals from Punjab and New Delhi

Secondary Lactase Deficiency

Underlying pathophysiological condition is responsible for lactase deficiency and subsequent lactose malabsorption. Acute infection (e.g. rotavirus) causing small intestinal injury with loss of lactase containing epithelial cells from tips of villi is a common cause. Immature cells that replace them are lactase deficient. Several reports indicate that lactose malabsorption in children with acute gastroenteritis is not clinically important. (18) Several recent studies and meta-analysis found that children with rotaviral and other infectious diarrheal illness who have no or only mild dehydration can safely continue human milk or standard lactose containing formula without any significant effect on outcome including hydration status, nutritional status, duration of illness or success of therapy. (19-21) However in at risk infant (e.g. younger than 3 months or malnourished) who develop infectious diarrhea, lactose intolerance may be a significant factor that will influence evolution of illness. Giardiasis, cryptosporidiosis and other parasites that infect proximal small intestine often lead to lactose malabsorption from direct injury to epithelial cells by parasite. It can also be seen in celiac disease, Crohn's disease and immune related and other enteropathies. Diagnostic evaluation should be directed towards these entities when infectious etiology is not found for secondary lactase deficiency.

Young infants with severe malnutrition develop small intestinal atrophy that also leads to secondary lactase deficiency. (22) This is common occurrence in developing countries. (23) Lactose malabsorption has also been associated with poor growth in these countries. (24) Most infants and children with malabsorption attributable to malnutrition are able to continue to tolerate dietary carbohydrate including lactose. (25) However World Health Organization (WHO) recommends avoidance of lactose containing milk in children with persistent post infectious diarrhea (diarrhea lasting more than 14 days) when they fail a dietary trial of milk or yogurt. (26)

Thus secondary lactase deficiency and lactose malabsorption attributable to any underlying condition generally does not require elimination of lactose from diet but rather treatment of underlying condition. Once the primary problem is resolved, lactose containing products can often be consumed normally and these excellent sources of calcium and other nutrients need not be unnecessarily excluded from diet.

Developmental Lactase Deficiency

Lactase and other disaccharidases are deficient until at least 34 weeks gestation. (27) Lactase appears later than other brush border disaccharidases in developing fetal intestine but is present in maximal amounts in full term infant. One study in preterm infants reported benefit from use of lactase supplemented feeds or lactose reduced formula. (28) Use of lactose containing formula and human milk does not seem to have any short or long term deleterious effects in preterm infants. (29) Up to 20% of dietary lactose may reach the colon in neonates and young infants. Bacterial metabolism

of colonic lactose lowers faecal pH (5.0-5.5) which has a beneficial effect favoring growth of bifidobacterium and lactobacillus species in lieu of potential pathogens (Proteus sp., Escherichia coli, and klebsiella sp.) in young infants. Antimicrobials may also affect this colonization. Lactose overload in breastfed babies arises if babies are not permitted to nurse long enough during feeds as in clock regulated feeds or if feeding is painful. Babies may also be inefficient feeders and thus deprived of fattier hind milk. Low fat feeds cause fast gastric clearance thus overloading small intestinal capacity to metabolize lactose. Management of lactose overload can be done successfully by ?finishing the first side first' according to Woolridge and Fisher's research. Inadequate fat intake in mother's diet appears to make a direct contribution to intensity of lactose overload symptoms resulting in lower fat and higher lactose levels in breast milk. (34)

Congenital Lactase Deficiency

It is a rare disorder reported only in few infants. (31,32) Affected newborn infants present with intractable diarrhea as soon as human milk or lactose containing formula is introduced. Small intestinal biopsies reveal normal histology but low or completely absent lactase concentration. (33,34) Unless recognized and treated quickly, this condition is life threatening due to dehydration and electrolyte losses. Treatment is removal and substitution of lactose with commercial lactose free formula.

Diagnosis

Symptoms including abdominal distention, flatulence, abdominal cramps and ultimately diarrhea are independent of the cause of lactose intolerance and are directly related to quantity of ingested lactose. These symptoms are not necessarily correlated with the degree of intestinal lactase deficiency. Malabsorbed lactose generates an osmotic load that draws fluid and electrolytes into intestinal lumen, leading to loose stools. As little as 12gm of lactose (amount of lactose in 8 oz glass of milk) may be sufficient to cause symptoms in children with chronic abdominal pain. (34)

In colon, bacteria metabolize unabsorbed lactose producing volatile short chain fatty acids and gases (methane, carbon dioxide and hydrogen) leading to flatulence. Fatty acids lower faecal pH making stool pH a non specific but helpful marker for lactose malabsorption. When sufficient intestinal gas in produced, intestinal distention stimulates intestinal nervous system leading to abdominal cramps.

Initial studies using lactose hydrogen breath tests documented malabsorption in up to 40% children and adolescents presenting with abdominal pain. (35) Prevalence of abdominal symptoms related to lactose intolerance documented by hydrogen breath tests is variable and ranges from 2% in Finnish children to 24% in southern US children. (36,37)

A good clinical history often reveals a relation between lactose ingestion and symptoms. When lactose intolerance is suspected lactose free diet can be tried (Table 2 & 3). (38) All sources of lactose should be eliminated requiring reading of food labels to identify "hidden" sources of lactose. Generally a 2 week trial of strict lactose free diet with resolution of symptoms and subsequent reintroduction of dairy foods with recurrence of symptoms can be diagnostic. In more subtle cases, hydrogen breath test is least invasive and most helpful test to diagnose lactose malabsorption. The test has been shown to be more reliable than history because some patients who think they are lactose intolerant when they prove not to be and vice versa. (39.40) The test is performed by administration of standardized amount of lactose 2gm/kg to a maximum of 25gm (equivalent to amount of lactose in two 8 oz glasses of milk) after fasting overnight and then measuring amount of hydrogen in expired air over 2-3 hr period. An increase (>20ppM) in the hydrogen expired after approximately 60 minutes is consistent with lactose malabsorption. Recent use of antimicrobial agents, lack of hydrogen producing bacteria (10-15% of population), ingestion of high fibre diet before test, small intestinal bacterial overgrowth or intestinal motility disorders produce false negative or false positive results. A pediatric gastroenterologist should be consulted to interpret results of this test.

Other conventional lactose tolerance test is not sensitive enough to determine if a subject is malabsorbing some lactose. Lactose intolerance was diagnosed by onset of symptoms and/or positive test result after ingestion of standard lactose dose (2gm/kg body weight or 50g/m2 of BSA; maximum 50gm in a 20% water solution). If maximum increase in blood glucose concentration was less than 26mg/dl after test dose, lactose malabsorption is diagnosed. Test is often falsely positive because of lack of increase of blood glucose concentration attributable to normal insulin response to the carbohydrate load. Due to high rate of false positive and negative results, currently this test has been replaced by hydrogen breath test.

If secondary lactose intolerance is suspected, stool examination for parasites such as giardia lamblia and cryptosporidia species, blood tests for celiac disease (total immunoglobulin A concentration and anti tissue transglutaminase antibody) (38,39) or immunodeficiency (quantitative immunoglobulins) should be undertaken. Intestinal biopsy may be needed to uncover any gastrointestinal mucosal problem. Status of brush border disaccharidases like lactase, sucrase, and maltase and isomaltase can be directly measured. However intestinal lactase concentration does not seem to correlate well with symptoms of lactose intolerance. (41)

Eventually newer tests like (13c) lactose breath test are being considered to augment accuracy of breath hydrogen test. (42,43) Newer tests may yield additional information pertaining to prevalence and significance of lactose intolerance. (44)

In infants faecal pH can be tested which decreases as a result of formation of volatile fatty acids from malabsorbed carbohydrates. Faecal pH is normally lower (5.0-5.5) in infants compared to older children and adolescents because of physiological overload of lactose in their diets which favors growth of lactobacillus

species in the colon. Faecal reducing substances can be measured. Reducing sugars include lactose, glucose, fructose and galactose but not sucrose. Stool pH is move sensitive test for carbohydrate malabsorption because some patients may only malabsorb enough carbohydrates such as lactose to lower faecal pH but not increase excretion of carbohydrate in the stools.

Table 2: Lactose and Calcium Content of Common Foods (69,70)

Dairy Products	Calcium content (mg)	Lactose content (mg)
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, 1 oz	204	0.07
Swiss cheese, 1 oz	224	0.02
Cottage cheese, creamed (small curd), 1 cup	135	1.4

Table 3: Hidden Sources of Lactose (71)

Bread and other baked goods
Processed breakfast cereals
Mixes for pancakes, biscuits, and cookies
Instant potatoes, soups, and breakfast drinks
Margarine
Nonkosher lunchmeats
Salad dressings
Candies and other snacks
Management

Management

Avoidance of milk and dairy products will relieve symptoms. Children with primary lactose intolerance tolerate varying amounts of dietary lactose due to varying degrees of lactase deficiency. Ingestion of dairy products resulting in symptoms leads to transient symptoms without causing harm to gastrointestinal tract as compared to celiac disease and milk protein intolerance which leads to ongoing inflammation and mucosal damage. Although lactose malabsorption does not predispose to calcium malabsorption (45), but avoidance of milk result in ingestion of less than recommended amounts of calcium needed for normal bone calcium accretion and bone mineralization. (46,47)

Lactose free and lactose reduced milks are available for children younger than two years. Beyond infancy, substitutes for cow milk based on rice, soy or other products are readily available and are generally free of lactose although nutrient content of most of these milk is not equivalent to cow's milk. Tolerance of milk products may be partial so that dietary maneuvers alone may help avoid symptoms in some individuals. Small amounts of lactose in portion of 4 to 8 oz spaced throughout the day and consumed with other foods may be tolerated with no symptoms. (48-52) Some children are able to drink 1 to 2 glasses of milk each day without difficulty but can not tolerate more without developing symptoms. (17) Many lactose intolerant individuals can tolerate milk chocolate (53) and/or yogurt (plain better than flavored) because bacteria in yogurt partially digest lactose into glucose and galactose before consumption.(54,55) In addition yogurt's semisolid state slows gastric emptying and gastrointestinal transit resulting in fewer symptoms of lactose intolerance. (56) Further more ingestion of other solid foods delays gastric emptying, providing additional time for endogenous lactase to digest dietary lactose. Aged cheese tends to have lower lactose content and thus may also be better tolerated. Oral lactase replacement capsules or predigested milk or dairy products with lactase will permit ingestion of some or all milk products freely. (57) Labels must be checked to verify vitamin D content of individual brands.

Importance of dietary dairy products has been stressed even among population groups with significant lactose intolerance It is recommended that black people consume 3 to4 servings per day of low fat milk, cheese, and/or yogurt and that lactose free milk be used as an alternative for lactose intolerant individuals to help reduce the risk of nutrient related chronic diseases such as hypertension and diabetes. (58)

Milk and dairy products are well tolerated by many children with underlying inflammatory conditions such as crohn's disease and ulcerative colitis in whom prevalence of lactose intolerance does not seem to be any greater than in general population. (59-62)

Lactose Free Formulas

In developed countries in case of acute gastroenteritis, enough lactose digestion and absorption are preserved so that low lactose and lactose free formulas have no clinical advantage compared with standard lactose containing formulas except in severely undernourished children. (63) Breast fed infants should be continued on breast milk in all cases. (58) Although lactose free cow milk protein based formulas are available, their impact on clinical outcome measures including colic, growth and development has not been documented. (64)

Lactose, Calcium Absorption and Bone Mineral Content

Recent evidence indicates that dietary lactose enhances calcium absorption and conversely that lactose free diets result in lower calcium absorption (65) predisposing to inadequate bone mineralization. (47,48) The effects of lactose free diets in childhood on long term bone mineral content and risk of fractures

and osteoporosis with aging remains to be clarified. Calcium homeostasis is also affected by protein intake and genetic and other factors making long term studies essential to determine risk of each or all of these to bone health. In future, genetic testing may be useful for identifying individuals at increased risk of lactase deficiency and consequent diminished bone mineral density potentially allowing early intervention with dietary manipulation or nutrient supplementation. (66) Gene replacement therapies might someday be available for susceptible individuals. (67)

Summary

Lactose intolerance has been recognized for many years as a common problem in many children and most adults throughout the world. Although rarely life threatening it can lead to significant discomfort, disrupt quality of life, loss of school attendance, leisure and sports activities and work time all at a cost to individuals, families and society. Treatment is relatively simple aimed at reducing or eliminating lactose from diet or predigesting it with lactase enzyme. Calcium must be provided by alternate non dairy dietary source or as a dietary supplement to individuals who avoid milk intake.

Key Messages

- Lactose intolerance is a common cause of abdominal pain in older children and teenagers.
- Primary lactose intolerance is uncommon before 2 to 3 years of age in all populations. When lactose malabsorption becomes apparent before 2 to 3 years other etiologies must be sought.
- Diagnosis can be easily made by dietary elimination and challenge and non invasive formal testing with faecal pH and hydrogen breath testing.
- Lactose free diets should include a good source of calcium and/or calcium supplementation to meet daily recommended intake levels.
- Use of partially digested products such as yogurts, cheese, products containing lactobacillus acidophilus and pretreated milks provide important alternatives to milk to avoid inadequate calcium intake and suboptimal bone mineralization. Dairy products remain principle sources of protein and other nutrients that are essential for growth in children.

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