Lactose and Fructose Intolerance

Eitan Amir and Peter J. Whorwell

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Lactose and fructose are important carbohydrates, which are included in the human diet throughout the world. Maldigestion or malabsorption of these carbohydrates is very common in both normal patients and those with bowel symptoms [1]. Studies show that the frequency of maldigestion of lactose may be as high as 98% [2] while the prevalence of fructose malabsorption has been shown to be as high as 60% [3–6]. Not all patients with such carbohydrate malabsorption develop symptoms. However, in selected subjects, carbohydrate malabsorption is associated with symptomatology such as bloating, flatulence, abdominal pain and diarrhoea. When these manifestations are present, the subject is considered to have “carbohydrate intolerance” [7].

This chapter will present the latest evidence regarding the intolerance to both lactose and fructose and explore how these disorders impact clinical practice in the field of functional bowel disease.

Lactose Intolerance

Introduction

Lactose is a disaccharide, which is present in milk and many processed foods. It is, therefore, found in significant quantities in the diets of people across the whole world. Since only monosaccharides are absorbed across the intestinal epithelium, disaccharides such as lactose must be enzymatically cleaved into their monosaccharide

E. Amir
Department of Medical Oncology, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 4BX, UK

P.J. Whorwell (✉)
University Hospitals of South Manchester, Education and Research Centre, Wythenshawe Hospital, Southmoor Road, Wythenshawe, Manchester, M23 9LT, UK

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components prior to absorption. Abnormalities of lactose hydrolysis lead to the build up of lactose within the gut and this is thought to contribute to symptomatology.

Epidemiology

Lactose maldigestion is a prevalent disorder with marked geographic variability. Evidence [8, 9] shows that at least 50% of people in South America, Africa and Asia suffer from this disorder. Certain areas in Asia in particular show prevalence rates approaching 100%. In North America it is estimated that 15% of Caucasians, 53% of Mexican-Americans and 80% of African-Americans are affected, while in Europe prevalence rates vary from 2% in Scandinavia to approximately 70% in Southern Europe.

This geographic variability is also seen in the age of manifestation of symptoms, with subjects of African or Asian origin developing symptoms in early childhood compared with Caucasians who are affected predominantly in adolescence [8].

Males and females tend to be affected equally [10]; however, several studies [11–13] have shown that women who are lactose intolerant regain the ability to digest lactose during pregnancy.

Clinical Features

Symptoms of lactose intolerance include diarrhoea, abdominal bloating and pain, flatulence, nausea and borborygmi. The mechanism of loose stools induced by unabsorbed carbohydrate is well documented: the osmotic load of the carbohydrate causes secretion of fluid and electrolytes until osmotic equilibrium is reached [14, 15]. Dilatation of the intestine, caused by the osmosis, induces an acceleration of small intestinal transit, which increases with the degree of maldigestion [16].

Pathophysiology

Lactose maldigestion occurs due to inability to break down lactose to its components galactose and glucose [17]. The effects of the processing of this maldigested lactose within the colon is thought to be the cause of intolerance symptoms.

Recent evidence shows that lactose maldigestion has two predominant causative factors: a deficiency of the enzyme lactase and abnormal oro-caecal transit time [18]. The latter of these incorporates both gastric emptying time and small bowel transit time.

Lactase Deficiency

Lactase, which is normally produced by the intestinal brush borders exists in high concentrations in neonates, but during weaning, its activity begins to decline. This
process, which has been shown to occur in the majority of the world's population, is thought to be genetically programmed and irreversible [19].

Following the neonatal period, all humans show a reduction of lactase activity with consequential reduction in lactose digestion. The level of this reduction in activity is highly variable. In the 1960s this variability was thought to be an acquired trait [20], but more recent evidence shows that it is, in fact, genetically determined. Enattah and colleagues [21] showed that lactose maldigestion is associated with a non-coding variation in the MCM6 gene (present on chromosome 4q21). This variation consists of a C/T(-13910) polymorphism located in an intron of the MCM6 gene. This locus is present 14 kb upstream from the lactase gene itself. The role of the variation in lactase may be unrelated to the MCM6 gene itself. This study showed that the presence of the C allele in place of the T allele was mostly associated with hypolactasia with all individuals with lactase deficiency being found to be homozygous with respect to the C allele. This polymorphism has now been developed into a screening test for lactose intolerance [22]. A further variation consisting of a G/A(-22018) polymorphism has also been described upstream of the lactase gene [23]; however, its significance in isolation is unclear.

**Mucosal Damage**

The concept of enteric infection causing lactose intolerance is well recognised. Intolerance can develop in people who had hitherto been tolerant to lactose. This phenomenon is likely to be secondary to mucosal injury, including infectious gastroenteritis, particularly if it affects the small bowel [24].

This theory is based on data from several observational studies. Langman and colleagues investigated endoscopic duodenal biopsies of symptomatic subjects. They found that the presence of moderate to severe duodenal lesions was associated with a significant decrease in all disaccharidase activity. However, in mild lesions, only lactase activity was reduced [25]. This may be explained by the fact that lactase activity is maximal at the distal part of the villus and hence is more susceptible to damage. Investigators also found that treatment of the underlying disorder leads to improvement in lactase activity, although this did lag behind the return of other intestinal function. In fact, it showed that symptoms of lactose intolerance persisted for months after resolution of other intestinal symptoms.

The transient nature of this post-inflammatory disaccharide maldigestion has also been shown in a study of children, with acute gastroenteritis, in Poland [26]. In this study, the authors showed that carbohydrate intolerance was present in approximately one in seven of their cohort. However, evidence of maldigestion was shown to persist for only 5 days. In view of the age of the sample population, assessment of symptoms was not undertaken.

Other causes of mucosal injury causing lactose intolerance have also been described. Studies have shown that diseases of the small bowel such as Coeliac and Crohn's disease can cause both lactose maldigestion [27, 28] and delayed oro-caecal transit time [38, 39]. Furthermore, Tursi et al. [29] showed that most
patients affected by symptomatic, uncomplicated diverticular disease developed transient lactose maldigestion. In this study, laboratory evidence of maldigestion continued for only a few days, but again data on duration of symptoms were not collected. Finally, further work has shown that reversible hypolactasia can result from administration of 5-Fluoro-uracil based chemotherapy [30].

Abnormal Oro-Caecal Transit Time

Studies have shown that non-absorbable sugars can accelerate small intestinal transit time [31–33]. This phenomenon is thought to be caused by an increased intestinal liquid volume resulting from the osmotic effect of the malabsorbed sugars. It is postulated that the increased volume causes intestinal distension and stimulation of motility [34]. However, work by Vonk and colleagues [18] showed that the increased rate of transit was likely to be a person-specific factor, independent of the lactase activity level. This is supported by various studies, which have shown large inter-individual differences in small intestinal transit time in lactose maldigestion [35–37].

Conversely, however, lactose maldigestion is often associated with disorders in which the oro-caecal transit time is prolonged. Small bowel diseases, such as Coeliac disease or Crohn’s disease are associated with both lactose maldigestion [27, 28] and delayed oro-caecal transit time [38, 39]. It has been proposed that small bowel bacterial overgrowth is the mechanism by which delayed transit time causes intolerance symptoms [40].

A review by Tursi [41] therefore, concluded that lactose intolerance is most likely influenced by a variety of factors such as lactose maldigestion, abnormal oro-caecal transit time (which may be shortened or prolonged) and small bowel bacterial overgrowth.

Diagnosis

Lactose intolerance is often diagnosed on a clinical basis. The most commonly utilised process is that of an empirical trial of dietary lactose avoidance. Despite the ease of this method, a number of methods of diagnosing lactose maldigestion have been developed, specifically, lactose breath test, direct lactase enzyme activity and genetic testing for common polymorphisms.

Lactose Breath Test

The lactose breath test involves the intake of 50 g of lactose orally, followed by measurement of breath hydrogen every 30 min for 3 h. A breath hydrogen of 20 ppm above the nadir indicates lactose maldigestion [42]. This test, although highly specific has a relatively poor sensitivity of approximately 34% [43]. It is
also weakened by the fact that symptoms are not routinely recorded during the test [44] and hence, includes those with asymptomatic lactose malabsorption as well as those with true intolerance.

**Direct Lactase Enzyme Activity**

Direct lactase enzyme activity can be performed on tissue obtained from a small intestinal biopsy. This test is invasive, as it usually requires an upper gastrointestinal endoscopy. Furthermore, its reliability is sometimes low because disaccharidase activity in a particular small biopsy specimen does not necessarily reflect the activity of this enzyme in the rest of the small bowel [45].

**Genetic Testing**

The presence of the two genetic polymorphisms described above have led to the development of specific genetic tests to help diagnose lactose malabsorption. These tests have only recently been developed and the literature has opposing data on their application. One study [46] has shown that genotyping for the C/T(-13910) polymorphism is a reliable test for adult-type hypolactasia with high sensitivity and specificity, while another [47] has suggested that its use should be restricted to patients of north European origin. The latter study based its advice on data showing that the presence of the alternative allele C at this site is not a good predictor of hypolactasia in many non-Northern Europeans [48, 49]. Furthermore, this method also, relies on a small bowel biopsy and is, therefore, associated with the risks that obtaining this entails.

In summary, despite the development of advanced methods, the ease of utilising dietary lactose avoidance makes this the most appropriate first line investigation. However, if this fails and lactose intolerance remains suspected, other investigations such as those detailed above may be helpful.

**Management**

Treatment of lactose malabsorption is only required in those with symptoms suggestive of lactose intolerance [50]. Unfortunately, there are no internationally accepted guidelines for the treatment of lactose intolerance and hence, the usual therapeutic approach is that of exclusion of dairy and dairy-related products from the diet of affected individuals. However, elimination of these from the diet has many nutritional disadvantages, especially relating to an associated fall in bone mineral density [51]. As a result, alternative approaches have been assessed, most of which have aimed to prolong contact time between enzyme and substrate, delay oro-caecal transit time and therefore, enhance colonic adaptation.
Beta-Galactosidase

Beta-Galactosidase is an exogenous lactase enzyme, which can be obtained from a variety of yeasts and fungi.

Initial studies of the use of Beta-Galactosidase were conducted by adding the soluble enzyme in liquid form to milk a number of hours prior to consumption [52–55]. These showed that this so-called “pre-incubated milk” both reduced hydrogen breath excretion on lactose breath testing, as well as reduced symptoms after ingestion. However, these studies relied on data derived from very small populations and the methodology did not involve control arms. Furthermore, practicality aspects have meant that the addition of lactase to milk prior to ingestion has never been routinely utilised as a treatment modality.

Consequently, multiple studies have looked into whether the addition of lactase at the time of eating instead of using pre-incubated milk were of any benefit [56–59]. The most recent of these studies, by Montalto and colleagues [59], randomised 30 lactose intolerant subjects into a double blind, placebo controlled trial and showed that hydrogen excretion and symptom score were no different in the two arms. Further work on Beta-galactosidase has studied its safety in laboratory animals [60]. This study showed that there were no significant dose-related changes in body weights, feed consumption, organ weights, urinalysis, haematological profiles, biochemistry, or histopathological profiles.

Solid lactase preparations of exogenous lactase have also been made available in the form of capsules or tablets. They are an alternative to the soluble liquid form of lactase described above, and their efficacy also appears to be confirmed [61]. However, they are less effective than pre-hydrolysed milk, most likely due to the inactivation of the enzyme by gastric proteases [50].

On balance, therefore, it appears that the addition of exogenous lactase in the form of Beta-galactosidase is effective, practical and safe.

Yoghurt and Probiotics

The association between ingestion of fermented milk products and improvements in lactose digestion is well established [62, 63]. The fermentation of milk into yoghurt is usually carried out by incubating milk with two species of lactic acid bacteria, specifically, L. bulgaricus and S. thermophilus [64]. These bacteria hydrolyse lactose during the fermentation process and it is estimated that the lactose content is subsequently reduced by 25–50%. Unfortunately, this process leads to the formation of lactic acid, which contributes to the sour taste of yoghurt that some patients find unpalatable.

To overcome this problem, L. acidophilus can be substituted for lactic acid bacteria to produce unfermented “sweet milk”. However, multiple studies [65–67] have shown the inadequate effectiveness of this milk in reducing symptoms. A proposed explanation for this is that the availability of bacterial Beta-galactosidase is the main factor in improving lactose digestion and this is reduced in the case of L. acidophilus. De Vrese and colleagues [68] showed that bacteria need an intact
cell wall to protect their intracellular enzymes during exposure to gastric acid and against the actions of bile. It has been suggested that *L. bulgaricus*, despite having equivalent Beta-galactosidase activity and the same lactose active transport mechanism as *L. acidophilus*, has a softer cell wall membrane and hence is better adapted to release its enzymes than *L. acidophilus* [69].

A further study [70] has shown that yoghurt can delay gastric emptying and intestinal transit and, therefore, it optimises the effect of Beta-galactosidase in the small intestine.

**Delaying Oro-Caecal Transit Time**

Pharmacological approaches that delay both gastric emptying and intestinal transit time have been well studied. Peuhkurie and colleagues [71] undertook a double blind placebo controlled trial of propantheline and metoclopramide on lactose digestion. They found that propantheline induced a prolongation of gastric emptying and thus improved lactose tolerance compared with both metoclopramide and placebo. A similar study looking at intestinal transit showed improvement in symptoms after administration of loperamide [72].

The use of high calorie foods in place of pharmacological agents has also been studied with varying results. Leichter et al. [73] showed that full-fat milk improved carbohydrate absorption by slowing both gastric emptying and intestinal transit. However, work by Vesa and colleagues [74] disputed this by showing no improvement in lactose tolerance after ingestion of high energy milk.

It therefore appears that pharmacological approaches are more efficacious than dietary attempts to delay transit, although some would question the advisability of using a pharmacological approach to this long term problem.

**Adaptation**

As described above, lactase undergoes an irreversible reduction in its activity after the neonatal period. However, it has been reported that continuous dietary intake of lactose reduces the severity of gastrointestinal symptoms [75, 76]. It has been proposed that this “adaptation” is related to both changes in the gut microflora as well as to changes in colonic function.

Various studies have tried to explain this phenomenon in detail: Hertzler et al. [77] showed that after daily ingestion of milk for 10 days, levels of faecal Beta-galactosidase were elevated. It was hypothesized that the origin of this enzyme was from gut microbes, which increased their level of lactose fermentation activity. This was confirmed by Hill and colleagues [78] who showed that the presence of malabsorbed lactose enhanced the fermentation ability of various gut bacteria. These included bifidobacteria and lactic acid bacteria, which can metabolise lactose without producing hydrogen. Further work by Perman et al. [79] suggested that the acidic products of fermentation inhibit the production of hydrogen and hence reduce symptoms.
However, work by Briet and colleagues [80] suggested that this adaptation could be explained by the placebo effect. In their double-blind controlled trial, it was shown that following intake of lactose for 13 consecutive days, there was a measurable increase in faecal Beta-galactosidase, reduced hydrogen excretion and improved symptoms. However, after comparison with the control group, no evidence of metabolic adaptation was found.

Montalto and colleagues [81] reviewed the above evidence and together with their clinical experience suggested a therapeutic management plan. This included a temporary lactose free diet to obtain remission of symptoms followed by gradual re-introduction of lactose without overcoming the individual threshold dose. It was recommended that the threshold dose could then be increased with the aid of both pharmacological and non-pharmacological strategies as detailed above.

**Lactose and Pharmaceutical Agents**

Lactose is widely used by the pharmaceutical industry as a filler or diluent in oral capsule, powder and tablet formulations. It is also used as a carrier for drugs in dry powder inhalers as well as in combination with sucrose in the preparation of sugar-coating solutions [82].

The total quantity of lactose that may be ingested through the administration of pharmaceutical agents seldom exceeds 2 g a day. Therefore, the use of medications containing lactose is unlikely to result in gastrointestinal symptoms in the majority of people [82]. A review of the literature has uncovered a few case reports of intolerance to lactose in medication [83–86]; therefore, for a small number of patients, lactose-free medication may be required.

**Complications**

Lactose intolerance is considered to be a relatively benign condition with few complications. Historically, it has been assumed that patients with lactose intolerance have a reduced intake of calcium as a result of either low-dairy or dairy-free diets. It has therefore been proposed that lactose intolerance could be a potential cause of osteopenia or osteoporosis.

The current literature is rather conflicting on the link between lactose intolerance and loss of bone mineral density. A large population based study of perimenopausal women in Finland [87] did show that lactose intolerance slightly reduced perimenopausal bone mineral density, possibly through reduced calcium intake. However, a smaller study of adult women in the United States [88] showed no correlation between expired hydrogen content and bone mass at various sites. It therefore concluded that there was no association between lactose intolerance and loss of bone density. A possible explanation for the disparity of the above results is the different methodologies for determining the presence of lactose intolerance, which were used in these studies.
A more recent case control study from Austria [89] showed that individuals with lactose intolerance, verified by the hydrogen breath test, did not appear to be at risk for accelerated bone loss. Nevertheless, a relationship between vertebral fractures and lactose intolerance cannot be excluded, as a few individuals with severe lactose intolerance had a large number of vertebral fractures.

**Fructose Intolerance**

*Introduction*

Fructose is a hexose monosaccharide, which is consumed frequently in Western diets. It is found in three main forms: as free fructose (present in fruits and honey); as a constituent of the disaccharide sucrose; or as fructans, a polymer of fructose (present in some vegetables and wheat) [90]. Unlike glucose, fructose does not have an active transport mechanism, but is absorbed by facilitative diffusion, a method that has limited capacity [91]. Therefore, fructose is liable to be malabsorbed and its presence in large quantities in the gut may give rise to symptoms similar to those in lactose intolerance.

Fructose Intolerance should not to be confused with Hereditary Fructose Intolerance (HFI), which is an autosomal recessive condition in which there is an inborn error of fructose metabolism caused by deficiency of the liver enzyme aldolase B.

**Epidemiology**

As described above, lactose intolerance is a well recognised cause of non-specific gastrointestinal complaints. However, less is known about the significance of other carbohydrates such as fructose.

Mishkin and colleagues [92] reported that between 40–55% of their cohort of patients with functional dyspepsia had fructose malabsorption. A Danish study [6], also showed a high proportion of fructose malabsorption in a small cohort of patients with functional bowel disorders. Several other uncontrolled studies [3, 93, 94] have also corroborated these data, and therefore, investigators have suggested that fructose malabsorption was more prevalent in patients with functional bowel disease (36–75%) than in healthy subjects (0–50%).

However, these data have not been confirmed by the only controlled study on the subject [95], which showed that the frequency of incomplete fructose absorption was not significantly different in patients with gastrointestinal symptoms than in controls. A possible explanation for this could be that patients with functional bowel disorders and incomplete fructose absorption describe higher symptom scores than those with functional bowel disease who absorb fructose adequately [6]. This might be a result of a heightened visceral sensitivity which is described in such disorders [96].
Clinical Features

Symptoms of fructose intolerance are similar to the constellation of symptoms associated with lactose intolerance. They can therefore, include abdominal distension, bloating and discomfort, excessive flatus and diarrhoea.

As is the case with lactose intolerance, it is the presence of an osmotic load in the gut, which draws fluid into the lumen and consequently leads to pain and bloating. Similarly, the fermentation of fructose by colonic bacteria has been shown to be the mechanism by which excess flatus and diarrhoea are manifested [3].

Pathophysiology

As described above, only monosaccharides can be absorbed across the intestinal epithelium. Glucose has a dedicated transporter, which actively transports it across the epithelium even against a concentration gradient. Other monosaccharides such as fructose rely on passive diffusion through a carrier mediated facilitated diffusion process.

Studies have isolated GLUT5, one of the glucose transport family transporters, as having a high affinity to fructose [97]. This transporter, which is found on the luminal surface of small intestinal epithelial cells, is thought to be responsible for fructose absorption from the intestinal lumen into enterocytes. A further glucose transporter called GLUT2 is thought to be responsible for the transportation of fructose from the enterocyte into the portal circulation.

Initial work on the mechanism of fructose malabsorption suggested the possible presence of mutant forms of the GLUT5 transporter protein. However, evidence from sequence analyses has shown that isolated fructose malabsorption does not result from the expression of a mutant GLUT5 protein [97].

Molecular studies have shown that GLUT5 expression can be induced by the presence of fructose within the gut lumen [98, 99]. However, if the capacity of diffusion of GLUT5 is exceeded, GLUT2 can be employed to assist in absorption of any excess luminal fructose. Gouyon and colleagues [100] reported that GLUT2, which is normally located in the basolateral membrane, could be recruited to the apical brush-border membrane upon ingestion of a fructose-rich meal. They therefore proposed that suboptimal recruitment of GLUT2 or its defective intestinal membrane insertion might be the mechanism for fructose malabsorption.

The mouse GLUT5 transporter has recently been cloned and it is hoped that this may allow for improved future investigation of the mechanisms regulating fructose absorption [101].

Other physiological principles underlying potential malabsorption of fructose have been identified from the literature. It has been shown that fructose absorption can be enhanced by the presence of either glucose [91] or amino acids [102] within the intestinal lumen. Furthermore, it has been shown that ingestion of fructose together with the sugar alcohol sorbitol impedes fructose absorption [103].
Lactose and Fructose Intolerance

The precise mechanism by which glucose enhances fructose absorption has not been definitively ascertained. However, it is postulated that glucose provides a stronger stimulus for increased expression of the GLUT family of transporters [91]. This phenomenon may explain why fructose, if given as sucrose, or in equimolar combination with glucose, can be well absorbed even in subjects with proven fructose malabsorption [6, 91, 104].

It is therefore proposed that the amount of fructose ingested in excess of glucose is likely to be an important determinant of fructose malabsorption. However, despite this, a high fructose load can still lead to malabsorption of fructose independently of the presence or absence of facilitators of its absorption [104].

Other hypotheses to explain the improved absorption of fructose in the presence of glucose and amino acids have been formed. Two studies have suggested that active transportation of amino acids and glucose into the enterocyte causes a “solvent drag” and hence enhances passive diffusion [105, 106]. A further study by Elias and colleagues [107] suggested that glucose caused a delay in gastric emptying and hence facilitated fructose absorption.

Sorbitol is one of several naturally occurring sugar alcohols and is used extensively as a “sugar-free” sweetener in many foods. It is incompletely absorbed [108] in the small intestine and appears to compete with fructose for absorption. Romsenss and colleagues [103] showed that sorbitol and fructose doses that are fully absorbed when ingested separately are incompletely absorbed when taken together. A further study [109] has suggested that the presence of both fructose and sorbitol in the gut accelerates transit by its synergistic osmotic effect and suggested this mechanism for the poor absorption of fructose in this context.

**Diagnosis**

Similar to other carbohydrates, incomplete absorption of fructose can be identified non-invasively by measuring breath hydrogen after a fructose load. Colonic fermentation of undigested carbohydrates produces a cocktail of short-chain fatty acids, hydrogen and carb higher doses on dioxide. Hydrogen cannot be metabolised by humans and hence must be excreted in breath or flatus or consumed by colonic bacteria to produce methane and sulphides. In general, a rise in breath hydrogen of more than 20 ppm peaking 2–3 h after ingestion of fructose is indicative of incomplete absorption [110]. Unfortunately, there is no international consensus over what constitutes an appropriate dose and concentration of fructose for such tests [111]. However, it is felt that lower fructose loads are more specific for recognition of fructose intolerance as higher doses are most likely to overwhelm the fructose absorptive capacity even of normal individuals [112].

Furthermore, the process of hydrogen breath testing is not without flaws. It relies on hydrogen-producing flora outnumbering hydrogen-consuming bacteria and is prone to false negative results. It has therefore been proposed that individuals should at first be subjected to a hydrogen breath test with lactulose (a non-absorbable,
synthetic disaccharide) and if this does not induce a hydrogen breath response, it is likely they lack the necessary flora. In this group of patients, testing for methane may identify malabsorption [113].

**Management**

Despite the substantial data on the pathogenesis of fructose intolerance, there are few published guidelines on its management. Shepherd and colleagues [114] attempted to address this deficiency in the literature by undertaking a retrospective study to evaluate a potentially successful diet therapy in patients with fructose malabsorption.

This diet included what was described as three “novel” principles. Firstly, there was an attempt to balance free fructose with glucose-rich foods. Secondly, the total fructose load was limited irrespective of whether the glucose content was equivalent or in excess to the fructose content. Finally, the diet included a reduced intake of fructans. Wheat is a major source of fructans in the diet [115] and hence reduction of its consumption was central. This leaves an important unanswered question, specifically, whether it is the reduction of fructans, which contributed to symptom relief or whether it was due to other dietary factors such as a reduction in the intake of insoluble fibre.

This diet was not effective for all patients with the authors reporting that 74% of their studied population showed significant symptomatic benefit. Furthermore, their methodology was limited in that it was not controlled, was analysed retrospectively, and the follow up period was as short as 2 months in some subjects.

**Complications**

Fructose intolerance is a benign condition with no known complications described in the literature.

**Summary**

The management of non-specific abdominal symptoms can sometimes prove to be a complex conundrum. Among the multitude of differential diagnoses is carbohydrate malabsorption, the prevalence of which is often underestimated. Lactose and fructose are important dietary carbohydrates that are included in human diet all over the world. Furthermore, there is a large body of evidence to show that malabsorption of these sugars is both prevalent and clinically relevant.
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