The consumption of milk and dairy products varies considerably in different regions of the world. Indeed, according to the statistics of the Food and Agriculture Organization of the United Nations (FAO), in 2007 the consumption of milk and dairy products averaged 240 kg and 360 kg per capita in the UK and Sweden, respectively, while in China it was about 29 kg per capita. Milk is a complex and nutrient-dense food [1] that may have positive or negative effects on adult health [2]. The major carbohydrate component in milk is lactose, a disaccharide whose concentration in bovine milk has been reported to range between 45 and 55 g/L [2–4]. Lactose needs to be digested by the small intestinal enzyme lactase into its constituent monosaccharides, glucose and galactose, before transport across the epithelial cell membranes.

Lactase activity is therefore essential for the development of young mammals, since their sole source of nourishment is their mother’s milk. In most mammals, including most humans, lactase expression decreases after the weaning period is over [5]. In humans, this condition is termed lactase non-persistence and is observed in around 65% of adults worldwide [6,7]. Lactase non-persistent individuals are sometimes described as having primary adult hypolactasia and are lactose maldigesters, while adults who have the genetically determined trait of lactase persistence (LP) and continue to produce lactase throughout life are termed lactose digesters.

The range of timing of lactase downregulation varies from one population to another; for example, most Chinese and Japanese become lactase non-persistent between 1 and 5 years old, while on average lactase non-persistence does not manifest in Finns and Estonians until somewhat later [8]. Even though the mechanisms of developmental lactase downregulation are not well understood, it is clear that it is not reversible [9,10]. Lactase production can also be lost through non-genetic mechanisms; this is called secondary hypolactasia and it can occur, for example, after any condition that damages the small intestinal mucosa brush border [11]. Adults with either primary or secondary hypolactasia are lactose malabsorbers and may exhibit symptoms of lactose intolerance after ingestion of lactose. Genetically determined lactase non-persistence is quite normal in the majority of humans worldwide and is distinct from congenital alactasia, the absence of lactase from birth. This, in contrast, is an extremely rare and potentially fatal condition. A number of mutations that affect the structure of the protein, and consequently its function, have been identified in Finnish patients suffering from this condition [12,13].

Two types of tests are available for determining lactase production status at the phenotypic level. Duodenal or jejunal biopsies can be taken by endoscopy and allow direct determination of lactase activity. A lactase assay is usually combined with routine histology and an assay of another enzyme such as sucrase, so that secondary deficiency of lactase can be readily identified. This procedure is the most accurate available, but it is invasive and performed routinely only if a pathological condition such as coeliac disease is indicated. Other methods
involve lactose ingestion after an overnight fast to inform indirectly on lactase activity [14]. For the glucose test, an increase in blood glucose is indicative of LP as lactase cleaves lactose into glucose and galactose. Although less commonly used for identifying LP, a urinary galactose test can also be performed, which also involves giving alcohol to block galactose uptake by the liver. Alternatively, the breath hydrogen test measures hydrogen production by colonic bacteria; in lactase non-persistent individuals, undigested lactose reaches the colon and hydrogen is released after fermentation by hydrogen-producing colonic bacteria, while in persistent individuals lactose is cleaved before reaching the colon. These tests require a baseline measurement of glucose, galactose or breath hydrogen before ingestion of the lactose load, and further measurements of the same at about 30-min intervals for 2–3h. It should be noted that these indirect tests are not 100% accurate (error rates are discussed in Mulcare et al. [15]) and cannot distinguish primary from secondary hypolactasia. For example, there are some individuals who do not have colonic bacteria that produce hydrogen, and therefore do not show a hydrogen rise irrespective of their lactase production status.

The passage of lactose into the colon in non-lactase producers can lead to GI symptoms, such as bloating, flatulence, abdominal pain and diarrhoea. These symptoms are described as ‘lactose intolerance’. Lactose intolerance should be distinguished from milk allergy; while the former is a non-toxic and non-immune adverse reaction to undigested lactose, milk allergy involves an immune response, usually to milk protein.

After an individual has been diagnosed as lactase non-persistent, dairy products are often removed from the diet. This may have serious nutritional disadvantages, such as reducing the intake of calcium, phosphorus and vitamins, and may be associated with decreased bone mineral density [2,16,17], while lactose-free milk products intake would avoid symptoms and be nutritious. In contrast, milk powder (which does contain lactose) has been used for famine relief in undernourished populations where the frequency of LP is often very low [18,19] and for whom symptoms of intolerance can potentially exacerbate diarrhoeal disease and mineral deficiency [18,20,21].

3.15.1 Lactase persistence

This section briefly summarises what is known about the genetics and evolution of the LP trait, but further details and references can be found in Gerbault et al. [22] and on the global lactase persistence database website (www.ucl.ac.uk/mace-lab/resources/glad).

The global distribution of lactase persistence

Figure 3.15.1 shows an interpolated map of the frequency of LP in indigenous populations worldwide. LP is particularly common in northern Europe, with frequencies of around 89–96% in the British Isles and southern Scandinavia; a declining gradient towards the south and east is seen in the rest of Europe. On other continents LP is not evenly distributed geographically. Indeed, in Africa and the Middle East it is often found at very different frequencies in neighbouring populations, such as 64% in the Beni Amir (pastoralists) and 23% in the Dounglawi (non-pastoralists) in Sudan.

The genetics of lactase persistence

Lactase persistence is inherited in an autosomal dominant manner. A single gene (LCT) codes for lactase. Several single nucleotide changes have been found in a lactase gene regulatory region (so-called enhancer, which is located in the adjacent gene MCM6), one of which occurs at high frequency in Europe. Estimates of the age of these changes range between 2,188 and 20,650 years ago [24] and between 7,450 and 12,300 years ago [25] for the $-13,910^T$ allele associated with LP in Europe and southern Asia, and between 1200 and 23,200 years ago for the $-14,010^C$ allele, one of the major LP-associated variants in Africa [26]. These date estimates bracket those for the domestication of milkable animals and the spread of agriculture and herding obtained from archaeological data (cave paintings, distributions of animal bones and dairy fat residues in pots).
Figure 3.15.1 Interpolated map of LP phenotype distribution in the ‘Old World’. Data points (dots) were taken from the literature (for details see Ingram et al. [6]). The key shows the frequency of the LP phenotype, black being used for the lowest frequency while white is used for the highest. Source: Itan et al. [7]. Reproduced with permission from BioMed Central Ltd.
Natural selection and evolution of lactase persistence in humans

A low frequency or absence of $-13,910^*T$ in early Neolithic central European farmers [27] and early Neolithic farmers from north-east Iberia [28], middle Neolithic Scandinavian hunter-gatherers [29] and late Neolithic farmers from southern France [30] suggests that dairying was practised before LP arose or became common. The age estimates for the LP-associated variants are remarkably young for alleles found at such high frequencies in multiple populations, suggesting that their spread has been boosted by natural selection. The strength of natural selection estimated for the LP-associated alleles is very high (1.4–19% [23] and 5.2–15.9% [31] for $-13,910^*T$, and 1–15% for $-14,010^*C$ [26]), amongst the highest for any human genes in the last 30,000 years.

Several lines of evidence (genetics, anthropology and archaeology) suggest that LP would not have provided a selective advantage without a supply of dairy products containing lactose to adults, implying that these traits evolved as the result of a co-evolutionary process involving both genes and culture. A spatially-explicit computer simulation study of this gene–culture co-evolutionary process in Europe indicate that LP and dairying began between 6856 and 8283 years ago in a region around modern-day Hungary [31].

3.15.2 Implications for diet today

Variable symptoms of hypolactasia in adults

Symptoms of lactose intolerance can arise after an individual with hypolactasia has ingested lactose. Firstly, when undigested lactose passes into the colon it creates an osmotic gradient across the GI wall, driving an influx of water to re-equilibrate the osmotic imbalance, which can lead to diarrhea. Secondly, the fermentation of lactose by colonic bacteria can lead to the production of fatty acids and various gases as by-products (including hydrogen), potentially causing discomfort, bloating and flatulence (reviewed in (Hammer et al. [32]). These symptoms usually manifest within 1–2 h of ingestion, but vary greatly from one individual to another.

The symptoms of lactose intolerance are a function of (1) the amount of lactose ingested at one time, (2) gut transit time, which itself is influenced by factors such as the presence and consistency of solid foods and the temperature of the food [33], and (3) the quantity of residual lactase expressed in the small intestine and, (4) the spectrum of microbiota present in the colon. In fact, most lactase non-persistent individuals can consume small amounts of fresh milk (such as in coffee or tea) without symptoms, and some can consume considerably larger quantities. It has variously been reported that lactose-intolerant individuals can tolerate daily amounts of lactose ranging from no more than 12–15g of lactose – the equivalent of a cup of milk [34,35] – up to 40–70 g of lactose [19,36]. Also, a controlled double-blind study showed a strong placebo effect in the production of symptoms [37]. It thus appears that lactase non-persistent individuals should not be warned off fresh milk, except like all people, while experiencing diarrhoea, but rather need to find their own lactose tolerance threshold. Lactose is often used as a bulking agent in pills. It is relevant to note that administration of capsules containing either 400 mg of lactose or a placebo failed to show any changes in $H_2$ in breath exhalation or GI symptoms [33].

Some interindividual variation in lactose intolerance symptoms can be explained by the composition of the GI microbiota. Lactase is not an inducible enzyme [10] but it has been suggested that adaptation can come from the GI microbiota when lactose is continuously consumed [33]. The microbial community within the human GI tract is diverse and dynamic in species composition, large in mass and complex in ecology [38]. Furthermore, its equilibrium composition can be shaped by diet [38]. Indeed, both an alteration of the composition of the microbiota and an increase in fecal beta-galactosidase activity have been observed after daily milk feeding and in association with a reduction in lactose intolerance symptoms [34,36]. There are also differences in the production of gases (such as hydrogen), which cause much of the discomfort in lactose intolerance. This highlights the fact that milk and lactose-containing products can often be consumed without provoking
symptoms of intolerance, and that dietary tolerance, rather than lactase expression, can be adaptive, as has been observed in lactase non-persistent Somali camel herders who often consume large quantities of milk [19].

**Dietary strategies**

Many dairy products contain only small amounts of lactose (Table 3.15.1), allowing their consumption by most lactase non-persistent individuals. Bacteria and yeast fermentation convert the lactose in milk into various by-products, reducing the content of lactose by 25–50% [33,39]. For example, yoghurt is made of milk incubated with micro-organisms that contribute to lactose hydrolysis both during the fermentation process and sometimes after ingestion (discussed in Montalto et al. [33]). Such micro-organisms are also called probiotics, i.e. live micro-organisms that are said to confer health benefits to the host when taken in adequate quantities. Even though different microbial species ferment lactose to different extents depending on their morphological and physiological characteristics [2,33], fermented dairy products ultimately contain less lactose, allowing consumption of dairy products without ill effects [39,40].

Should people wish to consume more milk products than they can tolerate, exogenous beta-galactosidase represents a possible therapy for primary lactase deficiency. Enzymes can be added in a liquid or solid (capsules or tablets) form together with milk and dairy products. The efficacy of enzymes extracted from distinct species has been assessed and compared [33,40]. For example, the beta-D-galactosidase from *Aspergillus oryzae* has shown good properties in decreasing symptoms of lactose intolerance for a relatively low dose of enzyme [41]. Pretreated lactose-free products, which were first introduced in Finland and the USA, are now becoming more widely available.

As an alternative approach, Ritter Pharmaceuticals has recently announced the successful completion of a phase II trial of a potential treatment for lactose intolerance, RP-G28, which is an orally administered proprietary oligosaccharide that is claimed to stimulate the growth of certain colonic lactose-metabolising bacteria (www.ritterpharmaceuticals.com/product-platform/rpg28).

### Table 3.15.1 Lactose content in different type of products (adapted from Holland et al. [53], with permission from the Royal Society of Chemistry)

<table>
<thead>
<tr>
<th>Product</th>
<th>Type</th>
<th>Lactose content in g per 100 g product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Milk</strong></td>
<td>Cattle (whole milk, pasteurised)</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>Cattle (semi-skimmed milk, pasteurised)</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Cattle (skimmed milk, pasteurised)</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>Sheep</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>Goat</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Yoghurt</strong></td>
<td>Whole milk, plain</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Greek style, plain</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Cream</strong></td>
<td>Single</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Double</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Crème fraiche</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Cheese</strong></td>
<td>Cheese spread</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Fromage frais</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Cottage cheese</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Feta</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Parmesan</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Cheddar</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Stilton</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Cream cheese</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td>Brie/Camembert</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td>Edam/Gouda</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td>Mozzarella</td>
<td>Trace</td>
</tr>
<tr>
<td><strong>Butter</strong></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Chocolate</strong></td>
<td>Milk</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>Plain</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Ice cream</strong></td>
<td>Dairy, vanilla</td>
<td>5.2</td>
</tr>
</tbody>
</table>

**Pros and cons of dairy intakes for lactose malabsorbers**

Many studies have investigated both the benefits and increased risks to health of dairy product consumption among LP and lactase non-persistent individuals, such as the risk of developing metabolic syndrome components [42–45], osteoporosis [46–49] and various cancers [50–52]. Results from these studies should be
treated with caution since confounding effects such as mixed ancestry, cryptic population structure or differences in diets are not always accounted for and can yield contradictory results.

The concentration of calcium in bovine milk is about 1 g/L and calcium intake from milk and yoghurt accounts for about 50% of the total calcium intake in Dutch people, though it accounts for only about 15% of the total calcium intake in Austrians [16,17]. This shows the importance of milk as a calcium source but also that other dietary sources of calcium can be used. It is nevertheless important to be aware that lactose malabsorbers need not avoid all milk and dairy products unnecessarily, and if they do, they should not do so without adequate advice.

3.15.3 Conclusion

Far from being a disease or a dysfunctional disorder, lactase non-persistence – causing lactose intolerance – is the norm and it is the adult consumption of milk that is the novel (cultural) variant. Nutritional epidemiology studies, and the staggering selective advantages that have favoured LP-associated alleles over the last 10,000 years, clearly show that adult milk consumption can be highly beneficial.

Lactase non-persistent individuals may or may not exhibit symptoms of lactose intolerance after consumption of lactose, whose intensity depends on both internal (amount of lactase still expressed in the small intestine, GI microbiota, gut transit times) and external factors (food consistency, the lactose content of the food, whether it contains probiotics or not, and if so what probiotics they are). An individual’s threshold of lactose intolerance should be assessed before deciding to avoid dairy products, and alternative lactose intolerance management strategies exist, including potential oligosaccharide-based treatments and bacterial beta-galactosidase activity.

References


