Probiotics—compensation for lactase insufficiency[1–3]

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ABSTRACT Yogurt and other conventional starter cultures and probiotic bacteria in fermented and unfermented milk products improve lactose digestion and eliminate symptoms of intolerance in lactose maldigesters. These beneficial effects are due to microbial β-galactosidase in the (fermented) milk product, delayed gastrointestinal transit, positive effects on intestinal functions and colonic microflora, and reduced sensitivity to symptoms. Intact bacterial cell walls, which act as a mechanical protection of lactase during gastric transit, and the release of the enzyme into the small intestine are determinants of efficiency. There is a poor correlation between lactose maldigestion and intolerance; in some studies, low hydrogen exhalation without significant improvement of clinical symptoms was observed. Probiotic bacteria, which by definition target the colon, normally promote lactose digestion in the small intestine less efficiently than do yogurt cultures. They may, however, alleviate clinical symptoms brought about by undigested lactose or other reasons. *Am J Clin Nutr* 2001;73(suppl):421S–9S.

KEY WORDS Probiotic, lactose digestion, lactose maldigestion, lactose intolerance, lactase

INTRODUCTION

Improvement of lactose digestion and avoidance of symptoms of intolerance in lactose malabsorbers are the most profoundly studied health-relevant effects of fermented milk products. However, these are not specifically probiotic effects, which are defined as being exerted by living microorganisms surviving gastrointestinal transit and affecting the indiginous microflora (1). Lactose digestion, on the other hand, is most improved by bacteria if the β-galactosidase of the bacteria is released by destruction of the bacterial cell wall. Those probiotic bacteria that improve lactose digestion do so, if at all, mostly to a lesser degree than do conventional yogurt cultures. The lack of a strong correlation between lactose maldigestion and the incidence of symptoms of intolerance, such as flatulence, abdominal pain, and diarrhea, suggests that probiotic baceria act by preventing symptoms of intolerance in the large intestine in addition to or rather than by improving lactose digestion in the small intestine.

LACTOSE MALDIGESTION AND INTOLERANCE

Lactase insufficiency means that the concentration of the lactose-cleaving enzyme β-galactosidase, also called lactase, in the brush border membrane of the mucosa of the small intestine is too small. This hypolactasia causes insufficient digestion of the disaccharide lactose, a phenomenon called lactose malabsorption or, more precisely, lactose maldigestion. Lactose maldigestion is defined by an increase in blood glucose concentration of <1.12 mmol/L or in breath hydrogen of >20 ppm after ingestion of 1g/kg body $wt^{0.75}$ or 50 g lactose (2). In addition to intestinal lactase activity and its determinants, ethnic origin, age, and possibly sex, other factors are known to influence lactose digestion or maldigestion: the lactose load, dietary components ingested together with lactose (meal effect), the rate of gastric emptying, gastrointestinal transit time, and interactions among these factors (3, 4).

There are several forms of lactose maldigestion. In primary or adult-type lactose malabsorption, lactase activity is high at birth, decreases in childhood and adolescence, and remains low in adulthood. This primary hypolactasia is also called lactase nonpersistence and is the normal (physiologic) situation for mammals and humans (5). With the exception of the population of Northern and Central Europe and its offspring in America and Australia, 70–100% of adults worldwide are lactose malabsorbers. The prevalence of primary lactose maldigestion is 3–5% in Scandinavia, 17% in Finland, 5–15% in Great Britain, 15% in Germany, 15–20% in Austria, 17% in northern France, 65% in southern France, 20–70% in Italy, 55% in the Balkans, 70–90% in Africa (exeptions: Bedouins, 25%; Tuareg, 13%; Fulani, 22%), 80% in Central Asia, 90–100% in Eastern Asia, 30% in northern India, 70% in southern India, 15% in North American whites, 80% in North American blacks, 53% in North American Hispanics, and 65–75% in South America (2, 4).

In population groups with predominant primary lactase deficiency, loss of lactase activity begins between the ages of 2 and 6 y. In white populations with a low prevalence of lactase maldigestion it starts later, in some cases after adulthood (20 y). The frequencies of lactose maldigestion at ages 2–3 y, 6 y, and 9–10 y, respectively, are 0%, 0%, and 6% in white Americans; 18%, 30%, and 47% in Americans of Mexican descent; 25%, 45%, and 60% in black South Africans; ≈30%, 80%, and 85% in Chinese and Japanese; and 30–55%, 90%, and >90% in Mestizos of Peru (6, 7).

Secondary forms of lactose malabsorption may be due to inflammation or functional loss of the small intestinal mucosa

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TABLE 1
Frequency of lactose maldigestion and intolerance in residents of northern Germany

Status according to breath hydrogen test	Total	Gastrointestinal symptoms during test	
		No	Yes
Digesters	173 (85.7)[1]	159 (91.9)	14 (8.1)
Maldigesters	29 (14.3)	15 (51.7)	14 (48.3)

[1] Percentage in parentheses.

(enteritis, Morbus Crohn, bacterial or parasitic infections, sprue, or small bowel syndrome) and by protein-energy malnutrition. Although some forms are transient, disappearing after recovery from the original disease, others are irreversible (8). Congenital lactose malabsorption, a rare autosomal-recessive heritable genetic defect, is evident immediately after birth. Afflicted newborns respond to their first milk feed with diarrhea (4).

Hypolactasia and lactase maldigestion accompanied by clinical symptoms such as bloating, flatulence, nausea, diarrhea, and abdominal pain is termed lactose intolerance. Symptoms are caused by undigested lactose in the large intestine, where the lactose serves as a fermentable substrate for the bacterial flora and osmotically increases water flow into the lumen. Whether and to what extent undigested lactose causes the above-mentioned symptoms depends first on the amount of lactose ingested but also on individual sensitivity, the rate of gastric emptying, gastrointestinal transit time, and the pattern of the flora in the large intestine, which is why diarrhea rarely occurs after the application of antibiotics. This means that lactose maldigestion is not the same as lactose intolerance.

Lactose-intolerant people can ingest a certain amount of lactose without having adverse symptoms. Most of these people tolerate ≥9–12 g (equivalent to 200 mL or 1 glass of milk) (4, 9, 10). Newcomer et al (11) found no significant difference in tolerance in American Indians (9% of subjects with symptoms) who were provided with 0–18 g lactose. Vesa et al (12) concluded that most lactose malabsorbers tolerate 0.5–7 g lactose without symptoms of intolerance. According to another study, people who had undergone jejunostomy or jejunocolostomy, conditions under which a secondary lactose maldigestion may occur, tolerated 20 g lactose in milk or yogurt (13).

In our own studies, data on the prevalence of lactose maldigestion and the proportion of lactose-intolerant people within the malabsorber population segment in Germany were assessed. Healthy male and female volunteers aged 18–36 y and living in northern Germany were screened with use of the breath-hydrogen test. To avoid over- or underrepresentation of participants who classified themselves as milk intolerant or lactose malabsorbing, we tested whole groups, eg, all the employees of a department or all the students of a class. Some 202 subjects took part in the screening; 29 (14.4%) of these were maldigesters as proven by an increase of breath hydrogen >20 ppm after the ingestion of 25 g lactose on 3 consecutive occasions. Of the breath hydrogen–positive subjects, 14 (48%) reported gastrointestinal symptoms during the lactose-tolerance test. Details are listed in **Table 1**.

Twenty-eight percent of all subjects had one or more ancestors born outside Germany. The prevalence of lactose maldigestion was only 11.7% in subjects whose parents and grandparents were all from Germany or Northern or Central Europe. The prevalence of lactose maldigestion was 14.6% when at least one ancestor was from South, southwestern, or Eastern Europe and 37.5% when neither parents nor grandparents were from Europe.

REASONS FOR GASTROINTESTINAL SYMPTOMS IN LACTOSE INTOLERANCE

The mechanisms by which undigested or unabsorbed lactose causes the symptoms of lactose intolerance are not yet fully understood. Osmotically enhanced water secretion into the small intestine, dilatation of and accelerated transit through the small intestine, and disordered peristalsis and water absorption in the colon caused by products of lactose fermentation (eg, lactic acid and short-chain fatty acids) may be the cause of diarrhea and loose stool (14). However, the involvement of the short-chain fatty acids needs further clarification (15).

The source of abdominal pain and cramps was often thought to be the small intestine, where motor events could be induced by the osmotic load of undigested lactose. However, in recent investigations similar symptoms were observed when the nonabsorbable sugar lactulose was ingested orally or when introduced directly into the colon, bypassing the small bowel (16).

Abdominal bloating, flatulence, and borborygmi are probably caused by gaseous products of lactose fermentation, such as hydrogen, CH_4, and carbon dioxide. Theoretically, <17 L of hydrogen are produced microbially from 50 g lactose in the colon (17). If allowed to accumulate, this volume would have major implications for intestinal distension and gas problems. However, most of this gas is consumed by other intestinal bacteria. Surprisingly, subjects complaining of excessive gas in the gut had the same degree of lactose maldigestion and the same gas production as did subjects without complaints, although the former showed disordered intestinal motility and increased pain response to gut distension. When the same volumes of gas were actively infused into the intestine of these patients, the gases caused much more discomfort and had a greater tendency to reflux back into the stomach than was the case in control experiments with healthy subjects (18, 19). Finally, subjective ("psychological") discomfort (20) or the symptoms of other functional disorders of the intestine (eg, irritable bowel syndrome) (21) may be mistakenly related to milk consumption by the subjects themselves.

CORRELATION BETWEEN LACTOSE MALDIGESTION AND SYMPTOMS OF INTOLERANCE

There is a causal relation between lactose maldigestion and symptoms of lactose intolerance. Lactose reduction or measures that improve lactose digestion also clearly improve gastrointestinal symptoms (**Tables 2** and **3**). However, owing to the complex interplay of causative factors, it is no surprise that lactose maldigestion or the results of breath-hydrogen tests correlate poorly with symptoms of lactose intolerance on the one hand and with self-reported milk intolerance on the other. This is confirmed by the following observations: *1*) Only some lactose maldigesters are lactose intolerant. *2*) The decline of lactase activity starts much earlier than does the manifestation of clinical symptoms. *3*) Lactose-free diets do not cure the symptoms of all lactose-intolerant subjects.

This lack of correlation was confirmed by earlier studies (**Table 4**) and by current studies. In our study of 202 healthy German adults, 23 participants reported that they could not drink milk without developing symptoms of lactose intolerance, although only 43% of these self-reported lactose-intolerant individuals were genuine maldigesters according to the breath-hydrogen criterion (**Table 5**).

TABLE 2
Studies on the influence on hydrogen exhalation of native and heated yogurt compared with milk in lactose-intolerant persons

Reference	Product	Lactose[1]	Hydrogen exhalation[2,3]
		g	
Kolars et al (22) (*n* = 10)	400 g milk	18	293 ppm/h
	270 g yogurt	11	72 ppm/h
	440 g yogurt	18	108 ppm/h
Savaiano et al (23) (*n* = 9)	410 g milk	20	≈180 ppm/h
	500 g yogurt	20	≈50 ppm/h
	500 g pasteurized yogurt	20	≈170 ppm/h
Martini et al (24) (*n* = 9)	415 g milk	20	185 Δ ppm/h
	455 g yogurt	20	37 Δ ppm/h
McDonough et al (25) (*n* = 14)	250 g milk	15.7	28.7 ppm
	250 g yogurt + lactose	15.7	15.5 ppm
	250 g yogurt	12	5.4 ppm
	250 g heated yogurt	12	14.9 ppm
Dewit et al (26) (*n* = 8)	Milk	18	12.5 ppm
	Lactose	18	17.0 ppm
	Yogurt	18	2.2 ppm
	Heated yogurt	18	12.4 ppm
Martini et al (27) (*n* = 7)	315 g milk	18	≈350 Δ ppm/h
	425 g yogurt 1[4]	18	≈60 Δ ppm/h
	425 g yogurt 2[4]	18	≈30 Δ ppm/h
	450 g yogurt 3[4]	18	≈20 Δ ppm/h
Rosado et al (28) (*n* = 14)	360 g milk	18	220 ppm/h
	454 g low-fat yogurt	20.4	76 Δ ppm/h
	454 g yogurt 1	18.6	36 Δ ppm/h
	454 g yogurt 2	18.6	26 Δ ppm/h
	454 g lactose-reduced yogurt	3.6	0.5 Δ ppm/h
Murao et al (29) (*n* = 30)	300 g milk	14	150 ppm_{max}
	500 g yogurt	14	32 ppm_{max}
Martini et al (30) (*n* = 12)	480 g milk	20	437 Δ ppm/h
	480 g yogurt	20	133 Δ ppm/h
	480 g breakfast	20	68 Δ ppm/h
	435 g yogurt + breakfast	20	62 Δ ppm/h
Gilliland and Kim (31) (*n* = 6)	Yogurt	—	9.9 ppm_{max}
	Heated yogurt	—	22.8 ppm_{max}
Varela-Moreiras et al (32) (*n* = 19)	200 g milk	11	135 ppm/h
	200 g yogurt	11	55 ppm/h
	200 g pasteurized yogurt	11	85 ppm/h
Marteau et al (33) (*n* = 8)	450 g milk	—	439 ppm/h
	450 g yogurt	—	103 ppm/h
	450 g heated yogurt	—	191 ppm/h
Lerebours et al (34) (*n* = 24)	125 g milk	18	34.7–39.0 ppm/h
	125 g yogurt	18	11.4 ppm/h
	125 g pasteurized yogurt	18	27.4 ppm/h

[1] Empty cells indicate values that were not determined or not published.
[2] Mean high of the breath hydrogen peak (ppm), maximum high of the breath hydrogen peak (ppm_{max}), area under the curve (ppm/h), and area under the curve above baseline (Δ ppm/h).
[3] Because of varying definitions of breath hydrogen peak width, breath hydrogen values were comparable with one another only within the same study.
[4] Yogurts 1, 2, and 3 contained 3.4, 2.3, and 5.0 U/g β-galactosidase, respectively, activity measured as μmol *o*-nitrophenyl-galactoside·min^{-1}·g^{-1}.

In another study, Johnson et al (46) compared the outcome of breath-hydrogen tests and the consumption of 240 mL milk in 164 African Americans who claimed to be milk intolerant; 50% were classified as intolerant maldigesters, 27% as tolerant digesters, 8% as tolerant maldigesters, and 15% as intolerant digesters.

In several studies, symptoms of intolerance were observed in some lactose malabsorbers and in some lactose absorbers, and hydrolysis of the lactose did not always remove these symptoms. In a study by Suarez et al (47), the degree of response to 250 mL milk was not significantly different between lactose absorbers and malabsorbers, regardless of whether milk or lactose-hydrolyzed milk was used as test products. Although studies showed that hydrogen exhalation after lactose ingestion is greater in men than in women, lactose maldigestion causes significantly more symptoms in women than in men (48, 49).

Lactose-maldigesting children showed the same total breath-hydrogen exhalation (area under the curve) after ingesting either milk or 12 g lactose added to yogurt with live cultures, but showed improved tolerance of lactose in the yogurt meal (50). Vesa et al (21) compared subjects with irritable bowel syndrome with healthy subjects; <60% of the patients and 27% of the healthy subjects classified themselves as lactose intolerant. However, according to the breath-hydrogen test, the percentage of actual lactose maldigesters was 24% in both groups. This

TABLE 3
Studies on the influence on gastrointestinal symptoms of yogurt or nonyogurt fermented milk products compared with milk in lactose-intolerant subjects

Reference	Product	Symptoms
Martini et al (27) (*n* = 7)	315 g milk [18][1]	2.0 ± 0.8[2,3]
	425 g yogurt[4] [18]	1.3 ± 0.7
	425 g yogurt[5] [18]	0.4 ± 0.2
	450 g yogurt[6] [18]	0.6 ± 0.3
Rosado et al (28) (n = 14)	360 g milk [18.0]	3.8 ± 0.7[7]
	454 g low-fat yogurt [20.4]	1.5 ± 0.5
	454 g yogurt 1 [18.6]	1.6 ± 0.5
	454 g yogurt 2 [18.6]	1.3 ± 0.5
	454 g lactose-reduced yogurt [3.6]	1.4 ± 0.6
Montes et al (35) (*n* = 20 children)	250 g low-fat milk [11.6]	4.0[7]
	250 g low-fat acidophilus (10^{10} CFU/g NCFM) milk [11.6][8,9]	1.8
	250 g low-fat *thermophilus*+ *Lactobacillus lactis* (10^{10} CFU/g) milk [11.6]	1.0
Gaon et al (36) (*n* = 18)	480 g fermented *Lactobacillus casei* + *Lactobacillus acidophilus* milk [25]	Fewer symptoms than with milk
Savaiano et al (23) (*n* = 9)	410 g milk [20][10]	11/33[11]
	500 g yogurt [20]	0/0
	465 g buttermilk [20]	44/90
	420 g acidophilus (NCFM) milk [20][8]	0/44
Jiang et al (37) (*n* = 15)	400 g low-fat milk [16][10]	47/60[11]
	400 g *Bifidobacterium longum* (B6, L + G)[12,13] milk [16]	27/87
	400 g *B. longum* (B6, L)[12,13] milk [16]	40/47
	400 g *B. longum* (15708)[14] milk [16]	27/80

[1] g lactose in brackets.
[2] $\bar{x}$ ± SD.
[3] 0 = no, 5 = severe diarrhea.
[4] 3.4 U/g β-galactosidase.
[5] 2.3 U/g β-galactosidase.
[6] 5.0 U/g β-galactosidase.
[7] 0 = no, 6 = severe symptoms.
[8] *Lactobacillus acidophilus* strain NCFM.
[9] CFU, colony-forming units.
[10] For β-galactosidase activities, *see* Table 6.
[11] Percentage of probands with pain or flatulence.
[12] Grown on a lactose-containing broth with (L + G) or without (L) glucose.
[13] *B. longum* strain B6.
[14] *B. longum* strain 15708.

illustrates that gastrointestinal problems are often wrongly attributed to the consumption of lactose or milk.

LACTOSE DIGESTION AND FERMENTED MILK PRODUCTS

It is generally accepted that fermented milk products such as yogurt can efficiently improve lactose digestion in lactose malabsorbers and therefore that they are well tolerated by most lactose-intolerant subjects. Numerous studies showed better lactose digestion and consequently less hydrogen exhalation in lactose malabsorbers who consumed nonheated yogurt rather than milk or pasteurized yogurt. A summary of the available data are presented in Table 2.

There are several possible reasons for these effects. First, active microbial β-galactosidase in bacteria-containing fermented or unfermented milk products survives gastric passage and is released by bile salts into the small intestine, where it supports lactose digestion. The role of increased permeability of the bacterial cell wall and of intracellular lactose hydrolysis caused by bile acids is unclear. Noh and Gilliano (51) found that 0.15% oxgall increased the microbial lactase activity of yogurt cultures but did not promote cell lysis or the release of the enzyme from the cells; 0.3% oxgall had an inhibitory effect on the microbial lactase activity. Second, delaying gastric emptying and slowing intestinal transit prolongs the action of residual β-galactosidase in the small intestine and decreases the osmotic load of the lactose (33, 52). Third, short-term and long-term ingestion of lactose and bacteria in the fermented milk product may affect the intestinal pH and other variables of the intestinal milieu, the intestinal microflora, lactose fermentation, or the sensitivity of the subject to gastrointestinal disorders and may thus alleviate symptoms of lactose intolerance or other gastrointestinal disorders.

ESSENTIALITY OF LIVE BACTERIA

To test whether live bacteria in the fermented or nonfermented milk product are a prerequisite for enhanced lactose cleavage by microbial β-galactosidase, we administered fermented milk products [≈800 U/L (*o*-nitrophenyl-galactoside as the substrate) active microbial β-galactosidase; 70 g/L lactose] to Göttingen miniature pigs and to healthy lactose malabsorbers. The lactobacilli (*Lactobacillus delbrüeckii* subsp. *bulgaricus*) in these products were viable [≈4×10^8 colony-forming units (CFU)/L], killed by gamma irradiation (intact cell walls), or killed through prolonged storage for 3 mo at 4 °C or by the shear forces in a flow centrifuge

TABLE 4
Responses of symptoms to lactose in double-blind studies

Reference	Population	240–250 mL milk		240–250 mL lactose-hydrolyzed milk	
		Maldigesters	Digesters	Maldigesters	Digesters
		% without symptoms			
Haverberg et al (38)	US juveniles[1] (14–19 y)	72	84	82	84
Unger and Scrimshaw (39)	US mixed adults (18–46 y)	67	85	88	76
Sadre and Ghassem (40)	Iranian children	86	—	100	—
Rosado et al (41)	Mexican adults[2] (19–53 y)	52	88	96	96
Cavalli-Sforza et al (42)	Italian adults	55	77	70	84
Paige et al (43)	US black juveniles (13–19 y)	86	—	86	—
Rorick and Scrimshaw (44)	US elderly (60–97 y)	79	81	70	83
Kwon et al (45)	US mixed juveniles (14–19 y)	91	81	73	83

[1] Different ethnic backgrounds.
[2] 360 mL milk.

during cell-harvesting (partly ruptured cell walls). A sterilized product without β-galactosidase activity served as the control.

When the diets with viable lactobacilli or with lactobacilli killed by irradiation were administered to pigs, the resulting postprandial plasma galactose peak concentrations and areas under the curve were almost identical and were significantly higher (>300%) than control values. However, lactose digestion was improved insignificantly when lactobacilli cell walls were damaged (**Figure 1**).

In human lactose malabsorbers, diets containing active microbial β-galactosidase but killed lactobacilli with partly broken cell walls led to an intermediate hydrogen exhalation response between that induced by the native and the sterilized product. The subjects reported fewer symptoms of lactose intolerance (eg, flatulence and diarrhea) after consumption of the stored product instead of the sterilized one. The native fermented milk product was tolerated best.

These results imply that lactose digestion in lactose malabsorbers and gastrointestinal well-being can be significantly improved if a milk product contains active microbial β-galactosidase. The bacteria need not be alive but (largely) intact cell walls are required to act as a mechanical protection of the enzyme during gastric passage.

However, a large β-galactosidase concentration in the yogurt is not in all cases sufficient for efficient lactose digestion. In a study by Martini et al (27), ingestion of yogurts prepared with different commercially available starter cultures and with β-galactosidase activities between 2.3 and 7.0 $\mu mol \cdot min^{-1} \cdot g^{-1}$ induced a similar hydrogen exhalation. This was 6–12-fold lower than when milk was ingested. Our own studies with rats showed the same result: 2 strains of *L. delbrueckii* (subsp. *bulgaricus* and subsp. *lactis*) similarly increased microbial β-galactosidase activity in the chyme, whereas the ratio of activity in the fermented *L. bulgaricus* milk product was 5-fold greater. This study differentiated between the ingested microbial enzyme and the endogenous (host) β-galactosidase by affinity chromatography (53). Therefore, it is not possible to predict the effect of lactose-fermenting bacteria (yogurt bacteria or probiotic strains) on lactose digestion and intestinal well-being in lactose malabsorbers without conducting in vivo studies.

OTHER FACTORS INFLUENCING LACTOSE DIGESTION

In addition to the effects of microbial β-galactosidase contained in them, fermented milk products improve lactose digestion and tolerance by delaying gastric emptying, orocecal transit time, or both. The delayed passage of the lactose alleviates the symptoms of gastrointestinal intolerance and gives the residual β-galactosidase activity in the small intestine of lactose malabsorbers more time to hydrolyze lactose. This explains the finding in most studies that pasteurized yogurt, which contains no active microbial β-galactosidase but prolongs transit time as much as does native yogurt, improves lactose digestion, although to a lesser extent than would a product containing live lactobacilli (23, 25, 26, 31–34; Table 2).

Fermented milk products delay gastric emptying because of the greater viscosity and lower pH (relative to milk) and the greater energy yield (relative to that of pure lactose solutions). The prolonged orocecal transit could be explained by the (probiotic) microorganisms, their metabolic products, or a lower osmotic load resulting from the improved lactose digestion in the upper small intestine. In a Finnish study of lactose maldigesters, gastric emptying ($P < 0.01$), and therefore orocecal transit time (NS), was delayed and hydrogen exhalation was diminished after the subjects switched from a low- to a high-energy diet. However, this had no significant effect on the symptoms of lactose intolerance (52). In another study (23), the consumption of native and pasteurized yogurt induced faster gastric emptying than did the consumption of milk. The gastrocecal transit time, however, was significantly prolonged in the order milk < heated yogurt < yogurt.

Adaptation to continuous lactose consumption is another open question. Lactase activity in mammals is not inducible. This means that mucosal lactase activity and, therefore, lactose digestion (34) is not increased by lactose consumption. Nevertheless, there are reports that continuous lactose consumption decreases hydrogen exhalation and the severity of gastrointestinal symptoms (54, 55). Decreased hydrogen exhalation is not nessessarily the consequence of improved lactose digestion. Adaptive changes in colonic functions (motility, transit, and pH) and

TABLE 5
Association between self-declared milk intolerance and actual lactose maldigestion according to the breath hydrogen test in healthy residents of northern Germany

	Total	Lactose digesters	Lactose maldigesters
Tolerant	179 (88.7)[1]	160 (89.4)	19 (10.6)
Intolerant	23 (11.3)	13 (56.5)	10 (43.5)

[1] Percentage in parentheses.

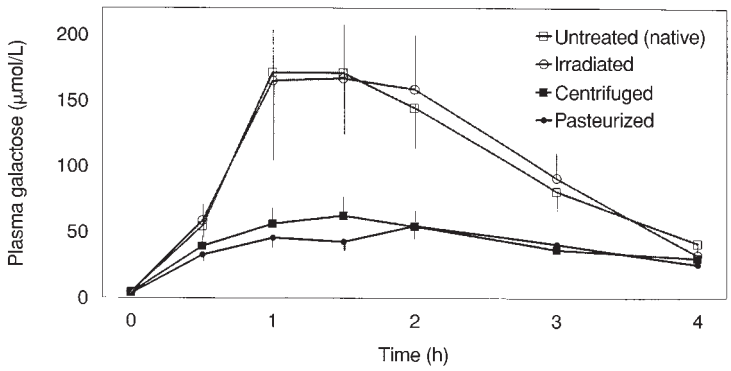

FIGURE 1. Postprandial plasma galactose in pigs fed 3 kefir-based fermented milk products containing active microbial β-galactosidase, or a pasteurized control without β-galactosidase activity. The native product contained viable lactobacilli (≈4×10^8 colony-forming units/L); in the 2 others the lactobacilli were killed by gamma-irradiation (intact bacterial cell walls) or by shear-forces in a flow-centrifuge during cell-harvesting (partly ruptured cell walls).

colonic flora, less gas (hydrogen) production by the microflora, more intestinal gas consumption, decreased perception of symptoms by the subjects, and the placebo effect have been suggested as explanations for these observations.

It has been suggested that undigested lactose enhances the fermentation capacity of bifidobacteria and other lactic acid bacteria, which metabolize lactose without hydrogen production (56). Hertzler et al (57) measured absolute microbial production in human fecal samples obtained after 10 d of lactose feeding. These authors observed lower hydrogen production, whereas fecal hydrogen consumption was unaffected. The hypothesis of Perman et al (58) that an acidic pH in the colon affects the bacterial metabolism and inhibits hydrogen production from malabsorbed carbohydrates is not supported by other investigators. The latter postulate that the prolonged ingestion of undigestible carbohydrates causes changes in colonic bacterial metabolism, resulting in a more efficient microbial carbohydrate digestion and the amelioration of gastrointestinal symptoms (59, 60).

Ito and Kimura (61) observed that 15 g lactose/d given to Japanese lactose malabsorbers increased the amount of lactobacilli, enterococci, and short-chain fatty acids and decreased clostridia and bacteroides in feces within 6 d. It seems that the continuous supply of lactose may shift intestinal flora in such a way as to increase lactic acid formation, decreasing bacterial metabolic byproducts that probably cause the adverse symptoms of intolerance. Another possibility is a lower pH in the colon and a certain desensitization toward osmotic agents.

Finally, Briet et al (62) concluded that the reduction of clinical symptoms in lactose malabsorbers brought about by extended lactose ingestion is at least in part a placebo effect. They found, in a controlled double-blind study, more fecal β-galactosidase, a decrease in pH, decreased breath hydrogen, and an amelioration of clinical symptoms in lactose-intolerant subjects after 2 wk lactose consumption. At the same time, they found an improved clinical tolerance without bacterial adaptation in the sucrose control group. More controlled clinical studies are necessary to enable us to answer these questions satisfactorily.

EFFECTS OF PROBIOTIC AND NONPROBIOTIC NONYOGURT BACTERIA

Although many probiotic strains have some lactase activity, they normally promote lactose hydrolysis in the small intestine less effectively than do conventional yogurt cultures. By definition, probiotics target the intestine. Their resistance toward bile acids or digestion helps them to survive intestinal passage but at the same time prevents β-galactosidase release into the small intestine. For example, bile-salt tolerant lactobacilli, like some strains of *Lactobacillus acidophilus,* hardly increase lactose digestion and seem to be unable to release β-galactosidase into the small intestine. Sonication of the acidophilus milk, which destabilizes the bacterial cell wall, improves lactose digestion (25). In a study by Lin (63), only one *L. acidophilus* strain, which showed an intermediate β-galactosidase activity and low bile resistance, was capable of decreasing hydrogen-exhalation significantly when administered in high concentration (10^8 CFU/mL milk).

Besides *L. acidophilus* species (64), particularly probiotic and nonprobiotic bifidobacteria, which produce enzymes that hydrolyze lactose (65) and other glycosides were studied. In most cases they affected lactose digestion less than did lactobacilli or had no effect at all (66). In some studies, this could be explained by the experimental design (pH > 7, *o*-nitrophenyl-galactoside as substrate), because β-galactosidase of bifidobacteria has a lower optimum pH than that of yogurt cultures (*Streptococcus thermophilus,* pH 7.2; *Bifidobacterium bifidum* and *Bifidobacterium longum* 401, pH 6.5) (67, 68) and because *o*-nitrophenyl-galactoside is metabolized more slowly than is the physiologic substrate lactose. Furthermore, the β-galactosidase activity of (probiotic) bacteria and their ability to improve lactose digestion and reduce hydrogen exhalation depends also on methods of cultivation, eg, on the type of carbohydrate in the culture medium. Jiang et al (37) studied the effect on lactose digestion of the consumption of milk together with 2 strains of *B. longum*, grown in a medium containing either lactose or lactose plus glucose. Growth of *B. longum* B6 in the lactose-containing but glucose-free MRS broth increased lactase activity, improved lactose digestion, and decreased hydrogen exhalation. However, it was shown that clinical symptoms were only partly less severe than after consumption of pure milk.

Experiments in animals indicated that kefir cultures may also improve lactose digestion (69). There was no such effect with buttermilk. Consumption of buttermilk was followed by a much higher hydrogen exhalation than was consumption of yogurt and was comparable with consumption of pasteurized yogurt (23). The phospho-β-galactosidase characteristic for mesophilic butter cultures (*Streptococcus lactis, Streptococcus cremoris,*

TABLE 6
List of studies on the influence on breath hydrogen exhalation of fermented-milk products other than yogurt compared with milk in lactose-intolerant probands

Reference	Product[1]	Lactose[2]	β-Galactosidase[2,3]	Hydrogen exhalation[4,5]
		g	*U/g*	
Martini et al (27) (*n* = 12)	≈275 g milk	15	0	≈520 Δ ppm/h
	≈275 g yogurt	15	2.7	≈30 Δ ppm/h
	≈275 g fermented *Streptococcus thermophilus* milk	15	—	≈160 Δ ppm/h
	≈275 g fermented *Lactobacillus bulgaricus* milk	15	—	≈80 Δ ppm/h
	≈275 g fermented *Bifidobacterium bifidus* milk	15	1.4	≈350 Δ ppm/h
	≈275 g fermented *Lactobacillus acidophilus* milk	15	2.0	≈260 Δ ppm/h
Savaiano et al (23) (*n* = 9)	410 g milk	20	0	≈180 ppm/h
	500 g yogurt	20	0.64	≈45 ppm/h
	465 g buttermilk	20	0.02	≈130 ppm/h
	420 g acidophilus (NCFM) milk[6]	20	0	≈200 ppm/h
McDonough et al (25) (*n* = 7)	250 g acidophilus milk, not sonicated	15.7	—	28.3 ppm
	250 g acidophilus milk, sonicated	15.7	—	12.3 ppm
Lin (63) (*n* = 10)	400 g low-fat milk	—	—	30.8 ppm
	400 g yogurt (10^7 CFU/g) milk	—	—	24.1 ppm
	400 g yogurt (10^8 CFU/g) milk	—	—	9.8 ppm
	400 g acidophilus (10^7 CFU/g LA1) milk	—	—	27.6 ppm
	400 g acidophilus (10^8 CFU/g LA1) milk	—	—	22.4 ppm
	400 g acidophilus (10^7 CFU/g LA2) milk	—	—	31.0 ppm
	400 g acidophilus (10^8 CFU/g LA2) milk	—	—	25.3 ppm
	400 g acidophilus (10^7 CFU/g NCFM) milk	—	—	36.3 ppm
	400 g acidophilus (10^8 CFU/g NCFM) milk	—	—	35.1 ppm
Onwulata et al (70) (*n* = 10)	400 g whole milk	18	0.00	37 ppm[a]
	400 g lactose hydrolized milk	5	0.23	18 ppm[b,c]
	454 g yogurt	18	4.00	12 ppm[c]
	400 g acidophilus milk	18	0.09	33 ppm[a]
Gaon et al (36) (*n* = 18)	480 g milk	25	—	90.5 ppm
	480 g fermented *Lactobacillus casei* + *L. acidophilus* milk	25	—	52.6 ppm
Kim and Gilliland (71) (*n* = 5)	10 mL/kg BW milk	50	—	46.8 ppm
	10 mL/kg BW acidophilus (10^6 CFU/g) milk	50	—	40.6 ppm
	10 mL/kg BW acidophilus (10^8 CFU/g) milk	50	—	28.4 ppm
Montes et al (35) (*n* = 20)	250 g low-fat milk	11.6	—	14 Δ ppm_{max}
	250 g low-fat acidophilus(10^{10} CFU/g NCFM) milk[6]	11.6	—	8 Δ ppm_{max}
	250 g low-fat S. *thermophilus* + *Lactobacillus lactis* (10^{10} CFU/g) milk	11.6	—	10 Δ ppm_{max}
Jiang et al (37) (*n* = 15)	400 g low-fat milk	16	0	347 Δ ppm/h
	400 g *Bifidobacterium longum* (B6, L + G)[9,10] milk	16	0.07	318 Δ ppm/h
	400 g *B. longum* (B6, L)[9,10] milk	16	1.41	192 Δ ppm/h
	400 g *B. longum* (15708) milk[11]	16	0.71	247 Δ ppm/h
Lin et al (72) (*n* = 12)	Low-fat milk	—	—	359 Δ ppm/h
	Acidophilus (fresh LA1) milk[7]	—	—	126 Δ ppm/h
	Acidophilus (frozen LA1) milk[7]	—	—	172 Δ ppm/h
	Acidophilus (fresh ADH) milk[12]	—	—	240 Δ ppm/h
	Acidophilus (frozen ADH) milk[12]	—	—	236 Δ ppm/h

[1] CFU, colony-forming units.

[2] Empty cells indicate that values were not determined or not published.

[3] β-galactosidase activity measured as μmol *o*-nitrophenyl-galactoside · $min^{-1} \cdot g^{-1}$.

[4] Mean high of the breath hydrogen peak (ppm), mean increase of breath hydrogen (Δ ppm), maximum increase of breath hydrogen (Δ ppm_{max}), area under the curve (ppm/h), and area under the curve above baseline (Δ ppm/h).

[5] Values within the column with different superscript letters were significantly different. Because of varying definitions of breath hydrogen peak width, breath hydrogen values are comparable with one another only within the same study.

[6] *L. acidophilus* strain NCFM.

[7] *L. acidophilus* strain LA1 reclassified as *L. johnsonii* strain LJ1.

[8] *L. acidophilus* strain LA2.

[9] Grown on a lactose-containing broth with (L + G) or without (L) glucose.

[10] *B. longum* strain B6.

[11] *B. longum* strain 15708.

[12] *L. acidophilus* strain ADH reclassified as *L. gasseri* strain ADH.

S. lactis subsp. *diacetyllactis*) hydrolyzes lactose only if it has been phosphorylated during its absorption into bacteria cells, which in turn requires intact cell walls. This is prevented by the partial damage of cell membranes, which is at the same time a prerequisite for efficient extracellular lactose hydrolysis. Finally, individual bacterial strains of the same species may be varyingly efficient in the intestine (63). Examples of this phenomenon were mentioned previously (27, 53).

All bacteria listed in **Table 6** improve lactose digestion and decrease hydrogen exhalation compared with milk, but they are less effective than is yogurt or unfermented *S. thermophilus* or *L. bulgaricus* milk. Nevertheless, probiotic bacteria may alleviate clinical symptoms brought about by undigested lactose for still other reasons (Table 3). The influence of colonic flora, the colonic milieu (eg, pH), and gas production (hydrogen) on symptoms of lactose intolerance was discussed above. These aspects have scarcely been studied in the context of probiotic bacteria.

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