Prevalence and Presentation of Lactose Intolerance and Effects on Dairy Product Intake in Healthy Subjects and Patients With Irritable Bowel Syndrome

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BACKGROUND & AIMS: **The effects of lactase deficiency on digestive symptoms and diet in patients with irritable bowel syndrome (IBS) have not been well defined. We assessed lactose absorption and tolerance and the intake of dairy products in healthy volunteers (controls) and patients with diarrhea-predominant IBS (D-IBS).**

METHODS: **Sixty patients diagnosed with D-IBS at the Sir Run Run Shaw Hospital, Hangzhou, China and 60 controls were given hydrogen breath tests to detect malabsorption and intolerance after administration of 10, 20, and 40 g lactose in random order 7–14 days apart; participants and researchers were blinded to the dose. We assessed associations between the results and self-reported lactose intolerance (LI).**

RESULTS: **Malabsorption of 40 g lactose was observed in 93% of controls and 92% of patients with D-IBS. Fewer controls than patients with D-IBS were intolerant to 10 g lactose (3% vs 18%; odds ratio [OR], 6.51; 95% confidence interval [CI], 1.38–30.8; $P = .008$), 20 g lactose (22% vs 47%; OR, 3.16; 95% CI, 1.43–7.02; $P = .004$), and 40 g lactose (68% vs 85%; OR, 2.63; 95% CI, 1.08–6.42; $P = .03$). H_2 excretion was associated with symptom score ($P = .001$). Patients with D-IBS self-reported LI more frequently than controls (63% vs 22%; OR, 6.25; 95% CI, 2.78–14.0; $P < .001$) and ate fewer dairy products ($P = .040$). However, self-reported LI did not correlate with results from hydrogen breath tests.**

CONCLUSIONS: **The risk of LI is related to the dose of lactose ingested and intestinal gas production and is increased in patients with D-IBS. Self-reported LI, but not objective results from hydrogen breath tests, was associated with avoidance of dairy products. ClinicalTrials.gov, Number: NCT01286597.**

Keywords: Randomized Controlled Trial; Lactose Dose; FODMAP; Intestinal Gas; Bloating; Functional Bowel Disease; Milk.

Lactose is the major carbohydrate found in milk, and lactose powder is widely used as an ingredient by the food industry. Lactose is hydrolyzed by the lactase enzyme in the small intestine. The most common cause of lactose malabsorption (LM) is genetically determined primary lactase deficiency that reduces lactase expression after weaning.[1] If lactose is not digested and absorbed in the small bowel, then fermentation by colonic bacteria produces short-chain fatty acids and gas including hydrogen, carbon dioxide, and methane. This process is associated with lactose intolerance (LI) in susceptible individuals, which is a syndrome of nausea, abdominal pain, bloating, and diarrhea.[1] Most patients with LM can take at least 12 g of lactose (equivalent to a cup of milk) without discomfort, whereas ingestion of 40–50 g lactose usually triggers symptoms[2,3] however, the prevalence of clinically relevant LI is uncertain. In practice, the situation is made still more complex because many patients, especially those with functional gastrointestinal diseases, are hypervigilant to diet-related symptoms and display marked avoidance behavior to various foods, including dairy products.[4] As a consequence, irritable bowel syndrome (IBS) patients may attribute digestive problems to LI but have no evidence of this condition on objective investigation.[5,6]

Abbreviations used in this paper: AUC, area under the curve; D-IBS, diarrhea-predominant irritable bowel syndrome; HBT, hydrogen breath test; IBS, irritable bowel syndrome; LI, lactose intolerance; LM, lactose malabsorption; OR, odds ratio; SNP, single nucleotide polymorphism; TSS, total symptom score.

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Thus, many individuals may be avoiding dairy products unnecessarily, with potential adverse effects on nutritional health.[7]

A recent consensus development statement from the U. S. National Institutes of Health recognized LI as a common and important cause of functional gastrointestinal symptoms[7]; however, the authors highlighted a lack of knowledge about epidemiology, diagnosis, and management strategies. The lactose hydrogen breath test (HBT) is a simple, noninvasive investigation for the assessment of lactose digestion and tolerance. Diagnosis of LI requires demonstration of an unequivocal, temporal association between lactose intake, increase in breath hydrogen, and symptoms. However, open label testing is suboptimal, especially in patients with self-reported LI and those with functional gastrointestinal diseases.[3,8]

This study assessed the prevalence of LI in a population-based cohort of healthy volunteers and patients with diarrhea-predominant irritable bowel syndrome (D-IBS). Genotype and phenotype were assessed, with diagnosis established by HBT at 10, 20, and 40 g lactose (reference standard) in a double-blind, randomized, controlled three-way crossover trial. In this context the National Institutes of Health consensus development statement recommended testing at multiple doses reduces response bias and delivers additional information that can inform decisions about the appropriate dose for diagnosis of LI by HBT. Moreover, in clinical practice, this approach demonstrates the dose of lactose that is tolerated by an individual patient. The clinical relevance of these findings was assessed by comparing the number and the severity of symptoms reported by healthy subjects and D-IBS patients during lactose HBT. In addition, to assess the role of dietary avoidance and hypervigilance to milk-related symptoms, the impact of self-reported LI and objective evidence of LI on dietary intake of dairy products were documented.

Methods

Participants

The study was performed in an adult Chinese population with a high prevalence of primary lactase deficiency.[9] Healthy volunteers (controls) with no history of gastrointestinal disorders were recruited by advertisement. Consecutive patients (>95% self-referred) who met Rome III criteria for D-IBS[10] were recruited after exclusion of other medical conditions by standard investigations including colonoscopy.

Random Assignment and Interventions

Eligible participants completed genetic sequencing of lactase gene regulatory sequence and questionnaire about food containing lactose. Then all participants underwent HBT at 10, 20, and 40 g lactose on 3 different days, each separated by 7–14 days in randomized order by using a random number table. A study nurse not involved in other study procedures dissolved the appropriate dose of lactose powder in 250 mL water on the examination day and labeled the cup with the patient number. Pilot studies demonstrated that participants could not identify the dose when presented in random order. Participants and investigators remained blinded to the dose of lactose and results throughout the study.

Genetic Sequencing of Lactase Gene Regulatory Sequence (Genotype)

White cells were isolated from a whole blood sample by using a modified salting-out procedure, and DNA was extracted (Axygen, Union City, CA). A 446-base pair region within intron 13 of MCM6 (13,807–14,253 base pairs upstream of the lactase gene) was amplified by 35 polymerase chain reaction cycles (forward primer (5′-CGGATGCACTGCTGTGATGA-3′), reverse primer (5′-ACTGACCTATCCTCGTGGAATG-3′)). Single nucleotide polymorphisms (SNPs) associated with lactase persistence in European (C/T-13910), African and Arabian (C/G-13907, T/G-13915, and G/C-14010) populations were identified by bidirectional sequencing by using Sequencher software (version 4.0.5; Gene Codes Corp, Ann Arbor, MI).[11,12]

Lactose Hydrogen Breath Test (Phenotype)

After lactose ingestion, breath samples were recorded at 15-minute intervals during a period of 3 hours. LM was diagnosed if peak H_2 breath excretion exceeded ≥20 ppm over the baseline value on at least 2 consecutive readings.[9] The number and the severity of individual symptoms (nausea, bloating, abdominal pain, borborygmi, and diarrhea) during and after the test within 24 hours were assessed by a Likert scale (0 = absence, 1 = trivial, 2 = mild, 3 = moderate, 4 = strong, and 5 = severe symptoms). The total symptom score (TSS) was calculated as the sum of the highest intensity value for each symptom.[13] LI was diagnosed if in the presence of LM, a greater than 1-point rise in TSS was reported on at least 2 consecutive measurements.

Parameters describing hydrogen excretion included (1) peak H_2 value and (2) total H_2 excretion, which was expressed as area under the curve (AUC) of H_2 concentration from 15–240 minutes.

Food Questionnaire

All participants detailed intake of dairy products (eg, milk, yogurt, ice cream) and other products containing lactose in the previous 3 months on a standardized questionnaire validated in the Chinese population.[14] In addition, participants were asked to self-assess tolerance to dairy products.

Intake frequency and portion sizes were documented, and the amount of lactose was calculated by reference to the U.S. Department of Agriculture National Nutrient Database (http://www.nal.usda.gov/fnic/foodcomp/search/, accessed on October 4, 2012).

Follow-up

Clinic records were reviewed at 6 months to ensure that no patient with occult "organic" disease had been included in the study.

Statistical Analysis

Variables were expressed as mean (standard deviation) or median (interquartile values). Peak H_2 value and amount of H_2 excretion (AUC) were logarithmically transformed to achieve normally distributed data. An unpaired *t* test was computed for the comparison between D-IBS with control groups. Qualitative data comparisons used the χ^2 test. The correlation between TSS and hydrogen excretion was calculated by using the two-tailed Spearman test. The optimal diagnostic cutoff value for IBS based on number of symptoms and TSS was calculated by

Table 1. Demographic Characteristics of Patients With D-IBS and Controls

Characteristic	D-IBS (n = 60)	Controls (n = 60)	*P* value
Mean age, *y* (SD)	40.8 (11.7)	40.8 (15.2)	.99
Mean BMI,[a] *kg/m²* (SD)	21.5 (3.19)	23.0 (3.52)	.04
Sex (male/female)	29/31	31/29	.72
Current smoker, n (%)	7 (12)	9 (16)	.59
Current alcohol use, n (%)	10 (17)	8 (13)	.61
Education level,[a] n (%)			.04
Less than high school	25 (42)	33 (55)	
High school/some college	9 (15)	14 (23)	
Bachelor's degree or higher	26 (43)	13 (22)	

BMI, body mass index; SD, standard deviation.
[a]$P < .05$ comparison between patients with D-IBS and controls.

analysis of receiver operating characteristic curves generated by using SPSS version 16.0 software (SPSS Inc, Chicago, IL). The criterion chosen to select the cutoff was the highest sum of the sensitivity and specificity (Youden index[15]). A value of $P < .05$ was significant.

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethical committee of Sir Run Run Shaw Hospital. All participants signed consent for study procedures. All authors had access to the study data and had reviewed and approved the final manuscript.

Results

Patient Characteristics

Study recruitment and participant progress are detailed in Supplementary Figure 1. The demographic and clinical characteristics of enrolled and excluded D-IBS patients were similar (Supplementary Table 1). Data from 60 controls and 60 D-IBS patients who completed 10, 20, and 40 g lactose HBT were analyzed. Demographic variables showed no significant difference in age, gender, body mass index, habit of smoking, or alcohol use between groups (Table 1). No patient was found to have occult "organic" disease as a cause of gastrointestinal symptoms at 6-month follow-up.

Genotype

The genotype in all participants was C/C-13910, and no other SNP was identified on gene sequencing of the putative lactase gene regulatory sequence in any participant.

Phenotype: Lactose Hydrogen Breath Test

The prevalence of LM and LI increased with lactose dose (Figure 1). As detailed in Table 2, there was no difference in LM prevalence at any dose, with a diagnostic rise in breath hydrogen for 93% of controls and 92% of D-IBS subjects at the 40-g lactose dose. Five controls and 4 D-IBS patients had <20 ppm rise in breath hydrogen during 40-g lactose HBT. Of these, 3 in each group reported abdominal symptoms indistinguishable from LI. Thus, only 3 subjects in this population had objective and subjective findings consistent with lactase persistence. The prevalence of LI was lower for controls than for D-IBS subjects at 10 g (3% vs 18%, $P = .008$), 20 g (22% vs 47%, $P = .004$), and 40 g lactose (73% vs 85%, $P = .03$). There were no significant differences in LI symptom rate and severity between LM-negative and LM-positive IBS patients except at the 10-g lactose dose (Supplementary Table 2).

Association Between Breath Hydrogen Excretion During Lactose Hydrogen Breath Test and Symptoms

Peak H_2 excretion and the total H_2 excretion (AUC) increased with lactose dose. There was an association between peak H_2 concentration and the AUC H_2 excretion with TSS in controls ($r = 0.34, 0.29$; both $P < .001$) and patients with D-IBS ($r = 0.28, 0.35$; both $P < .001$).

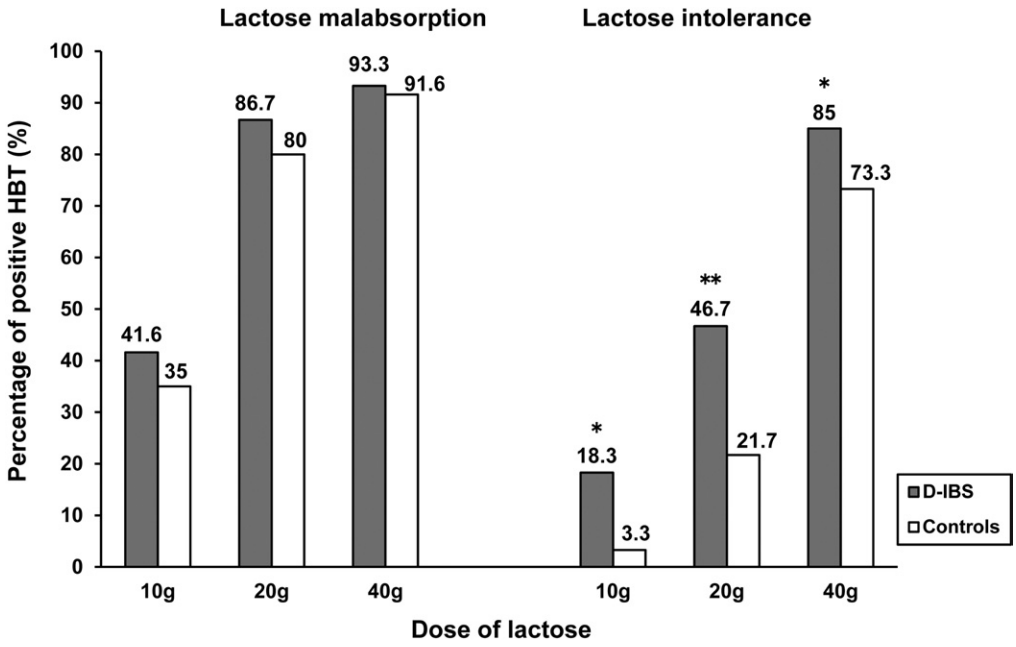

Figure 1. Prevalence of LM and LI in patients with D-IBS and controls at 10-, 20-, and 40-g lactose HBTs. *$P < .05$; **$P < .01$. *There was no difference in the demographic or clinical characteristics of patients that completed screening investigation but withheld consent from completing the full study.

Table 2. Lactose HBT Results for 10-g, 20-g, and 40-g Lactose Dose

	10 g				20 g				40 g			
	D-IBS	Controls	*P* value	OR (95% CI)	D-IBS	Controls	*P* value	OR (95% CI)	D-IBS	Controls	*P* value	OR (95% CI)
LM, n (%)	25 (42)[a]	21 (35)[b]	.45	1.32 (0.63–2.78)	52 (87)	48 (80)	.33	1.63 (0.61–4.32)	56 (93)	55 (92)	.73	1.27 (0.33–4.99)
LI, n (%)	11 (18)[a]	2 (3)[c]	.008	6.51 (1.38–30.8)	28 (47)[d]	13 (22)[e]	.004	3.16 (1.43–7.02)	51 (85)	41 (68)	.03	2.63 (1.08–6.42)
TSS (SD)	1.8 (0–4)[f]	0.1 (0–1)	.064		2.24 (0–4)[d]	0.68 (0–1.0)[e]	.014		4.5 (3.0–6.0)	3.3 (0–5)	.079	
Number of symptoms (SD)	0.73 (0–1.3)[a]	0.09 (0–1)	.165		1.28 (0–2.5)[d]	0.34 (0–1.0)[e]	.008		2.29 (1.25–3.0)	1.53 (0–3.0)	.08	
Peak H_2 value (*ppm*)[g]	38 (27–47)[f]	38 (29–46)[c]	.98		57 (32–85)[d]	66 (36–90)[e]	.53		92 (58–127)	99 (56–135)	.98	
Amount of H_2 excretion (*ppm* × *min*)[g]	2580 (1053–3793)[a]	2302 (1113–3172)[c]	.45		3637 (2070–5632)[d]	4020 (2028–6401)[e]	.63		6877 (4065–11,468)	6292 (3442–13,388)	.86	

NOTE. Data are expressed as median and 25%–75% quartile values.
CI, confidence interval; OR, odds ratio; SD, standard deviation.
Comparison between 10 g and 20 g in D-IBS patient: [d]$P \leq .01$, [a]$P \leq .001$; between 20 g and 40 g in D-IBS patient: $P \leq .01$, [d]$P \leq .001$; between 10 g and 20 g in controls: [c]$P \leq .01$, [b]$P \leq .001$; between 20 g and 40 g in controls: [e]$P \leq .01$, [e]$P \leq .001$.
[g]Amount of H_2 excretion (ppm × min): expressed as area under the concentration–time curves (ppm, 3 h).

Discrimination of Diarrhea-predominant Irritable Bowel Syndrome From Controls by Lactose Hydrogen Breath Test

LM prevalence was similar in both study groups; however, LI prevalence was higher in D-IBS patients than in controls at each lactose dose (Figure 1). In addition, D-IBS patients reported a larger number of symptoms and higher TSS than controls (Figure 2).

Dietary Intake

Most participants (83/120, 69%) included milk and dairy products in their diet; however, D-IBS patients reported less frequent intake of dairy products than controls (Table 3) and a smaller amount of lactose in the diet (D-IBS, 9.0 g (4.5–17.3) vs controls, 19.5 g (6.0–36.4); $P = .040$).

Association of Objective and Subjective (Self-reported) Lactose Intolerance

A higher proportion of D-IBS patients than controls self-reported LI (63%, 38/60 vs 22%, 13/60; odds ratio, 6.25; 95% confidence interval, 2.78–14.0); $P < .001$); however, in both groups, participants with and without subjective LI had similar frequency and severity of abdominal symptoms on objective lactose HBT (Table 4).

Discussion

This study reports the prevalence of LI in healthy volunteers (controls) and D-IBS patients with LM and the impact of LI on the intake of dairy products. Breath hydrogen excretion and symptom response after ingestion of 10, 20, and 40 g lactose were assessed by HBT under a randomized double-blind study design that addresses the limitations of open label testing used in many previous studies. The prevalence of LM diagnosed by the 40-g lactose HBT was 91.6%, similar to results in other Chinese and Southeast Asian populations.[16] This may be an underestimate because symptomatic patients in whom colonic fermentation did not produce hydrogen (~10%) are not included in this statistic.[17] Consistent with this view, the genotype in all participants was C/C-13910, and no SNP associated with lactase persistence was present in the lactase gene regulatory sequence.

The frequency of positive tests for LM and LI in both controls and D-IBS patients increased with lactose dose (Figure 1), and the concentration of breath hydrogen (peak and AUC H_2 excretion) was associated with the severity of abdominal symptoms. Thus, the results of lactose HBT depend on the dose of lactose ingested and the amount of gas produced by colonic bacteria.[18] These data demonstrate that the intensity of this stimulus, likely mediated by luminal distention of the intestines,[19] is directly related to the likelihood that an individual will experience symptoms and the severity of those symptoms.

The prevalence of LI was significantly higher in D-IBS patients than in controls. Especially at low and intermediate doses of lactose, the presence of functional gastrointestinal disease increased the likelihood that an individual would report abdominal pain, bloating, and diarrhea. This finding is consistent with the hypothesis that D-IBS patients are more sensitive and/or more likely to report symptoms (hypervigilant) than healthy controls in response to "events" in the gastrointestinal tract, even those within "physiologic limits." Specifically, it adds

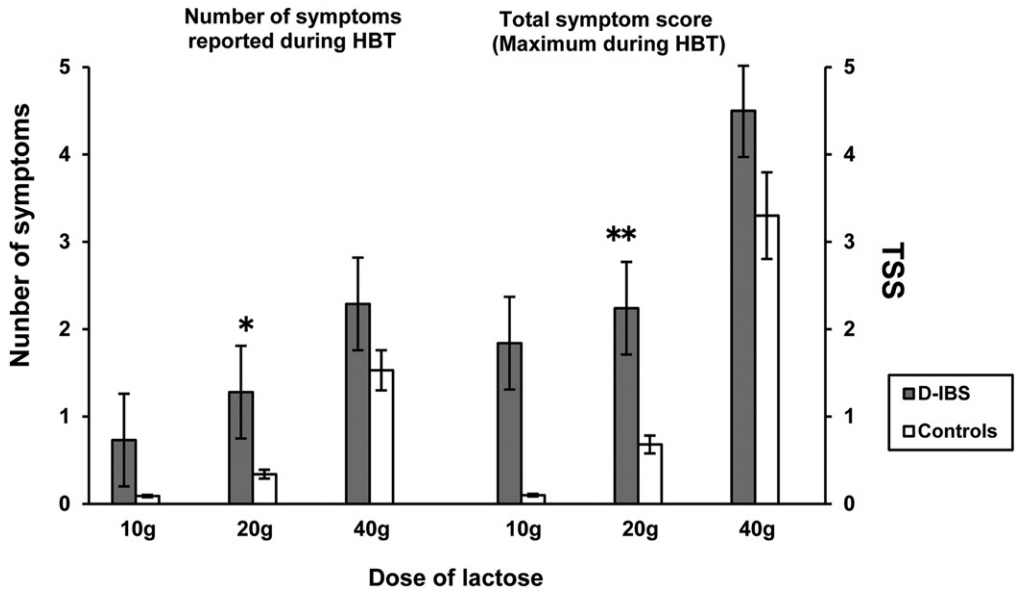

Figure 2. The number of symptoms and severity of symptoms (TSS) for 10-, 20-, and 40-g lactose HBT. Patients with D-IBS reported a greater number and also more severe symptoms than controls at the 20-g dose; $^{*}P < .05$, $^{**}P < .01$ compared with controls. Subjects who reported ≥3 different symptoms or had a ≥5 TSS at the intermediate 20-g lactose HBT were likely to have D-IBS (92% specificity), although many D-IBS patients did not meet these "diagnostic criteria" (30% sensitivity).

to the evidence that visceral hypersensitivity and hypervigilance to gas retention are key factors in the sensation of bloating and abdominal pain.[19,20]

In our study, 3 doses of lactose were used for testing. High doses (ie, 40 g, 50 g) are appropriate for epidemiologic studies of lactase deficiency; however, testing at lower doses more typical of normal dietary intake may provide clinically relevant findings that can be used to guide nutritional management without a great loss of test sensitivity.[2,21] Thus, the number of patients who reported LI symptoms was significantly lower after ingestion of 20 g than 40 g lactose (controls, 22% vs 68%; D-IBS, 47% vs 85%), with concordant results for LM diagnosis for 20-g and 40-g lactose HBT in 88% of participants. Indeed, participants who reported a high number of different symptoms (≥3) and/or a high TSS (≥5) were very likely to have D-IBS (Figure 2), and these criteria may identify patients who should benefit from nutritional intervention.

This study also assessed the impact of LI, both real and imagined, on the diet. Although consumption of dairy products is less in China than in Northern Europe and the United States,[22] it is increasing rapidly,[23] and most study participants did include milk and other lactose-containing products in their food choices. Controls were less likely to self-report LI and had a greater intake of lactose than patients with D-IBS (Table 3). However, the diagnostic value of self-reported LI appears to be limited because participants with and without self-reported LI in both groups had similar severity of abdominal symptoms during lactose HBT, and the presence of LI on investigation was not independently associated with dietary behavior. The reason for the discrepancy between self-reported LI and LI reported during HBT remains unclear, but it is likely to be related to anxiety and hypervigilance for symptoms related to dairy intake by IBS patients and possibly the form and context (ie, alone or with other food) in which dairy products are consumed.[3,24] This is consistent with a systematic review of 26 studies that found little association between self-reported intolerance to dairy products and the findings of lactose HBT also in white populations.[5] It follows that self-reported LI has been of limited use in directing therapy in IBS patients.[6] These findings underline the difficulty that patients have in identifying dietary triggers for their functional gastrointestinal symptoms and the need for objective testing. As a result of this confusion, many IBS patients completely avoid dairy products, an approach that may adversely impact on nutritional health and that rarely provides adequate relief of symptoms.[7] Certainly, consistent with previous trials,[2,3,8] 97% of controls and 82% of D-IBS patients in this study had no digestive discomfort after ingestion of 10 g lactose (equivalent to a cup of milk), even though all had lactase deficiency.

This study addresses many limitations of the existing evidence base identified by the recent National Institutes of Health report on LI.[7] First, an unselected, population-based cohort of controls and D-IBS patients with similar baseline characteristics was investigated. Studying a Chinese population with primary lactase deficiency facilitated our analysis of the interaction between lactose dose and functional gastrointestinal disease on the development of LI and helped to disentangle the relationship of these 2 common conditions. We consider that the results can be generalized from the Chinese population to other groups because (1) LI prevalence in subjects with LM lies within the range of reported values in whites[25] and (2) the prevalence and etiology of IBS appear to be similar in China, Europe, and

Table 3. Frequency of Subjective LI and Dairy Intake in Participants

	Self-reported LI	*P* value	Rarely, <1/mo	Occasionally, >1/mo	Often, >1/wk	Daily	*P* value
D-IBS (n = 60)	38 (63%)	<.001	23 (38%)	25 (42%)	8 (13%)	4 (7%)	.02
Controls (n = 60)	13 (22%)		14 (23%)	18 (30%)	22 (37%)	6 (10%)	

Table 4. Association Between Subjective (Self-reported) and Objective (Lactose HBT) Lactose Tolerance

	D-IBS			Controls		
HBT	SLI (n = 38)	SLT (n = 22)	*P* value	SLI (n = 13)	SLT (n = 47)	*P* value
10 g						
n (%)	8 (21)	3 (14)	.47	0	2 (4)	.45
TSS	3.50 (2.01)	3.67 (2.52)	.91	0	1.0	NA
20 g						
n (%)	19 (50)	9 (41)	.50	3 (23)	10 (21)	.89
TSS	3.81 (2.11)	4.30 (1.95)	.54	3.33 (1.52)	2.20 (1.03)	.16
40 g						
n (%)	34 (90)	17 (77)	.20	9 (69)	32 (68)	.94
TSS	4.97 (2.67)	5.80 (2.67)	.23	3.64 (2.29)	4.14 (2.43)	.55

SLI, subjective lactose intolerance; SLT, subjective lactose tolerance.

the United States.[26,27] Furthermore, diagnostic criteria for LM and LI on lactose HBT were applied that have been validated in other populations with a high prevalence of lactase deficiency[9] and that have a high degree of agreement with intestinal lactase level and genetic tests.[28]

In this study, randomized, double-blind testing of lactose digestion and tolerance was performed at multiple doses with a low dose (10 g, control), an intermediate dose (20 g, reflecting typical intake at a single meal), and high dose (40 g, reference standard). Advantages of this approach over placebo-controlled testing include (1) improved blinding and taste matching, (2) reduced response bias, (3) the presence of a dose-response relationship that supports the likely cause-and-effect relationship between lactose intake and symptoms, and (4) the delivery of information that can guide nutritional management. The absence of a "true placebo" study arm does not impact the primary aim to assess the clinical relevance and impact of LI in IBS patients and healthy subjects. Previous studies have shown that <12 g lactose does not cause symptoms more frequently than placebo in health or disease.[29] The number responding to 10 g lactose was <20%, which is much lower than the rate of placebo response (more than 30%) in most randomized controlled trials.[30] Confirmed gastrointestinal reactions to smaller doses of milk are more likely to represent an allergic reaction to milk protein than LI.

In conclusion, this study shows that the likelihood of developing abdominal symptoms after lactose ingestion was related to the dose of lactose, expression of lactase in the intestine, action of colonic flora, and the presence of functional gastrointestinal disease. Patient intake of milk products was associated more closely with patient perception of lactose tolerance than objective evidence on HBT. Consistent with National Institutes of Health recommendations, these findings indicate that blinded and controlled testing would increase the specificity of LI diagnosis and provide clinically relevant data that can guide rational nutritional management and avoid unnecessary food restrictions.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2012.11.034.

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Conflicts of interest

The authors disclose no conflicts.

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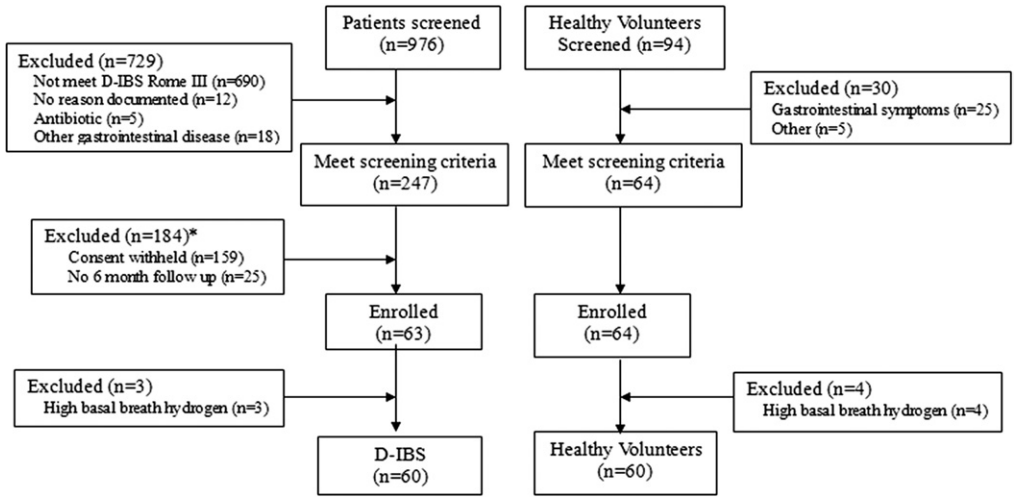

Supplementary Figure 1. Study flow chart. *There was no difference in the demographic or clinical characteristics of patients that completed screening investigation but withheld consent from completing the full study.

Supplementary Table 1. Demographic and Clinical Characteristics of Enrolled and Excluded Patients With D-IBS

Characteristic	Enrolled (n = 63)	Excluded (n = 184)	*P* value
Mean age, *y* (SD)	40.7 (11.3)	39.8 (11.4)	.63
Mean BMI, kg/m^2 (SD)	21.5 (3.20)	22.6 (3.64)	.54
Sex (male/female)	31/32	105/89	.46
Current smoker, n (%)	8 (13)	35 (16)	.47
Current alcohol use, n (%)	11 (18)	29 (14)	.53
Education level, n (%)			
Less than high school	25 (40)	76 (41)	.38
High school/some college	11 (18)	46 (25)	
Bachelor's degree or higher	26 (42)	62 (34)	
Severity of gastrointestinal symptoms[a]	4.38 (1.91)	3.97 (1.91)	.21
Frequency of abdominal pain or discomfort[a]	2.96 (0.80)	3.06 (0.67)	.37

BMI, body mass index.
[a]According to Gastrointestinal Symptom Questionnaire. Severity of gastrointestinal symptoms (0 = absence; 1 = minimal symptoms; 2 = mild, symptom could be ignored; 3 = moderate, symptom could not be ignored; 4 = severe, symptoms affect daily life; 5 = very severe, symptoms affect daily life significantly). Frequency of abdominal discomfort or pain (0 = never; 1 = <1 day/month; 2 = 1 day/month; 3 = 2–3 days/month; 4 = 1 day/week; 5 = >1 day/week; 6 = every day during the last 3 months before interview.

Supplementary Table 2. LI Symptom Rate and Severity Between LM-Negative and LM-Positive IBS Patients

	10 g			20 g			40 g		
	LM(−)	LM(+)	*P* value	LM(−)	LM(+)	*P* value	LM(−)	LM(+)	*P* value
LI symptom rate	8.57% (3/35)	44% (11/25)	.001	37.5% (3/8)	53.8% (28/52)	.338	75% (3/4)	91.1% (51/56)	.301
LI severity	2 (0–3)	2 (1–4)	.083	3.5 (2–5.5)	4 (2–6.5)	.555	4 (4–7)	5 (5–10)	.978