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Low intestinal lactase activity – a 40 years perspective

By Nils-Georg Asp

ABSTRACT

Low intestinal lactase activity (hypolactasia) was discovered in the early 1960s as a cause of lactose intolerance. Since then, it has become clear that hypolactasia in adults is a normal phenomenon in man as in other mammals. Lactase persistence is a dominant autosomal trait, enriched during thousands of years in cattle-raising populations, where continued high capacity to digest lactose might have been related to better health and more children. Hypolactasia is a cause of lactose intolerance, but it should be noted that most people with hypolactasia tolerate considerable amounts of milk products, especially when distributed throughout the day and taken with meals. Perceived intolerance to a few grams of lactose may be due to other food components or related to a general "sensitivity" of the gastrointestinal tract.

Keywords: Hypolactasia, lactose intolerance, malabsorption, milk

Terminology

The original term *lactase deficiency* was questioned during the 70s, when it became clear that down-regulation of lactase is a normal phenomenon in man as in other mammals. *Primary low intestinal lactase activity, hypolactasia* and *lactase restriction* are terms considered more appropriate to describe the low lactase activity in adults due to down-regulation. *Lactase persistence* is a logical corresponding term for keeping a high intestinal lactase activity throughout life. *Secondary hypolactasia* means that the low intestinal lactase activity is due to damage of the small-intestinal mucosa as a result of infection, infestation, cæliac disease, allergy or malnutrition. The "normal" lactase activity will then be restored when the underlying condition is cured.

Lactose malabsorption or *lactose maldigestion* or *low lactose digestion capacity* means that lactose is incompletely absorbed in the small intestine, with the result that lactose passes to the large intestine. This is demonstrated through a lactose tolerance test, in which a standardised amount of lactose, usually 50 g, is given. *A small blood-glucose elevation, a small blood-galactose elevation, or a small urinary galactose excretion* in a lactose tolerance test with ethanol (to inhibit galactose metabolism), or an *elevated breath hydrogen excretion* (as a result of fermentation) are measurements used to demonstrate lactose malabsorption, which is almost always due to low intestinal lactase activity.

Lactose intolerance means the experience of symptoms due to lactose malabsorption. Obviously, lactose intolerance is dose-dependent, and it has been demonstrated repeatedly that hypolactasia does not always mean intolerance to normal amounts of milk products in the diet.

Milk intolerance can be due to lactose intolerance, but also to milk protein allergy, and possibly related to other milk components.

Pseudolactose intolerance not always means gastrointestinal symptoms related to milk in subjects with lactase persistence.

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Introduction

Lactose – the predominating carbohydrate in milk – is a 1,4-β-galactoside that is synthesised in the mammary gland by an energy-demanding process. It has to be hydrolysed again by lactase to galactose and glucose before absorption in the small intestine. The biological advantage of lactose as the carbohydrate source in milk is not known. In human milk with 7% lactose, it is the predominant source of energy. Cow's milk contains 4–5% lactose. An inverse relationship between lactose and fat content in milks from various species shows Nature's alternative ways to provide energy to the offspring, human milk being one extreme with high lactose and rather low fat content at 4%, but still half of the energy content. Sealion milk is the other extreme with no lactose and 40% fat.

Digestion and absorption of lactose

In 1957, Borgström et al. (1) published their first paper using an intestinal intubation technique in man and showed that both glucose and lactose were almost completely absorbed in the upper small intestine. In 1959, Holzel et al. (2) reported defective lactose absorption causing malnutrition in infancy, and a number of reports describing different forms of congenital disaccharide intolerances appeared around that time (for review see 3). Dahlqvist then performed a series of studies of glucosidases in the intestinal mucosa, and collaboration with Auricchio, Mürset, Prader and Semenza in Zürich, and Crane, Dunphy and Littman in Chicago was established. Dahlqvist published his first paper on digestion and absorption of disaccharides in man in 1962 (4). The next year, the first cases of intestinal lactase deficiency, as a cause of lactose intolerance in adults, were published jointly with the American group (5), and simultaneously by the Swiss-Italian group (6). Studies published 1969–75 revealed that low lactase activity is prevalent in adults in most populations, and that the low lactase activity appeared from age 1–2 years in some populations but later in other populations and not until the age of 20 years in some cases (3,7). The terminology for this condition was reviewed by Sahi (8) and is summarised to the left.

The intestinal lactase was characterised in more detail, separated from two other small-intestinal β–galactosidases that seemed unrelated to the digestion of dietary lactose, and studied in subjects with lactose malabsorption from various populations (9,10). It could be demonstrated that adults with low lactase activity had a variable residual activity of seemingly normal

lactase, whereas no residual activity could be measured in cases of congenital lactose malabsorption (10). Immunoelectrophoretic studies by Skovbjerg, Sjöström, Norén, Gudmand-Höyer and Fenger (11,12) confirmed that low lactase activity in adults is due to a small amount of normal lactase and not to a modified inactive enzyme.

Studies since around 1980 have lead to the understanding in considerable detail of biosynthesis and regulation of small-intestinal lactase activity as reviewed in this issue by Norén and Sjöström (13).

Genetics and clinical importance of hypolactasia

During the 70s, it became apparent that low intestinal lactase activity in adults is the rule in most humans, as in other mammals. Two hypotheses were put forward to explain the decline or persistence of intestinal lactase in man, an adaptative one and a genetic one. Simoons (14,15) pointed out the striking similarity between areas of lactase persistence and traditional areas of milking, with possible nutritional advantages as a selection pressure for lactase persistence. Sahi and coworkers showed conclusively that lactase activity in adults is genetically determined in a recessive way (for review, see 16). The genetics and epidemiology of hypolactasia are reviewed by Sahi in this issue (17).

Fermentation

Lactose that is not absorbed in the small intestine reaches the colon. Mechanisms for lactose intolerance include osmotic effects of lactose and its degradation products interfering with water and electrolyte absorption, as well as gas formation during fermentation. Recent years' focus on the importance of colonic fermentation in man has implied a complete change in the perception of this process in man, i.e. a paradigm shift. The fate of malabsorbed lactose should be regarded in this context.

In this issue, fermentation is reviewed by Henningsson et al. with emphasis on short-chain fatty acid formation (18). Langkilde (19) provides data on available substrates, based on ileostomy studies. Olesen and Gudmand-Høyer comments on the clinical significance of fermentation, suggesting that malabsorbed lactose could be regarded as having a prebiotic effect (20) and Fondén reviews recent studies indicating adaptation of the intestinal flora to lactose (21).

Clinical importance of hypolactasia

The literature on the frequency, distribution, importance and treatment of low lactase activity, lactose malabsorption and lactose intolerance appearing after 1963 is immense (for review see e.g. (22)). The clinical importance of hypolactasia has been intensively debated, from the perspective of both developing countries and affluent countries. Low lactase activity has often been, and is still often regarded as synonymous with lactose intolerance. But to what extent are subjects with low lactase activity intolerant to normal amounts of lactose in the diet? A number of recent studies in Finland have addressed the clinical importance of hypolactasia in Western societies and are summarised by Korpela in this issue (23).

The question whether very small amounts, i.e. a few grams or less of lactose can provoke symptoms of lactose intolerance is of considerable importance in designing lactose-free diets and for the requirements of "lactose-free" products. In a double-blind randomised cross-over study (24), however, the same proportion (64%) of lactose maldigesters experienced symptoms after lactose-free milk and after milk containing 7 g lactose. As concluded by Korpela (23), the gastrointestinal symptoms in most lactose maldigesters are not induced by 0.5–7g lactose. This is in agreement with previous studies showing that many lactose maldigestors tolerate 1–2 dl of ordinary milk (25). Fermented milk products are tolerated even better (26). A generally increased "sensitivity" of the gastrointestinal tract in patients with lactose intolerance is suggested in the paper by Nilsson (27).

During the meeting *Lactose intolerance revisited* it was questioned whether the present requirement, that lactose-free products must have lactose content below the detection limit, is relevant. Furthermore, such a limit changes with the development of analysis methods (28).

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