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Relationship between lactose digestion, gastrointestinal transit time and symptoms in lactose malabsorbers after dairy consumption

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SUMMARY

Background: The relationship of symptoms with objective measurements, as well as some of the mechanisms involved in lactose tolerance after yoghurt consumption, remain unclear.

Methods: The trial had a double-blind design in which 22 lactose malabsorbers received 25 g daily lactose in fresh (living bacteria $> 10^8$ cfu/g) yoghurt or heated ($< 10^2$ cfu/g) yoghurt for 15 days, followed by a cross-over (15 days) after a wash-out period (14 days). The lactose digestion was determined by the breath H_2 test, the gastric emptying (GE) with a ^{13}C-acetate breath test and the revealed transit time (OCTT) by ^{15}N-lactose-ureide test. Subjects reported their gastrointestinal symptoms (GIS) in a validated questionnaire.

Results: Breath H_2 test indicated more effective lactose digestion after fresh yoghurt intake. The OCTT was shorter after heated yoghurt ingestion as compared with the fresh. There was lower severity of GIS ($P < 0.05$) after fresh yoghurt intake, and this showed an inverse correlation with OCTT ($P < 0.05$).

Conclusions: Delayed orocoecal transit time was associated with fewer gastrointestinal symptoms. The improved lactose digestion and tolerance of fresh yoghurt should be mainly attributed to the presence of living bacteria.

INTRODUCTION

Most of the world's adult population exhibits partial lactose maldigestion as a result of the physiological decline in intestinal lactase, and may suffer from intolerance symptoms following lactose ingestion.[1] It is now well established that lactase deficient subjects tolerate lactose better from yoghurt, even from pasteurized yoghurt,[2, 3] than from other dairy products.[4] The mechanisms of this improved tolerance are poorly understood, but the following three mechanisms have at least been involved: (i) stimulation of endogenous lactase, which has not been shown to be relevant in humans,[5] (ii) the presence of β-galactosidase released from yoghurt-producer organisms, which only occurs if the culture is still alive in the yoghurts,[6] and (iii) delayed gastric emptying and orocoecal transit time.[7] The rapid gastric emptying and small bowel transit of a lactose load seems to induce appreciable gastrointestinal symptoms in most lactose malabsorbers. However, an accurate assessment of lactose intolerance manifestations, such as flatulence, abdominal bloating and pain, nausea or diarrhoea requires double-blind testing.[8]

The purpose of this study was to determine whether subjects with lactose malabsorption have fewer symptoms of intolerance and better absorption of lactose after the ingestion of yoghurt when compared with

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pasteurized yoghurt, in order to evaluate the possible mechanisms involved in this response. In addition, this trial aimed to elucidate the relationship between lactose digestion with tolerance (symptoms) and gastrointestinal kinetics.

METHODS

Subjects

Volunteers ($n = 182$) were recruited through advertisements displayed at the University of Navarra. Subjects were excluded if they had undergone gastrointestinal surgery, had other major illness, drank excessive amounts of alcohol, had peptic ulcer disease, received antibiotic therapy within the previous three months, or were smokers. Thirty-one were found to be maldigesters as identified by rises in breath-hydrogen concentration above baseline (fasting value) > 20 p.p.m. in a 3 h period after the ingestion of a 200 mL aqueous solution containing 25 g lactose. Twenty-two subjects (12 women and 10 men, mean age 21.8 ± 1.6 years) were selected to participate in this study. Four were withdrawn for personal reasons as the study proceeded. Participants had normal haematologic indexes (white blood cells counts, haemoglobin, haematocrit, mean corpuscular volume and platelet counts), normal serum albumin concentration, and normal values from tests of liver (alkaline phosphatase, total bilirrubin and transaminases) and kidney (blood urea nitrogen and creatinine concentration) functions. Written informed consent was obtained from all subjects and the study protocol was approved by the Ethical Committee of the Health Department of Navarra.

Dairy products

Two test meals which had been produced and processed at the D. Carasso Research Center in Paris (France) were given to the subjects: (i) yoghurt containing active live cultures and (ii) pasteurized yoghurt, made from the same skimmed milk and whose lactose concentration, pH and viscosity were similar (Table 1). The nonpasteurized yoghurt contained at least 10^8 colony forming units (CFU/g) each of *Lactobacillus bulgaricus* and *Stroptococcus thermophilus*. The fresh and heated yoghurts were stored at 4 °C and ingested between day 8 and day 24 after their production, following routine procedures for transport and storage.

Table 1. Composition and characteristics of the two yoghurts per test dose (500 mL)*

	Product	
	Fresh yoghurt	Heated yoghurt
pH	4.11 ± 0.11	4.17 ± 0.02
Lactose (g)	25.7 ± 1.1	25.5 ± 1.1
L. bulgaricus (CFU/g)	$1.75 \times 10^8 \pm 3.4 \times 10^8$	< 15
S. thermophilus (CFU/g)	$5.93 \times 10^8 \pm 1.38 \times 10^8$	< 15

* Values are mean ± S.E.M.

Study design

The subjects were invited to attend a meeting where they were given detailed instructions about the study and the tests meals to be eaten at home. A double-blind, crossover design was used (Figure 1). The fresh or heated yoghurts were consumed in random order, with a 14-day wash-out period between each dairy product intake period (15 days). The H group (7 women and 4 men) begun the study with the heated yoghurt intake period, and the F group (5 women and 6 men) started with the fresh yoghurt intake period.

In the morning on days 1 (D1), 15 (D15), 30 (D30) and 44 (D44) after a 12-h fast, breath H_2 and serum glucose were measured at baseline and after ingestion of 4 units of test yoghurts (25 g lactose), and the volunteers scored their gastrointestinal symptoms at the conclusion of the 7 h test period. On days 15 and 44, at the end of each yoghurt intake period, gastric emptying, orocoecal transit time (OCTT) and faecal weight and frequency were measured. Just before being consumed, 1 g ^{15}N-lactose-ureide (99 atom %) and 150 mg ^{13}C-acetate (99 atom %) were added to one

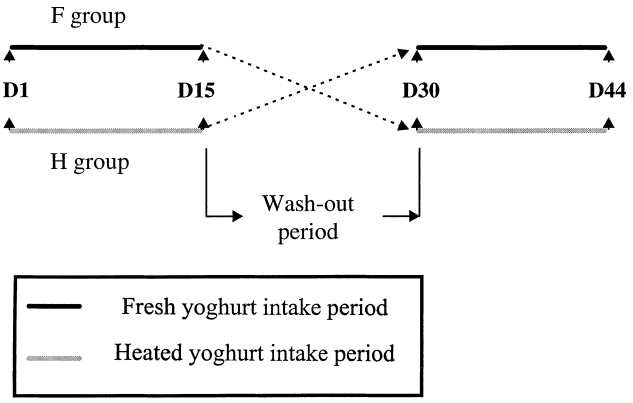

Figure 1. Diagram of study design.

yoghurt and then carefully stirred. From day 2 (D2) to day 14 (D14) and from D31 to D43, the 4 units of test yoghurts (25 g lactose) were consumed in two or three intakes over the day, with half of the quantity at dinnertime during the evening.

Dietary fibre was restricted the evening before testing. A standard hamburger and rice meal, which did not produce increases in hydrogen, was provided to all subjects 4 h after they ingested the four test yoghurts, to allow sampling follow-up over a 7 h period without hunger.

Hydrogen analysis

Lactose absorption was assessed by breath hydrogen analysis with portable equipment (EC60 Gastrolyser, Isomed). End-alveolar breath samples obtained twice in the fasting state were used, every 15 min for first 60 min and each 30 min for the 7 h following ingestion of the test meals. Changes in breath hydrogen concentration (Δ) were calculated by subtracting the baseline (fasting) hydrogen concentration from subsequent test values.

Labelled $^{13}CO_2$ analysis

Gastric emptying was assessed by breath $^{13}CO_2$ analysis (Breath MAT^{plus}, Finnigan ThermoQuest) in the fasting state, every 5 min for 30 min and each 15 min for 3 h following ingestion of the test meal. The results of breath $^{13}CO_2$ measurements were expressed as a percentage of the administered dose of ^{13}C recovered in the breath per hour (%^{13}C dose/h) and as the cumulative percentage of the administered dose of ^{13}C in the breath over 3 h (%^{13}C cumulative dose) according to Maes *et al.*[9–12] Carbon dioxide production was assumed to be 300 mmol/hxm^2 body surface, and the body surface area was calculated by using the formula of Haycock *et al.*[13] Using least-square algorithms, the curves percentage ^{13}C recovery were fitted to the following two formulas:

$$\%^{13}\text{C dose/h} = at^b e^{-ct} \quad (1)$$

and

$$\%^{13}\text{C cumulative dose} = m(1 - e^{-kt})^{\beta} \quad (2)$$

where t is time, and a, b, c, m, k and β are constants determined by nonlinear-regression analysis. Three parameters describing gastric emptying were calculated from the constants obtained: (i) gastric emptying half time $t_{1/2} = (-1/k)\ln(1 - 2^{-1/\beta})$, (ii) gastric emptying coefficient GEC = ln a and (iii) the lag phase $t_{lag} = \ln \beta/k$.

Labelled ^{15}N analysis

Orocoecal transit time (OCTT) was assessed through urine $^{15}NH_3$ output determination (Delta E, Finnigan MAT). Urine was collected baseline, at 2 h intervals over a period of 14 h after tracer administration, and a final sample was obtained 23 h after ingestion of the test yoghurts. The urine volumes were recorded, 2 mL of each sample were acidified with 6N H_2SO_4 to attain a pH < 4, and stored at −20 °C until analysis. The results were expressed as the total urine ^{15}N excretion over time and the OCTT was calculated as the point of inflexion of the obtained curve.[14]

Gastrointestinal symptoms

The occurrence and severity of symptoms (flatulence, abdominal bloating and pain) was recorded by the subjects and self-rated on a scale of 0–4 on each test day after the 7 h experimental period as follows: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms and 4 = intolerable symptoms.[15] The number of points for each category was totalled to determine the total symptom score.

Statistical analysis

Data were expressed as means ± S.E.M. The lack of differences between the two groups (F and H groups) due to the randomization, led us to present the results as fresh or heated test days (D1: the first day of fresh or heated yoghurt intake period, and D15: the last day of treatment period). Differences in breath hydrogen concentration results and in GEC, $t_{1/2}$, t_{lag} and OCTT values between the fresh or heated yoghurt intake days were evaluated by using paired Student's t-tests. Intolerance symptoms after fresh or heated yoghurt intake in each experimental day were compared by the Wilcoxon signed-rank test. The correlation between lactose digestion, gastric emptying parameters, OCTT and intolerance symptoms were calculated using the Spearman rank order test. Results were considered statistically significant if two-sided P-values were < 0.05. All statistical analysis were performed by using the SPSS 7.5 version for Windows.

RESULTS

Breath hydrogen excretion and biochemical analysis

The mean changes in breath hydrogen concentration for the measured 7 h period (Figure 2) indicated a more effective lactose digestion after fresh yoghurt intake as compared to heated yoghurt. Indices of H_2 excretion were compared among the two experimental days, before and after 4 units of dairy product intake, in three ways: (i) mean peak rise above fasting baseline levels seen in each study subjects (Peak H_2) (ii) cumulative H_2 excretion over the 7 h period (H_2 cum), and (iii) the area under the curve of H_2 excretion calculated by a trapezoidal method (H_2 AUC). Fresh yoghurt ingestion resulted in lower peak H_2, H_2 cum and AUC H_2 than pasteurized yoghurt intake, indicating a more effective lactose digestion (Table 2).

Serum glucose, insulin and free fatty acid (FFA) concentrations measured over the 7 h period were similar after heated or fresh yoghurt intake treatment.

Gastrointestinal symptoms

Overall, the lactose malabsorbers exhibited few symptoms during the two study periods (Figure 3). Thus, the mean symptom-severity scores were between 0.5 and

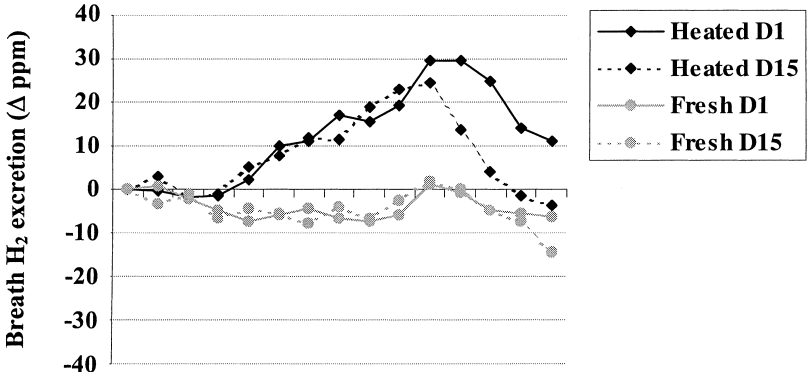

Figure 2. Changes in breath hydrogen concentration before (D1) and after (D15) 25 g lactose load intake treatment as fresh or heated yoghurt. $n = 18$ lactose malabsorber subjects.

Table 2. Parameters describing lactose digestion, gastric emptying, orocoecal transit time and gastrointestinal symptoms at final of each test yoghurts intake period*

	Dairy intake		
	Heated yoghurt D15	Fresh yoghurt D15	*P*
Peak H_2 (p.p.m.)†	47.6 ± 6.8	17.2 ± 3.8	0.001[a]
H_2 cum (p.p.m.)†	116.2 ± 57.2	−68.8 ± 43.2	0.013[a]
AUC H_2 (p.p.m.min)†	3605.0 ± 1696.9	−1752.8 ± 1190.4	0.012[a]
AUC glucose (mmol/L.min)†	−58.5 ± 20.5	−45.4 ± 19.3	0.575
AUC insulin (mU/L.min)†	1742.4 ± 205.9	1822.9 ± 694.0	0.908
AUC FFA (mmol/L.min)	52.58 ± 3.29	54.70 ± 3.64	0.482
t_{lag} (min)†	48.48 ± 4.80	50.55 ± 5.37	0.722
$t_{1/2}$ (min)†	95.08 ± 4.59	90.16 ± 3.96	0.377
OCTT (h)†	12.1 ± 0.5	10.5 ± 0.6	0.054[ts]
GIS†	2.6 ± 0.5	1.4 ± 0.3	0.037[a]

* Abbreviations used: Peak H_2: peak of hydrogen excretion; H_2 cum: summation of the breath H_2 concentration over 7 h; AUC H_2: area under curve for breath H_2 excretion; $t_{1/2}$: gastric emptying half time; t_{lag}: lag phase; OCTT: orocoecal transit time; GIS: gastrointestinal symptoms score expressed as the mean of the sum of flatulence, abdominal pain and bloating scored rated from 0 to 4 (none to intolerable); AUC glucose: area under curve for blood glucose concentration; AUC insulin: area under curve for serum insulin concentration; AUC FFA: area under curve for serum free fatty acid concentration.

† $n = 19$. Values are mean ± S.E.M.

[a] Significantly different between the two test groups, $P < 0.05$ (paired Student's *t*-test or Wilcoxon rank test when appropriate).

[ts] marginal significance $0.05 < P < 0.1$ (two-sided).

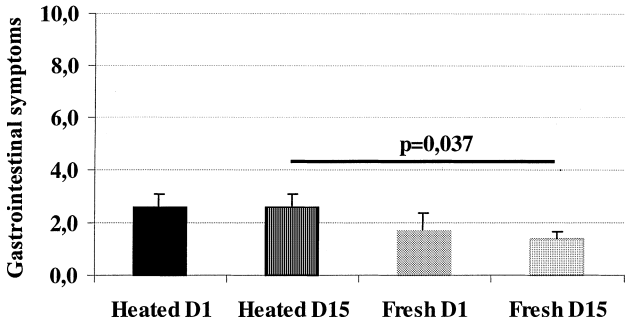

Figure 3. Gastrointestinal symptoms (flatulence, abdominal pain and bloating) on a scale from 0 (no symptoms) to 4 (intolerable symptoms), before (D1) and after (D15) 25 g lactose load intake treatment as fresh or heated yoghurt. GIS was significantly fewer after fresh yoghurt intake as compared to the heated product (D15 yoghurt), $P < 0.05$. Results are as mean ± S.E.M.

3.0, indicating symptoms of mild severity. Nevertheless, there was a significantly lower severity of scored symptoms after yoghurt containing active live cultures than after ingestion of pasteurized yoghurt (Table 2). The highest symptom score in both groups was for flatulence, and others such as nausea or diarrhoea were rare during either intervention period. On the other hand, the regular ingestion of 25 g lactose did not result in significant decreases in breath hydrogen indices and lactose intolerance symptoms, as revealed by the results before and 15 days after 25 g lactose ingestion as heated yoghurt intake treatment (data not shown).

Faecal weight and frequency

Faecal weight and frequency measured at the end of each yoghurt intake period was not significantly different between the two test yoghurt intakes, i.e. 86.2 ± 17.4 g/1 day and 1.2 ± 0.1 no. faeces/day for fresh yoghurt and 88.0 ± 14.9 g/1 day and 1.2 ± 0.2 no. faeces/day for heated yoghurt.

Gastric emptying and orocoecal transit time

Gastric emptying half time ($t_{1/2}$) and t_{lag} were unaffected after fresh or heated yoghurt ingestion (Table 2). However, OCTT was shorter after pasteurized yoghurt (10.5 ± 0.6 h) than after fresh yoghurt ingestion (12.1 ± 0.5 h) and showed a significant negative correlation with the gastrointestinal symptoms score (GIS) according to Spearman rank correlation ($r = -0.413$; $P = 0.014$).

DISCUSSION

A number of studies have demonstrated that lactose tolerance is enhanced when consumed as yoghurt containing active live cultures, as compared with other dairy products.[16] Pasteurization of yoghurt, which results in a virtual elimination of β-galactosidase activity, could also reduce most beneficial effects on lactose digestion.[17] Nevertheless, several investigators have found that heated yoghurt retains some capacity to alleviate lactose intolerance symptoms.[2, 5] Thus, a slower gastric emptying and orocoecal transit time, probably due to osmolality and/or the physical form of both dairy products, have been associated with less severe symptoms of lactose intolerance.[6, 18, 19]

Data from this study showed that lactose malabsorber subjects digest lactose more effectively in fresh yoghurt than in pasteurized yoghurt.[20, 21] The subjects consuming 4 units of fresh yoghurt (25 g lactose) no longer appeared to be lactose maldigesters on the basis of breath hydrogen criteria, in the two experimental groups. As a result of this improved lactose digestion from yoghurt containing living bacterial, the lactose was apparently better tolerated than the other dairy products tested.

In this study, gastric emptying was similar between the two test yoghurts (fresh and heated), while the orocoecal transit time of fresh yoghurt was markedly slower than that of the heated yoghurt. Furthermore, gastrointestinal symptoms displayed a strong inverse correlation with OCTT. These findings suggest that when intestinal transit time increases, lactose digestion and tolerance may improve.[22]

Other researchers have compared lactose tolerance and gastric emptying between different test milks, taking into account the milk viscosity or energy content.[23, 24] They concluded that, in lactose maldigesters, raising the viscosity of the milk to a level that was similar to that of yoghurt did not affect lactose tolerance or gastric emptying, and that raising the energy content of milk slowed down gastric emptying of lactose, but did not improve tolerance. Furthermore, other reports have revealed that longer transit time values were associated with fewer gastrointestinal symptoms.[25] However, this effect was not observed in all studies.[26] Interestingly, the slowing down of OCTT by loperamide was associated with less severe symptoms of lactose intolerance, which seems to argue in favour of a direct link between motility and symptoms.[25]

However, it does not establish whether this link is causative, and if so, which factor is the cause or the consequence. Other authors have shown that in some individuals, lactose digestion (presumably due to the residual mucosal mammalian lactase) from pasteurized yoghurt is slightly improved compared with that from milk, as estimated by small reductions in overall gas production.[4, 17] Furthermore, the appearance of gaseous symptoms depends not only on the residual lactase capacity,[27] but also on the balance between the production and the removal of these fermentation products, which depends on colonic flora composition.[9]

The unusual tolerance observed in this trial may be due to the lactose test dose assayed, which was more physiological than in previous studies.[9, 28, 29] The lack of diarrhoea or headache in these lactose maldigester subjects indicated that the colon removed the bulk of the osmolar load provided by the malabsorbed lactose.[30] The excessive flatus observed with pasteurized yoghurts indicates that gas removal mechanisms were overwhelmed by the rate of gas production; however, this excess gas did not accumulate to the extent that subjects recorded increased bowel movement frequencies or stool weight. In this context, several controlled studies have shown that one cup of milk or its lactose equivalent (12 g) produces minimal symptoms, if any, in lactose deficient subjects, and that fermented dairy products are better tolerated than other dairy products.[31–35]

On the other hand, receiving fresh yoghurt for 15 days did not result in any significant change in breath H_2 test data and in the scored gastrointestinal symptoms, when lactose is consumed in subsequent experimental days as pasteurized yoghurt, suggesting the absence of a prolonged intestinal survival by the yoghurt microorganisms.[36]

Previous studies have reported colonic adaptation to regular lactose ingestion, improving lactose tolerance via several mechanisms.[10] However, the lack of differences in the results between the first day (D1) and 15 days after receiving heated yoghurt showed that the continuous ingestion of lactose did not appear to result in significant reductions in breath hydrogen values or in symptomatic response to lactose.[37]

In conclusion, these results indicate that the lactose malabsorber subjects digest and tolerate better a lactose load of 25 g in fresh yoghurt than in the pasteurized yoghurt. The mechanism responsible for this enhanced lactose digestion and tolerance was attributable to the presence of bacterial β-galactosidase in the fresh product. On the other hand, the slower mean transit time induced by fresh yoghurt intake was associated with fewer lactose intolerance symptoms. A recent study concerning chronic consumption of fresh yoghurt confirms the benefits on breath hydrogen status in men with lactose maldigestion.[38]

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