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# High prevalence of lactose absorbers in Northern Sardinian patients with type 1 and type 2 diabetes mellitus[1,2]

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**ABSTRACT**

**Background:** Increased intestinal lactase activity has been shown to occur in alloxan and streptozotocin diabetic rats.

**Objective:** The objective of this study was to determine whether increased intestinal lactase activity is present in humans with diabetes mellitus.

**Design:** We assessed the capacity to digest lactose by measuring breath-hydrogen production after oral administration of lactose in 50 patients with type 1 diabetes, 50 patients with type 2 diabetes, and 50 healthy control subjects from Sassari, Sardinia, Italy, a population characterized by a low prevalence of lactase persistence (lactose absorbers).

**Results:** Fourteen percent of control subjects were lactose absorbers, compared with 48% of patients with type 1 diabetes and 52% of patients with type 2 diabetes ($P < 0.005$). The odds ratio of lactase persistence in patients with type 1 diabetes was 5.3 (95% CI: 2.0, 14.0) and in patients with type 2 diabetes was 5.5 (95% CI: 2.1, 14.5).

**Conclusions:** Diabetes is associated with increased intestinal lactase activity in humans. Consequently, there is a greater exposure to glucose and galactose in diabetic patients with high lactose consumption. This may explain the association between diabetes and the risk of cataract. *Am J Clin Nutr* 2001;73:582–5.

**KEY WORDS** Lactase, lactose absorption, type 1 diabetes, type 2 diabetes, Italy

## INTRODUCTION

Activities of the intestinal disaccharidases maltase, sucrase, and lactase are increased in the intestinal mucosa of alloxan and streptozotocin diabetic rats (1–5). This was shown to be independent of the feeding route and dietary composition (6) and was interpreted as a possible response to the diabetic state, such as insulin deficiency or elevated blood glucose concentrations. The abnormally elevated sucrase-isomaltase complex in the small intestine of diabetic rats was normalized within a few hours by insulin administration; insulin may have a suppressive effect on synthesis of these enzymes, presumably by decreasing the transcriptional level of the gene encoding the sucrase-isomaltase complex (7). In addition, a study in diabetic rats and in rats with parenterally induced hyperglycemia showed that hyperglycemia directly increases intestinal disaccharidase activities (8).

There is limited information regarding the activity of intestinal disaccharidases in humans with diabetes mellitus. Two studies of a small number of patients with diabetes (14 subjects overall) showed 2-fold greater intestinal lactase, sucrase, and maltase activities in patients with diabetes compared with control subjects (9, 10). In addition, a substantial decrease in the activities of all disaccharidases was observed after 2–5 wk of treatment with insulin or with glibenclamide, which increases insulin production and peripheral tissue sensitivity to insulin (9).

If patients with diabetes have increased intestinal activities of lactase, those with high lactose consumption would be exposed to greater amounts of the monosaccharides glucose and galactose, and this may result in greater difficulty in achieving adequate blood glucose control. In addition, increased exposure to galactose, the metabolism of which was shown to be impaired in diabetic patients (11), may explain the increased susceptibility of these patients to cataract.

To obtain further information on this issue, we studied the capacity to digest lactose by means of the breath-hydrogen test in patients with type 1 or 2 diabetes and healthy control subjects from a well-defined population in Sardinia characterized by a low prevalence of lactase persistence (lactose absorbers).

## SUBJECTS AND METHODS

Between February and October 1997, we studied 50 patients with type 1 diabetes and 50 patients with type 2 diabetes, ranging in age from 19 to 56 y, and 50 healthy adults of comparable age. All subjects were from Sassari (Northern Sardinia) or the surrounding areas. The subjects' demographic characteristics are reported in **Table 1**.

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**TABLE 1**
Characteristics of the study subjects

| | Patients with type 1 diabetes ($n$ = 50) | Patients with type 2 diabetes ($n$ = 50) | Control subjects ($n$ = 50) |
|---|---|---|---|
| Sex (M/F) | 31/19 | 29/21 | 26/24 |
| Age (y) | 24.0 ± 2.8 (19–45)[1] | 53.5 ± 3.5 (47–56) | 34.5 ± 7.8 (19–51) |
| Regular milk consumption (%)[2] | 78 [39] | 74 [37] | 80 [40] |
| Weight (kg) | 64.14 ± 9.6[3] | 80.9 ± 17.2 | 69.5 ± 17.0 |
| BMI (kg/m$^2$) | 24.28 ± 2.5 | 31.03 ± 6.0 | 24.35 ± 4.3 |
| Glycated hemoglobin (%) | 8.16 ± 1.4 | 6.31 ± 1.1 | 4.93 ± 0.67 |
| Plasma glucose (mmol/L) | 11.38 ± 5.49 | 3.49 ± 2.27 | 4.66 ± 0.50 |
| Triacylglycerols (mmol/L) | 2.27 ± 1.01 | 3.10 ± 1.24 | 1.94 ± 0.72 |
| Total cholesterol (mmol/L) | 4.99 ± 0.83 | 5.22 ± 1.14 | 4.86 ± 0.46 |
| LDL cholesterol (mmol/L) | 2.92 ± 0.88 | 3.36 ± 1.19 | 2.71 ± 0.90 |
| HDL cholesterol (mmol/L) | 1.55 ± 0.41 | 1.21 ± 0.31 | 1.60 ± 0.44 |

[1] $\bar{x}$ ± SD; range in parentheses.
[2] More than once daily. $n$ in brackets.
[3] $\bar{x}$ ± SD.

The type of diabetes was diagnosed in all subjects according to standard published criteria (12). Patients with type 1 diabetes were receiving insulin therapy (30–72 U/d), whereas patients with type 2 diabetes received glibenclamide (2.5–15 mg/d) or metformin (500–2500 mg/d). A diet containing 50–60% carbohydrates was prescribed, providing an average energy intake of 9211 kJ (2200 kcal)/d.

All patients had good glucose control at the time of the study, with fasting blood sugar concentrations ranging from 790 to 1580 mg/L; dietary history was based on consumption of milk and dairy products and was satisfactorily reproducible (13).

In the morning, after an overnight fast, blood was drawn from all patients and control subjects for determination of glycated hemoglobin, which was assayed with use of low-pressure cation exchange chromatography in conjunction with gradient elution and with use of a 765 Glycomat (Ciba Corning Diagnostics Limited, Halstead, United Kingdom).

The breath-hydrogen test was also carried out in the morning after an overnight fast to evaluate lactase activity. This test measures the hydrogen concentration in the expired air after oral administration of lactose. Hydrogen in expired air comes almost exclusively from colonic fermentation of nonhydrolyzed lactose in the small intestine (14). A fiber-free diet was prescribed for the last dinner, and smoking was not allowed on the morning of the test. To avoid an excessive glucose intake in patients with diabetes, one-half of the dose commonly used in the breath test (25 compared with 50 g) was administered orally to all subjects as a 15% water solution. Expired air samples were obtained at baseline and at 30-min intervals for 240 min after lactose administration (15). Hydrogen concentrations were determined with a gas chromatographic method using a 12 i Quintron Microlyzer (Quintron Instrument Co, Inc, Milwaukee). Lactose malabsorption was diagnosed according to the definition of Flatz et al (16), ie, if the maximum increase in hydrogen in the expired air was >20 ppm. During the breath test and for ≥3 h after its completion, all subjects were observed for the development of abdominal symptoms resulting from lactose malabsorption (flatulence, abdominal distension, abdominal pain, and diarrhea). The study protocol was registered at the University of Sassari.

### Statistical analysis

Areas under the curve (AUC) were calculated on the whole response curve from time 0 to time 240 by using the polygonal rule; the data were logarithmically transformed before analysis because of the nonnormality of the data and expressed as integrated concentrations in ppm/min. Analysis of variance was used to compare differences in mean values among groups. The odds ratios (ORs) of type 1 and type 2 diabetes in lactose absorbers and malabsorbers were computed, together with the corresponding 95% CIs, after allowance for sex and age (17). All statistical analyses were performed with use of SPSS for WINDOWS (version 6; SPSS Inc, Chicago).

## RESULTS

Mean glycated hemoglobin concentrations were significantly higher in patients with type 1 (8.05 ± 1.27%) or type 2 (8.09 ± 2.08%) diabetes than in the control subjects (4.93 ± 0.67%). No significant difference was found in body weight or dietary energy intake.

Fourty-eight percent of patients with type 1 diabetes and 52% of those with type 2 diabetes were lactose absorbers, compared with 14% of the control subjects (**Table 2**); these differences were significant ($P < 0.005$). The OR of lactose malabsorbers compared with absorbers was 5.3 (95% CI: 2.0, 14.0) for patients with type 1 diabetes and 5.5 (95% CI: 2.1, 14.5) for patients with type 2 diabetes. Both ORs were highly significant.

The maximum hydrogen concentration in the expired air after oral lactose administration was significantly lower in patients with type 1 or type 2 diabetes than in the control subjects ($P < 0.01$;

**TABLE 2**
Prevalence of lactose absorbers and malabsorbers among patients with type 1 or type 2 diabetes and control subjects and corresponding odds ratios

| | Patients with type 1 diabetes ($n$ = 50) | Patients with type 2 diabetes ($n$ = 50) | Control subjects ($n$ = 50) | Odds ratio[1] (95% CI) | |
|---|---|---|---|---|---|
| | | | | Type 1 diabetes | Type 2 diabetes |
| Lactose absorbers | 24 [48][2] | 26 [52] | 7 [14] | 1[3] | 1[3] |
| Lactose malabsorbers | 26 [52] | 24 [48] | 43 [86] | 5.3 (2.0, 14.0) | 5.5 (2.1, 14.5) |
| Maximum breath-hydrogen concentration (ppm) | 31.42 ± 24.73[4] | 33.52 ± 28.94 | 46.08 ± 21.97 | | |

[1] Adjusted by age and sex.
[2] $n$; % in brackets.
[3] Reference category.
[4] $\bar{x}$ ± SD.

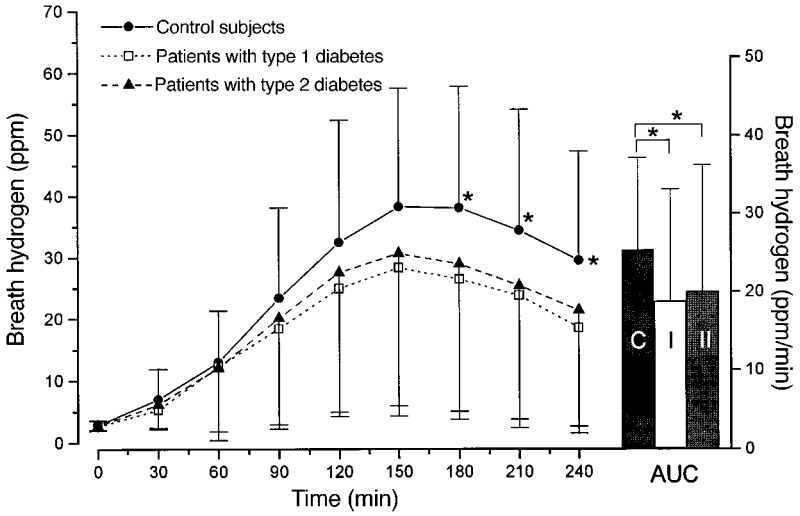


**FIGURE 1.** Mean (±SD) breath-hydrogen concentrations after oral administration of lactose in patients with type 1 or type 2 diabetes and in healthy control subjects and area under the curve (AUC). $^{*}P < 0.05$.

Table 2). Analysis of the hydrogen expiration curves showed a significant difference between values in control subjects and patients with diabetes at 180, 210, and 240 min ($P < 0.05$) (**Figure 1**); AUCs were also significantly lower in patients with diabetes: 18.77 ± 14.3 and 19.98 ± 16.2 ppm/min in patients with type 1 and 2 diabetes ($P = 0.014$ and $P = 0.023$ by Tukey's test), respectively, compared with 25.34 ± 11.8 ppm/min in control subjects.

## DISCUSSION

By means of the breath test, we showed a high prevalence of lactose absorbers among diabetic patients from Sardinia, where the prevalence of primary lactase deficiency is relatively high (18), as in other areas of southern Italy (15). Although absolute numbers were limited, the differences were significant. Patients and control subjects came from the same population, the test used was satisfactorily reproducible and valid (14, 16), and no major potential selection bias or confounding variable were identified. To avoid an excessive glucose intake in diabetic subjects, the breath-hydrogen test was performed with use of one-half the standard dose (25 g compared with 50 g) in both patients and control subjects. However, this should not have reduced the sensitivity of the test because the proportion of lactose absorbers in the control population was similar to that found in previous studies by our group in healthy subjects from the same geographic area using the standard lactose dose (18, 19).

The results of our study support the hypothesis that, in humans, diabetes is associated with increased intestinal lactase activity. Disaccharidases are known to be adaptive enzymes (20); however, average body weight was comparable between patients with diabetes and control subjects, so this adaptation of disaccharidases could not have been responsible for the observed differences in lactase activity.

A possible clinical implication of our finding may be related to the higher susceptibility to cataract of patients with early- or late-onset diabetes (20, 21). In fact, the presence of diabetes for >5 y was identified as a risk factor for cortical and posterior subcapsular cataracts (22). Galactose-induced cataract occurs in infants with inborn errors of galactose metabolism (23) and in animals fed a galactose-rich diet (24). Incidence of cataract has been related to consumption of milk and lactose-rich dairy products (21). In addition, a high frequency of lactose absorbers was found among adults with idiopathic cataract in populations with different prevalences of primary adult lactose malabsorption (15, 25–27). Although galactose is converted to glucose in the liver, disturbed galactose metabolism was shown to occur in elderly and diabetic subjects (28, 11). Alcohol consumption may further reduce the hepatic conversion of galactose to glucose (29). This suggests that idiopathic presenile and senile cataract formation may be at least partly related to persistent lactase activity, resulting in the absorption of significant amounts of galactose from dietary lactose. Further studies that specifically address this issue are therefore warranted before avoidance of lactose-containing products (cow milk and dairy products) can be recommended as a strategy for prevention of cataract in patients with diabetes.

## REFERENCES

1. Caspary WF, Rhein AM, Creutzfeldt W. Increase of intestinal brush border hydrolases in mucosa of streptozotocin-diabetic rats. Diabetologica 1972;8:412–4.
2. Madara JL, Wolf JL, Trier JS. Structural features of the rat small intestinal microvillous membrane in acute experimental diabetes. Dig Dis Sci 1982;27:801–6.
3. Olsen WA, Rogers L. Jejunal sucrase activity in diabetic rats. J Lab Clin Med 1972;77:838–42.
4. Olsen WA, Korsmo H. The intestinal brush border membrane in diabetes. Studies of sucrase-isomaltase metabolism in rats with streptozotocin diabetes. J Clin Invest 1977;60:181–8.
5. Goda T, Hosoya N, Moriuchi S. Changes of the activity and content of sucrase-isomaltase complex in the intestinal mucosa during the development of streptozotocin-induced diabetes in rats. J Nutr Sci Vitaminol (Tokyo) 1983;29:571–8.
6. Schedl HP, Al-Jurf AS, Wilson HD. Elevated intestinal disaccharidase activity in the streptozotocin-diabetic rat is independent of enteral feeding. Diabetes 1983;32:265–70.
7. Takenoshita M, Yamaji R, Inui H, Miyatake K, Nakano Y. Suppressive effect of insulin on the synthesis of sucrase-isomaltase complex

in small intestinal epithelial cells, and abnormal increase in the complex under diabetic conditions. Biochem J 1998;329:597–600.
8. Murakami I, Ikeda T. Effects of diabetes and hyperglycemia on disaccharidase activities in the rat. Scand J Gastroenterol 1998;33: 1069–73.
9. Tandon RK, Srivastava LM, Pandey SC. Increased disaccharidase activity in human diabetics. Am J Clin Nutr 1975;28:621–5.
10. Cerda JJ, Preiser H, Crane RK. Brush border enzymes and malabsorption: elevated disaccharidases in chronic pancreatic insufficiency with diabetes mellitus. Gastroenterology 1972;62:841 (abstr).
11. Birlouez-Aragon I, Stevenin L, Rouzier C, Brivet M. Consommation de lactose et activité lactasique: deux facteurs de risque de la cataracte sénile et diabétique. (Lactose consumption and lactase activity: two risk factors for senile and diabetic cataracts.) Age Nutr 1990;1:74–9 (in French).
12. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20: 1183–97.
13. D'Avanzo B, La Vecchia C, Katsouyanni K, et al. An assessment and reproducibility of food-frequency data provided by hospital controls. Eur J Cancer Prev 1997;6:288–93.
14. Fernandes J, Vos CE, Douwes AC, Slotema E, Degenhart HJ. Respiratory hydrogen excretion as a parameter for lactose malabsorption in children. Am J Clin Nutr 1978;31:597–602.
15. Rinaldi E, Albini L, Costagliola C, et al. High frequency of lactose absorbers among adults with idiopathic senile and presenile cataract in a population with a high prevalence of primary adult lactose malabsorption. Lancet 1984;1:355–7.
16. Flatz G, Kuhnau W, Naftali D. Breath hydrogen test for lactose absorption capacity: importance of timing of hydrogen excretion and of high fasting hydrogen concentration. Am J Clin Nutr 1984;39:752–5.
17. Breslow NE, Day NE. Statistical methods in cancer research. The analysis of case-control studies. Vol 1. Lyon, France: IARC Science, 1980. (Publication no. 32.)
18. Meloni T, Colombo C, Ogana A, Mannazzu MC, Meloni GF. Lactose absorption in patients with glucose 6-phosphate dehydrogenase deficiency with and without favism. Gut 1996;39:210–3.
19. Meloni GF, Colombo C, La Vecchia C, et al. Lactose absorption in patients with ovarian cancer. Am J Epidemiol 1999;150:183–6.
20. Semenza G, Auricchio S. Small-intestinal disaccharidases. In: Scriver CHR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular bases of inherited disease. 7th ed. New York: McGraw-Hill, 1995:4451–82.
21. Hodge WG, Whitcher JP, Satariano W. Risk factors for age-related cataracts. Epidemiol Rev 1995;17:336–46.
22. Hiller R, Sperduto RD, Ederer F. Epidemiologic association with nuclear cortical and posterior subcapsular cataract. Am J Epidemiol 1986;124:916–25.
23. Segal S, Berry GT. Disorders of galactose metabolism. In: Scriver RC, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular bases of inherited disease. 7th ed. New York: McGraw-Hill, 1995:967–1000.
24. Ohta Y, Yamasaki T, Niwa T, et al. Cataract development in 12-month-old rats fed a 25% galactose diet and its relation to osmotic stress and oxidative damage. Ophthalmic Res 1999;31:321–31.
25. Miglior S, Marighi PE, Musicco M, Balestreri C, Nicolosi A, Orzalesi N. Risk factors for cortical, nuclear, posterior subcapsular and mixed cataract: a case-control study. Ophthalmic Epidemiol 1994;1:93–102.
26. Spinelli D, Vota MG, Formenti F, et al. Idiopathic presenile and senile cataract formation and changes in lactase activity. Fortschr Ophthalmol 1987;84:666–8.
27. Meloni G, Ogana A, Mannazzu MC, Meloni T, Carta F, Carta A. High prevalence of lactose absorbers in patients with senile cataract from Northern Sardinia. Br J Ophthalmol 1995;70:709 (letter).
28. Birlouez-Aragon I, Ravelontseheno L, Villate-Cathelineau B, Cathelineau G, Abitbol G. Disturbed galactose metabolism in elderly and diabetic humans is associated with cataract formation. J Nutr 1993;123:1370–6.
29. Mion F, Geloen A, Minaire Y. Effects of ethanol and diabetes on galactose oxidative metabolism and elimination in rats. Can J Physiol Pharmacol 1999;77:182–7.