Lactose Intolerance in General Practice

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Introduction

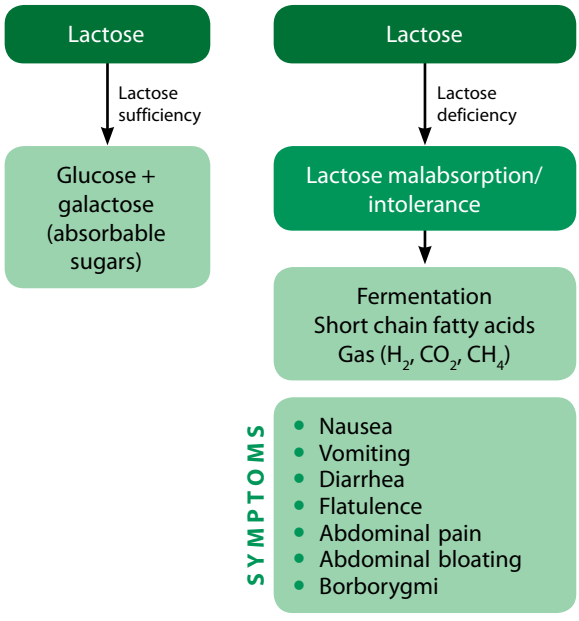
Lactose intolerance is the most common clinical problem that limits milk and dairy products consumption worldwide and it is defined as the experience of gastrointestinal symptoms due to the intake of lactose-containing food products.[1] Lactose is a disaccharide sugar that is mainly found in human and mammalian milk and vital for the nourishment of newborn infants. It is naturally metabolized into absorbable sugars, namely glucose and galactose, by the enzyme lactase in the mucosal brush-border of the intestine.[2-5] It has been found that only about 35% of people worldwide are lactase persistent, who continue to produce lactase throughout adulthood, and thus are able to digest the sugar in milk without discomfort.[6] The remaining majority of global population, owing to a deficiency of intestinal lactase enzyme, is unable to digest considerable amounts of lactose and thus presents with lactose intolerance.[4-6]

The unabsorbed lactose is metabolized by colonic bacteria to produce short-chain fatty acids and gas, mainly hydrogen (H_2), carbon dioxide (CO_2), and methane (CH_4).[4] The gas distends the intestines and likely explains the clinical syndrome that manifests with a range of gastrointestinal symptoms including abdominal cramps, bloating, and flatulence.[4,7-9] Moreover, undigested lactose creates an osmotic load that draws fluid and electrolytes into the intestinal lumen, often resulting in loose stools or osmotic diarrhea (Figure 1).[10,11]

Burden of Lactose Intolerance

Almost three-fourth of the human population worldwide has a reduced ability to digest lactose after infancy. The wide prevalence of lactose intolerance varies with different races and geographical distribution.[12-14] Data in this context has revealed that lactose intolerance can be seen in up to 22% of people of Northern European descent and the US white population, 50-80% of blacks and Latinos, and up to 100% of American Indians and Asians.[4,5,13]

Figure 1: Lactase deficiency leading to lactose malabsorption and intolerance



Lactose Intolerance in India

The global trend of lactose intolerance is reflected in the Indian population as well, with high prevalence of lactase non-persistence being observed in India. However, studies conducted in India have shown certain demographic variations within the nation. In India, it has been observed that the frequency and degree of lactose intolerance is higher in the Southern Indian populations compared to the North Indian populations, which could be attributable to possible genetic variations among these subpopulations (Figure 2A,2B).[9,15] This signifies that the varying pattern of milk consumption in different Indian subgroups is influenced not only by their dietary habits, but also by their genetic structure and ancestral history.[16,17]

Figure 2: Incidence/prevalence of lactose intolerance among Indian population

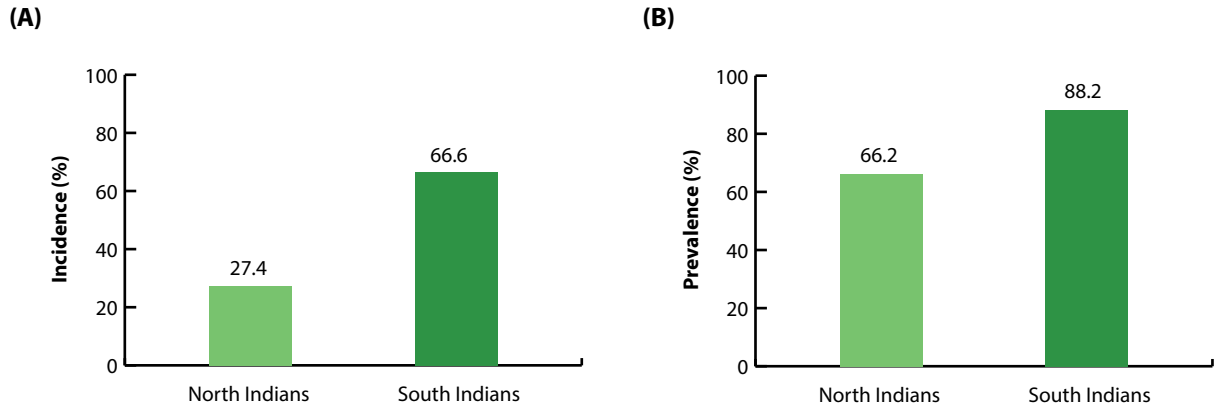
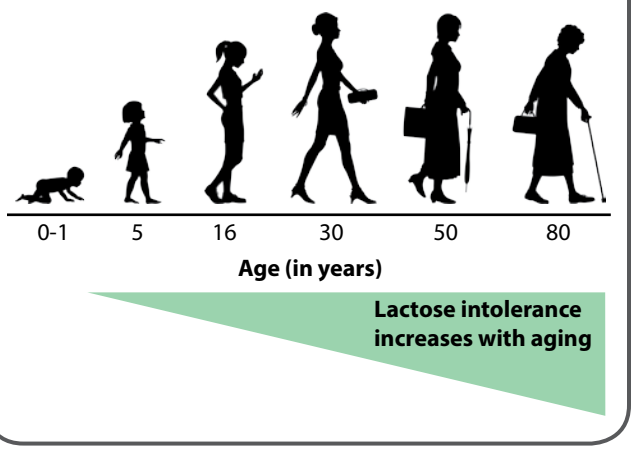


Figure 3: Relationship between age and lactose intolerance



Furthermore, it has been shown that lactase activity is highest at birth and declines after weaning, thus signifying a relationship between age and lactose intolerance. This association translates to an increase in prevalence of lactose malabsorption with an increase in age (Figure 3).[13,14,18,19]

Lactose Intolerance and Quality-of-Life

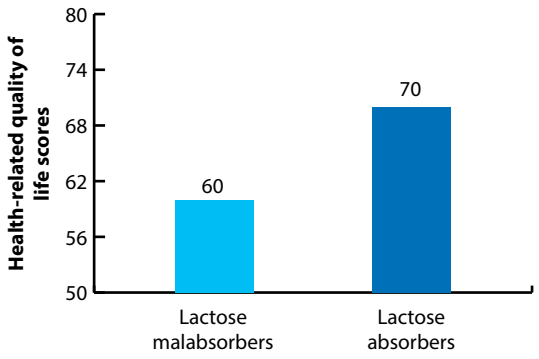
Lactose intolerance and its symptoms can be disabling enough to interfere with the daily life.[4,20] The symptoms associated with lactose intolerance or malabsorption have great relevance and, probably, a substantial impact on well-being of the patients. In fact, symptoms of lactose intolerance have been suggested to reveal a tendency towards somatization that could impair quality of life or may be detrimental to quality of life in patients with functional gastrointestinal symptoms.[20] Similar concerns have been reflected in a 3-year prospective, cross-sectional study,[20] wherein it was revealed that both self-perception of lactose intolerance and objective lactose malabsorption were associated with poorer perceived quality-of-life. Health-related quality of life (HRQOL) scores were remarkably lower in lactose malabsorbers as compared to the absorbers (Figure 4), thus underscoring the effect of lactose malabsorption/intolerance on daily life.[21]

Effects of Limiting Dairy Products in Patients with Lactose Intolerance

In practice, it has been observed that not all patients with lactose intolerance require absolute restriction of dairy products since many of them are not necessarily totally allergic to milk and can consume dairy foods without developing symptoms. Yet, it is often seen that many individuals avoid dairy products due to the often mistaken belief that they are lactose intolerant, while the truth is that many individuals who think they are lactose intolerant are not actually lactose malabsorbers. A complete cessation of milk and dairy products by these individuals might result in certain unwarranted nutritional and health consequences. It may be underscored by the fact that milk and dairy products provide a nutritional package with several necessary nutrients such as calcium, phosphorous, potassium, vitamin D and riboflavin, which is usually difficult to replicate.[14,22-25]

Dietary surveys of the sources of calcium in human diet demonstrate that most calcium requirements in developed countries are provided by milk and dairy products, whereas lack of adequate calcium intake in

Figure 4: Difference in health-related quality of life scores among lactose malabsorbers and absorbers



developing countries is associated with low intake of dairy products.[14] If milk and dairy products are restricted in the diet owing to lactose intolerance, it could probably lead to not only protein malnutrition but also poor dietary calcium intake, especially in predominantly vegetarian populations as in India.[9,22,26]

According to the National Institute of Health (NIH) experts, individuals do not need to eliminate the dairy consumption completely in most cases of lactose intolerance.[27] Yet, many individuals with objective or perceived lactose intolerance avoid dairy products and expose themselves to inadequate amounts of calcium and vitamin D, which may contribute to relative secondary hyperparathyroidism, and an increase in the rate of bone remodeling to maintain normal serum calcium levels that may lead to reduced peak bone mass, increased incidence of osteopenia and greater risk of osteoporosis and bone fractures. It is quite evident that avoidance of milk and dairy products negatively affects the quality of life in these patients (Box 1).[22,26] Altogether, avoiding milk and dairy products does not seem a rational approach, and efforts should be made to devise effective strategies to increase dairy food consumption even in individuals with documented lactose intolerance.[21]

Types of Lactose Intolerance

Generally, lactose intolerance can be described in three different forms, i.e., congenital, primary late onset, and secondary. Congenital lactose intolerance is usually rare, with symptoms attributable to congenital deficiency of lactase enzyme; symptoms occur short after birth on

Box 1: Consequences of lactase deficiency

- Deficiency of calcium, vitamin D and riboflavin
- Secondary hyperparathyroidism
- Malnutrition
- Unhealthy weight loss
- Reduced peak bone mass
- Increased risk of developing various conditions, such as osteopenia, osteoporosis, and bone fractures
- Malabsorption of the essential amino acid L-tryptophan that may lead to serotonin deficiencies, clinical depression, and anxiety
- Reduced quality of life

introduction of milk.[3,17] In Asia, vast majority of children are proposed to develop late onset congenital lactase deficiency, which again rarely causes symptoms before the age of 4-5 years.[28] The prevalence of lactose malabsorption in adults increases with ageing, owing to a maturational decline in lactase activity.[19,29]

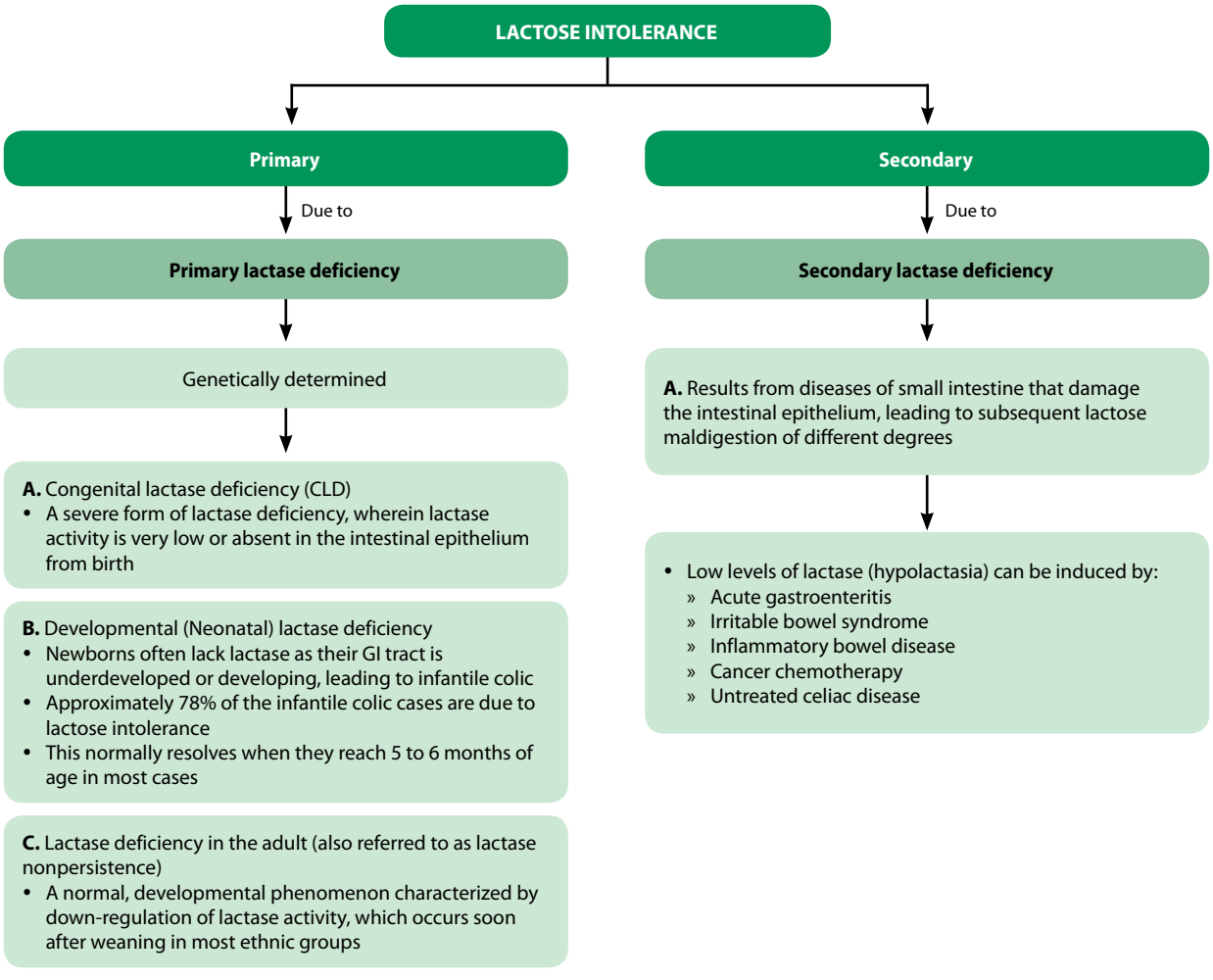
In adult patients, lactose intolerance can either be due to primary or secondary lactase deficiency. While primary lactase deficiency would result in symptoms on consuming a glass of milk, secondary lactase deficiency occurs when lactase is reduced because of diseases affecting the intestinal mucosa.[1] A number of causes have been identified as possible etiologies for secondary lactose intolerance, such as infectious gastroenteritis, inflammatory bowel disease, and irritable bowel syndrome (IBS) (Figure 5).[30-38]

Lactose malabsorption in such secondary cases occurs temporally; since lactase activity gradually returns to normal on treatment of the underlying cause.[28] In IBS, the incidence of lactose intolerance is particularly higher in the diarrheal type of IBS compared to other subtypes.[39]

Clinical Features of Lactose Intolerance

Clinical features of lactose intolerance are attributable to most of the dietary lactose passing unaltered through the small intestine into the colon – due to hypolactasia; where it is rapidly metabolized by the colonic bacteria. Consequently, the patient will typically experience excessive fluid and gas in the bowel. Common symptoms of the lactose intolerance thus include abdominal pain and bloating, excessive flatus, and watery stool, and typically occur following the ingestion of lactose containing foods by individuals intolerant to lactose. However, the extent and severity of symptoms that patients experience will vary dependent on the quantity of the lactose ingested and individual's ability to digest lactose. Symptoms thus

Figure 5: Types of lactose intolerance/deficiency



depend on the amount and rate of lactose reaching the colon, and also on the amount and type of colonic flora.[4,23,30]

Diagnosis of Lactose Intolerance

Lactose intolerance can be diagnosed through history and symptoms. There are few diagnostic tests for detecting lactase deficiency. Usually, in most of the cases, diagnosis of lactose intolerance can be made based on typical clinical history of development of symptoms following ingestion of milk and milk products. This subjective diagnosis can be further firmed using a subjective lactose challenge test, wherein patients are advised to take 500 ml of milk (25 grams of lactose). Subsequently, with fasting for about 1-3 hours, if patients experience bothersome symptoms of abdominal pain, bloating, flatulence, diarrhea, nausea, and vomiting, this suggests the presence of lactose intolerance. If required, an objective confirmation of the diagnosis can be done through additional testing, such as breath hydrogen test (BHT) and/or lactose tolerance test (LTT) that are based on changes in breath hydrogen levels or serum glucose levels after ingestion of standard doses of lactose.[5] Often, a positive breath test in presence of clinical symptoms induced by ingestion of a lactose load, and relieved by removal of lactose from the diet, is considered definitive of the diagnosis in most suspected cases of lactose intolerance.[40]

It is important to note that the diagnosis of lactose intolerance is mostly clinical and the breath tests are not easy and with less specificity and sensitivity. This often leads to both false positive and negative results, posing problem in diagnosis in individual cases.[30] This is because

Box 2: Differential diagnosis for lactose intolerance

- Irritable bowel syndrome
- Regional enteritis
- Ulcerative colitis
- Cystic fibrosis
- Celiac disease
- Bowel neoplasm or polyp
- Diverticular disease
- Iatrogenic: inadvertent ingestion of laxative
- Mechanical bowel compromise from previous endometriosis, adhesions, or gynecologic mass
- Tropical sprue
- Viral, bacterial, and parasitic infections

some leading differential diagnoses, such as IBS, can possibly be present in patients being evaluated for lactose intolerance (Box 2).[5,41] Further more definite investigation would be required in these patients to identify and manage the underlying primary condition.

Management of Lactose Intolerance

Dietary Management

The therapeutic approach aims at improving the symptoms while maintaining an adequate intake of calcium, thus preventing secondary bone disease caused by a milk-restricted diet.[3] Resonating the same notion, guidelines from various authorities including the European Food Safety Authority and National Institute of Health (US) do not recommend avoidance of milk/dairy consumption.[27,30]

Evidence from the clinical practice has shown that some people with lactose intolerance can consume milk and dairy foods without developing symptoms, thereby reducing the need for strict elimination of dairy products from the diet; however, some others will require more strict lactose restriction.[22,42] Herein, it should be noted that there are considerable variations in the amount of lactose that can be tolerated among lactose-intolerant individuals. In this context, the NIH suggests that adults and adolescents with lactose malabsorption could consume at least 12 gm of lactose (the amount of lactose in 1 cup of milk) without symptoms or with only minor symptoms, although symptoms may become more prominent at doses above 12 gm, and substantial after 24 gm of lactose.[14,22] Therefore, intake of milk could carefully be limited to about 1 cup or <250 ml per day for lactose maldigesters.[43] This dairy/milk intake may preferably be taken with meals or in small amounts throughout the day.[14]

Moreover, the choice of food product is also important since amount of lactose may depend upon the quantity of milk or milk product used in making a particular food preparation.[44] For instance, cheese, yoghurt and curds may be better tolerated; since lactose in these preparations is partially hydrolyzed by the bacteria during preparation and thicker consistency of these products allow slower gastric emptying.[4,45] Nevertheless, for patients with a lower threshold to lactose intolerance, the key to management is dietary removal of the lactose.[8]

Table 1: Calcium content present in common milk products

Food	Portion size	Calcium (mg)
Milk, nonfat	1 cup (≈250 mL)	299
Milk, buttermilk	1 cup (≈250 mL)	282–350
Milk, whole (3.25% milk fat)	1 cup (≈250 mL)	276
Yogurt, plain, low fat	≈225 gm	415
Cheddar cheese	≈42.5 gm	307
Cheese, cream, regular	1 tablespoon	14
Ice cream, vanilla	≈113 gm	84

Furthermore, considering that dairy products are expected to provide most of the dietary calcium (Table 1),[46] milk avoidance with subsequent restriction of calcium intake below the recommended level of 1 g per day for men and women, and 1.3 g per day for adolescents, is cause for serious concern.[22] Therefore, adult patients with lactose intolerance should also be advised to maintain a calcium intake of 1,200 to 1,500 mg per day, regardless of their actual intake of dairy products up to their individual symptoms' threshold. Patients may thus consider drinking lactose-reduced milk or taking calcium supplements to maintain the body calcium levels.[5]

Lactase Enzyme Replacement Therapy

Overall, since dairy avoidance is not the practical solution in most cases with lactose intolerance, physicians should devise additional and effective strategies to not only counter the symptoms of lactose malabsorption, but increase dairy food consumption even in those with documented lactose intolerance; thus striving to achieve an overall improvement. Lactase enzyme supplementation therapy, wherein lactase from nonhuman sources (yeasts or fungi) is used to hydrolyze the dietary lactose, is such an important adjunctive measure that has shown appreciable results in patients with lactose intolerance.[5,23,47]

It has been found to be highly effective in decreasing the symptoms of lactose intolerance The efficacy and tolerability of the lactase preparation used may however vary dependent on the source; this besides other factors

may be influenced by the pH stability of the preparation. In this regard, Aspergillus oryzae has been identified as a good source for the enzyme. These preparations are stable in an acidic environment and are practically pH independent, thereby exhibiting high activity throughout the gastrointestinal tract, even in lower stomach where pH is less than 3.5. Aspergillus oryzae preparation has been approved and recommend by agencies in both the United States (United States Food and Drug Administration, USFDA) and Europe (European Food Safety Association, EFSA). Besides, the preparation is Generally Regarded as Safe (GRAS).[30,48-50]

Evidence Based Efficacy of Lactase Replacement/ Supplementation

The effectiveness of lactase supplementation has been demonstrated in a number of studies in increasing dairy consumption, and promoting overall health of lactose intolerant people, likely by improving lactose absorption and intolerance symptoms.[51]

In an Asian study,[51] a group of researchers evaluated the effects of lactase supplementation on lactose malabsorption and its intolerance symptoms, as well as the available way to improve lactose absorption. Healthy adults with a history of lactose intolerance were screened by 25 g lactose tolerance test and those with higher H2 expired and/or lactose intolerance symptoms were selected for evaluation. These selected individuals were challenged twice with '400 ml low fat milk' and '400 ml low fat milk + 9000Fcc lactase' separately in three days interval. The breath H2 concentration and intolerance symptoms were evaluated in 4 hours after the challenge. Findings of the study revealed that exogenous lactase supplementation can considerably decrease the incidence of lactose malabsorption (the abnormal expiration of H2 decreased from 100% to 48.9%; Figure 6) and milk intolerance symptoms (from 51.1% to 13.3%; Figure 7). Altogether, it was revealed that lactose malabsorption and intolerance symptoms could be attributed to the reduced enzyme activities of individuals, and supplementation with exogenous lactase can ameliorate lactose absorption and intolerance symptoms.

Figure 6: Incidence of abnormal expiration of H2 following exogenous lactase supplementation in lactose intolerant adults

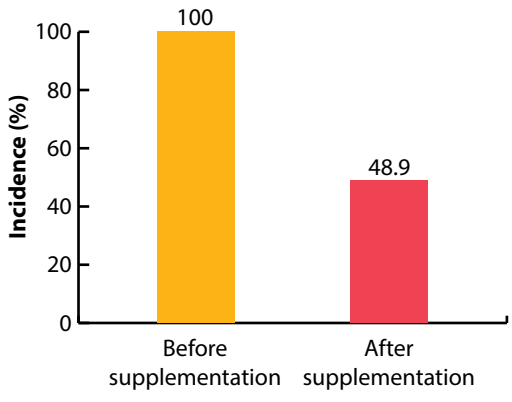
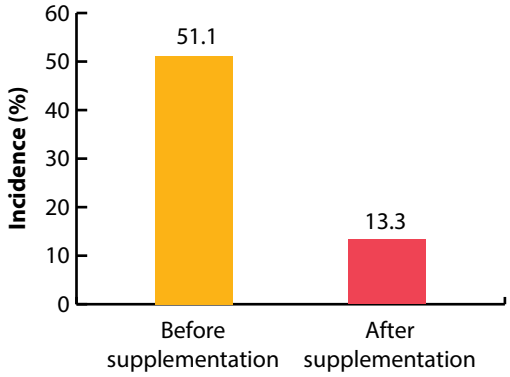


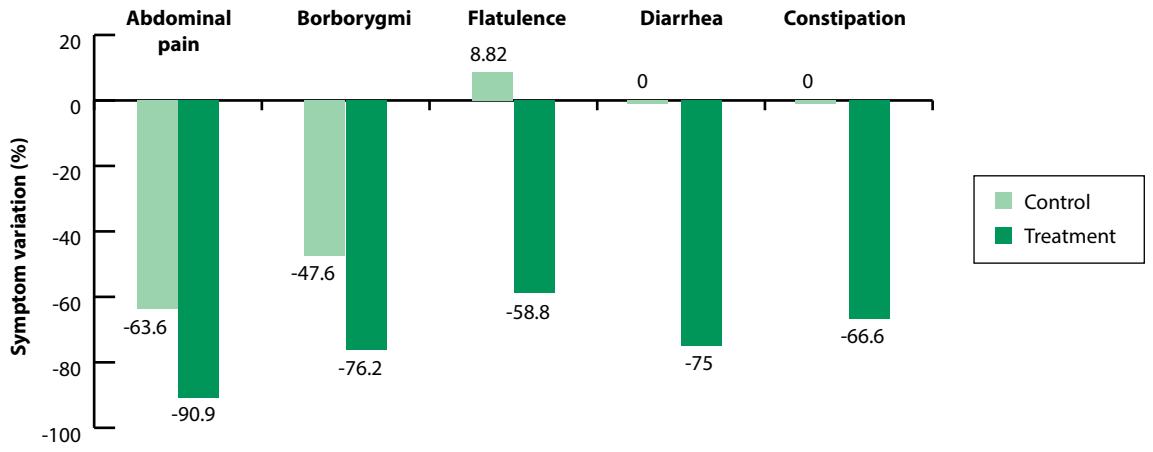
Figure 7: Incidence of milk intolerance symptoms following exogenous lactase supplementation in lactose intolerant adults



Di Pierro and colleagues[52] evaluated the impact of lactase supplementation on gut symptoms in lactose intolerant patients by categorically subjecting them to uncontrolled diet, diet devoid of offending foods, and uncontrolled diet along with lactase supplementation through a seven-week trial. Findings of the study revealed that even with the uncontrolled diet, intolerant patients treated with lactase supplementation exhibited reduced gut symptoms (bloating, flatulence, diarrhea, and constipation) significantly better than the control treatment as well as having a diet devoid of offending foods (Figure 8). Therefore, it could be deduced that lactase supplementation is a valid, well-tolerated, and effective therapeutic option to counteract lactose intolerance in patients who prefer not to avoid, at least partially milk and dairy products.

It is evident from the above mentioned studies that exogenous lactase supplementation with milk and dairy products could be an effective strategy in ameliorating lactose maldigestion, and may represent a convenient approach in milk/lactose intolerance.[53]

Figure 8: Variation in gastrointestinal symptoms of lactose intolerance in patients treated with lactase supplementation compared to the control group



Lactase Supplementation in Secondary Lactose Intolerance

Secondary lactose intolerance is attributable to lactase deficiency, secondary to various etiologies, such as small bowel bacterial overgrowth, infectious gastroenteritis, mucosal damage due to celiac disease, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), gastrointestinal surgery, short bowel syndrome, or radiation enteritis that often lead to destruction of intestinal lining (epithelial cells). Patients are unable to digest milk and are often advised to restrict milk and dairy products. Avoidance of milk and dairy products impairs the quality-of-life in these patients. Therefore, besides managing the underlying etiology, it is crucial to manage the ensuing lactose intolerance, which could be effectively achieved by lactase enzyme supplementation therapy.[7,28,30,46,51]

Conclusion

Lactose intolerance is a common problem in clinical practice that occurs due to a deficiency of the gastrointestinal lactase enzyme limiting the consumption of milk and dairy products. Many individuals, especially in Asia, have some sort of lactose intolerance, and are unable to digest lactose present in milk and milk products. In India, the frequency and degree of lactose intolerance is higher in the Southern Indian populations compared to the North Indian populations, which could be attributable to possible genetic variations among these subpopulations.

While diagnosis of lactose intolerance can be made by clinical history and supported by findings of breath hydrogen or lactose tolerance test, the management typically initiates with dietary modulation. Patients are often advised or they try to reduce or stop their intake of milk and other dairy products. However, such a practice of restriction of milk ingestion is not rational, because many patients of self-perceived or documented lactose intolerance may tolerate adequate amount of milk products depending on their individual symptoms' threshold. Furthermore, avoiding dairy products may have other consequences of leading to nutritional deficiency and poor quality-of-life in these patients.

The therapeutic approach aims at improving the symptoms while maintaining an adequate intake of calcium, thus preventing secondary bone disease caused by a milk-restricted diet. In such scenario, oral supplementation of exogenously derived lactase enzyme is an important adjunct to manage lactose intolerance. Herein, exogenous lactase is administered as an enzymatic supplement with an aim to hydrolyze the dietary lactose. While lactase enzyme supplementation decreases the symptoms of bloating, abdominal pain and disturbed bowel movement in majority of patients with lactose intolerance, this may also possibly alleviate certain long-term consequences of dairy restriction that people begin to follow while suffering from self-perceived or real lactose intolerance. Studies have substantiated the effectiveness of lactase supplementation in increasing dairy consumption, and promoting overall health of lactose intolerant people.

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