

Effects of Oral Administration of Erythritol on Patients with Diabetes

MASASHI ISHIKAWA,* MINORU MIYASHITA,† YUKIKO KAWASHIMA,† TEIJI NAKAMURA,†
NOBUHIKO SAITOU,‡ AND JOHN MODDERMAN§¹

*Department of Metabolic Endocrinology, Yokohama-shi Seibu Hospital, †Department of Nutrition, and ‡The Third Department of Internal Medicine, Yokohama-shi Seibu Hospital, St. Marianna University School of Medicine, Japan; and §Keller and Heckman, LLP, 1001 G Street, N.W., Washington, DC 20001

Received July 29, 1996

Erythritol (20 g in solution) was administered orally in a single-dose to 5 patients with diabetes. Serum erythritol levels reached a peak 1 hr after administration and then declined rapidly. Total urinary excretion was $82.0 \pm 3.7\%$ within 24 hr and $88.5 \pm 3.3\%$ within 72 hr. Serum glucose and insulin levels remained unchanged until a meal was taken (3 hr after erythritol administration) and then increased. Free fatty acids and 3-hydroxybutyric acid levels increased after erythritol administration but dropped after ingestion of food. In a separate clinical trial, erythritol (20 g) was administered orally daily for 14 days to 11 patients with diabetes. Mean serum glucose and hemoglobin A1c levels decreased over the time period. Indices of renal function—blood urea nitrogen, creatinine, and β 2-microglobulin—did not change significantly. The single dose study suggests that erythritol exerts no significant effects on the metabolism of diabetic patients. Two-week daily administration of erythritol had no adverse effect on blood glucose control. © 1996 Academic Press, Inc.

INTRODUCTION

More than 90% of an ingested dose of erythritol is excreted unchanged in the urine, indicating that, in humans, erythritol is efficiently absorbed, not metabolized, and excreted by renal processes (Noda *et al.*, 1994). Consequently, the sweetener has potential value in the diets of patients with diabetes, who frequently show a craving for sweets, which can adversely affect blood glucose levels. In the present study, the effects of single and continuous (14-day) oral doses of erythritol on blood glucose levels and associated parameters were measured. Since most of the ingested erythritol is excreted in the urine via the kidneys, the effect of erythritol loading on the kidneys was also examined.

¹ To whom correspondence should be addressed.

MATERIALS AND METHODS

Test Substance

Erythritol powder ($\geq 99\%$ purity) was obtained from Nikken Chemicals Co., Ltd., Tokyo.

Single Oral Load Test

Subjects. Five patients with noninsulin-dependent diabetes mellitus (NIDDM), while hospitalized at Yokohama-shi Seibu Hospital, St. Marianna University School of Medicine, were the subjects of this study. The mean age of the patients was 52.4 ± 19.2 years, and the mean duration of their diabetes was 5.0 ± 4.6 years. All subjects relied only on dietary therapy as treatment, and none showed any sign of hepatic dysfunction.

The subjects were fully informed about the nature of the study and freely participated.

Test procedure. Each patient received a solution of 20 g erythritol in 100 ml water. The test solution was taken orally, in a fasted state, at 9:00 AM, and 10-ml blood samples were taken before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hr after erythritol administration. Subjects were allowed to eat food 3 hr after administration of the test solution. Urine was collected 24 hr before and 0-24, 24-48, and 48-72 hr after erythritol administration.

Blood samples were analyzed for glucose, insulin, free fatty acids (nonesterified fatty acids, NEFA), 3-hydroxybutyric acid (3-OHBA), and erythritol. Urine was analyzed for erythritol. Blood glucose was analyzed by the glucose oxidase (GOD) electrode method, insulin by a standard radioimmunoassay method, and NEFA and 3-OHBA by standard enzymatic methods. Erythritol was analyzed in blood and urine by gas chromatography (GC).

Urine samples were desalted with Amberlite MB-3 and centrifuged at 2000 rpm for 2 min. Serum samples were deproteinized with methanol and centrifuged at 3000

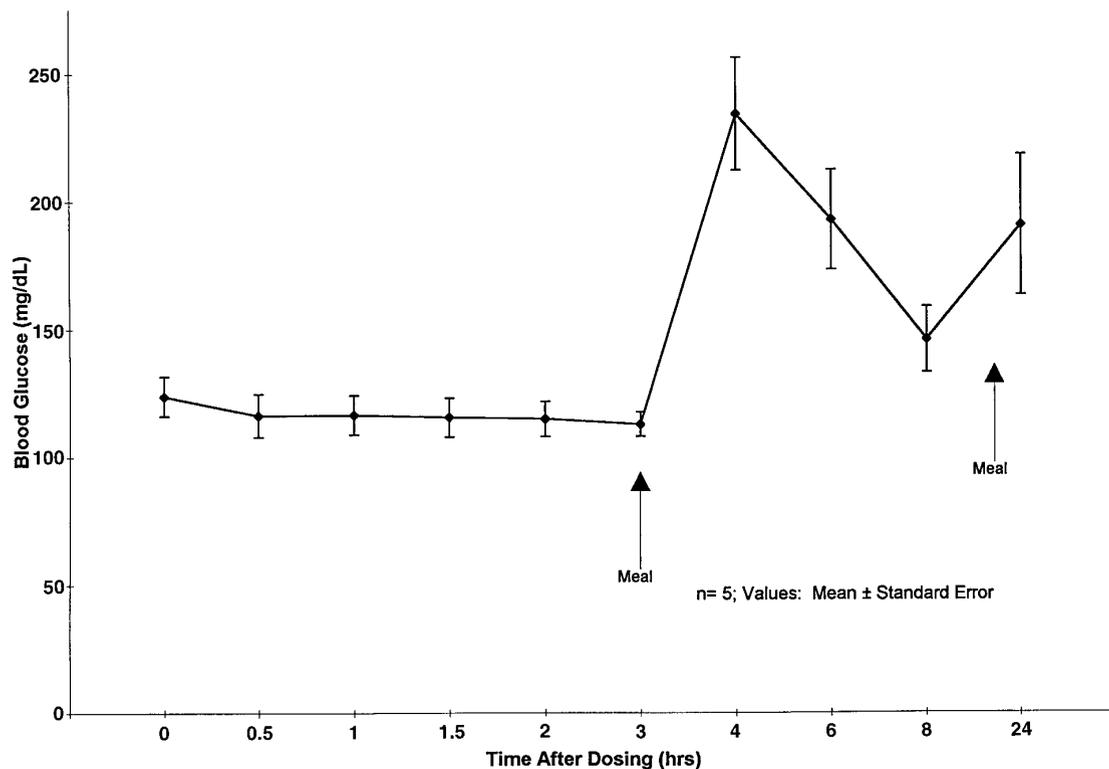


FIG. 1. Change in blood glucose after a single oral dose of 20 g erythritol in diabetics.

rpm for 15 min. The supernatants were dried under a nitrogen stream. Erythritol in the dried samples was acetylated with acetic anhydride:pyridine (2:1) at 80°C for 20 min. Water was added to the resultant mixture and the solution partitioned with hexane:chloroform (3:1). The organic phase was dried with sodium sulfate and evaporated to dryness, and the acetylated erythritol was taken up in 200 μ l acetone. Five microliters of the solution was injected into the gas chromatograph (Shimadzu GC-15, equipped with a flame ionization detector) and glass column packed with 5% SP-2340 on Chromosorb W (AW-DMCS) 60/80 mesh. Pentaerythritol and methyl- α -D-mannopyranoside were the internal standards used for serum and urine analysis, respectively.

Statistical analysis. Repeated-measures analysis of variance was used to test the significance of changes in the various blood and urine parameters during the course of the experiment.

Fourteen-Day Ingestion Test

Subjects. The subjects in this study were 11 NIDDM outpatients (three males, mean age 65 ± 6 years; eight females, mean age 50 ± 14 years). They were fully informed about the nature of the study and freely participated.

Test procedure. The subjects received 20 g erythritol/day for 14 days. The dose was ingested in solution

throughout the day with the subjects' usual diet, but there were no specific restrictions as to the timing or division of the daily dose. Food intake was monitored 3 days pretest and 3 days before completing administration. Blood samples were taken twice—before the first dose and after the final dose.

Body weight, fasting blood sugar (FBS), and hemoglobin A1c (HbA1c) were measured as indices of diabetes control and blood urea nitrogen (BUN), creatinine, β 2-microglobulin (β 2-MG), and urinary proteins as indices of renal function. Blood/serum analyses for these substances were done using standard clinical methods: FBS and BUN by enzymatic methods, HbA1c by an HPLC method, creatinine by the Jaffé reaction, β 2-MG by radioimmunoassay, and urinary protein by colorimetry (Pyrogallol-Red method). (Due to experimental convenience, all parameters were not determined for every participant. For example, β 2-MG was determined in the blood/serum of only four subjects.)

Statistical analyses. The paired *t* test using a significance level of $P < 0.05$ was used to assess the significance of observed changes.

RESULTS

Single Oral Load Test

No subject reported adverse effects from consumption of 20 g erythritol.

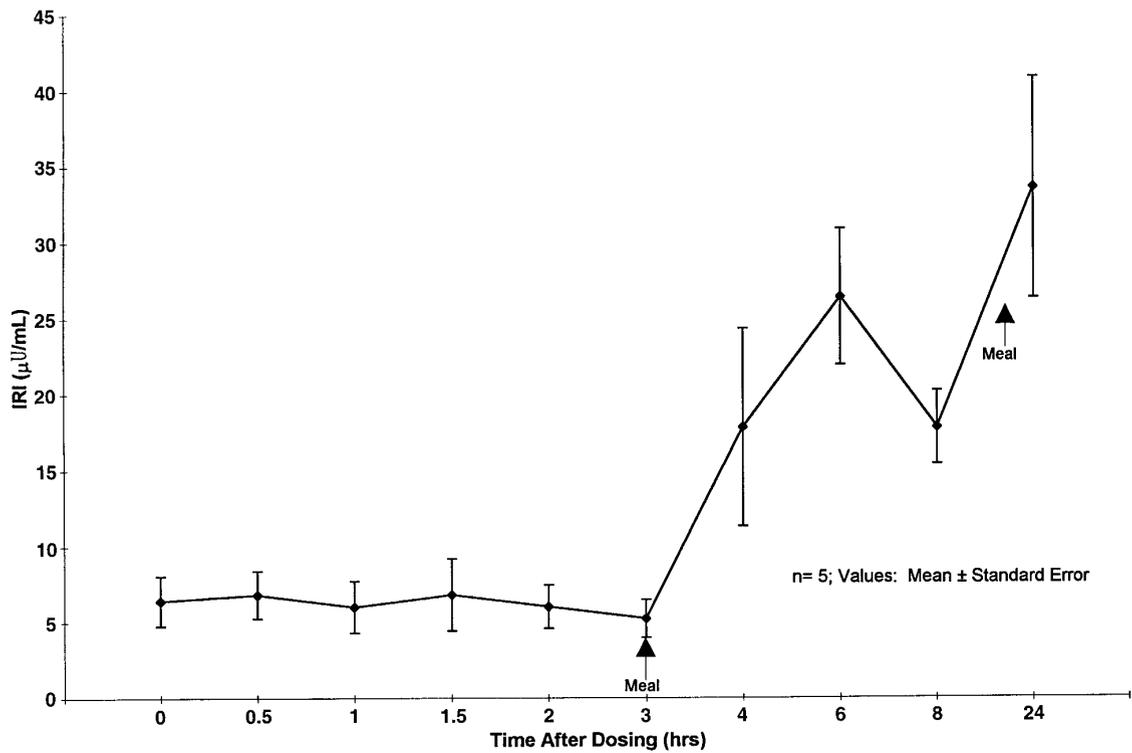


FIG. 2. Change in blood insulin (IRI) concentration after a single oral dose of 20 g erythritol in diabetics.

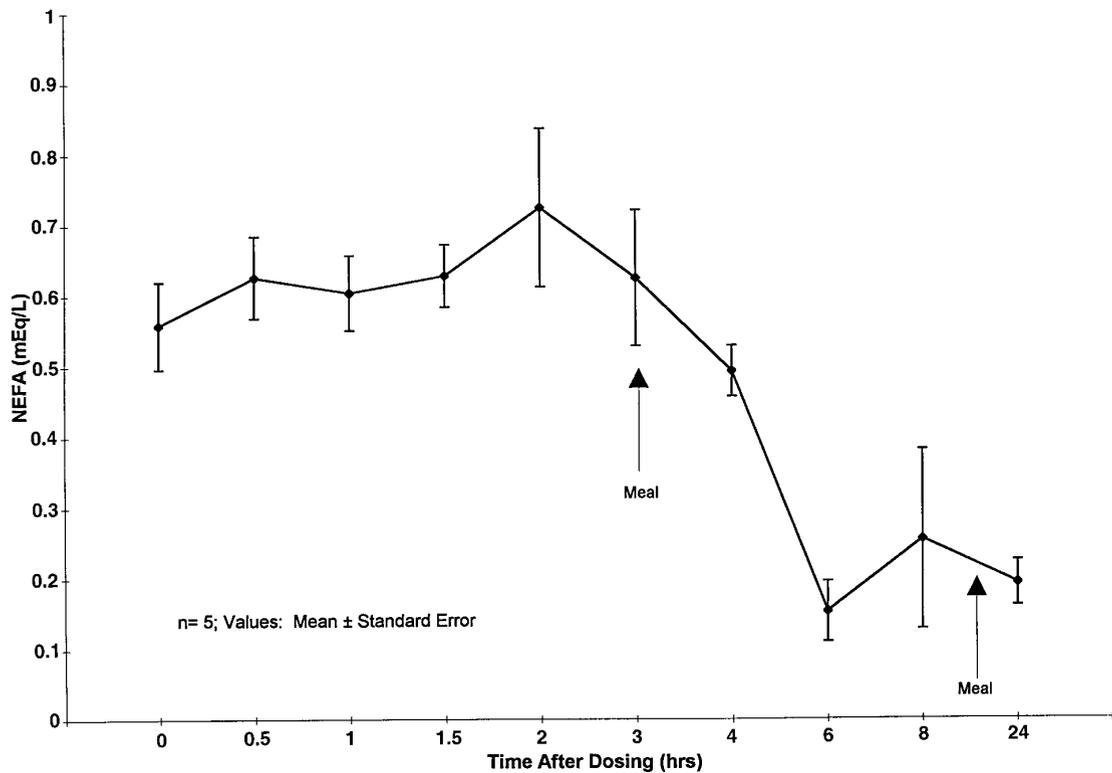


FIG. 3. Change in nonesterified fatty acids (NEFA) after a single oral dose of 20 g erythritol in diabetics.

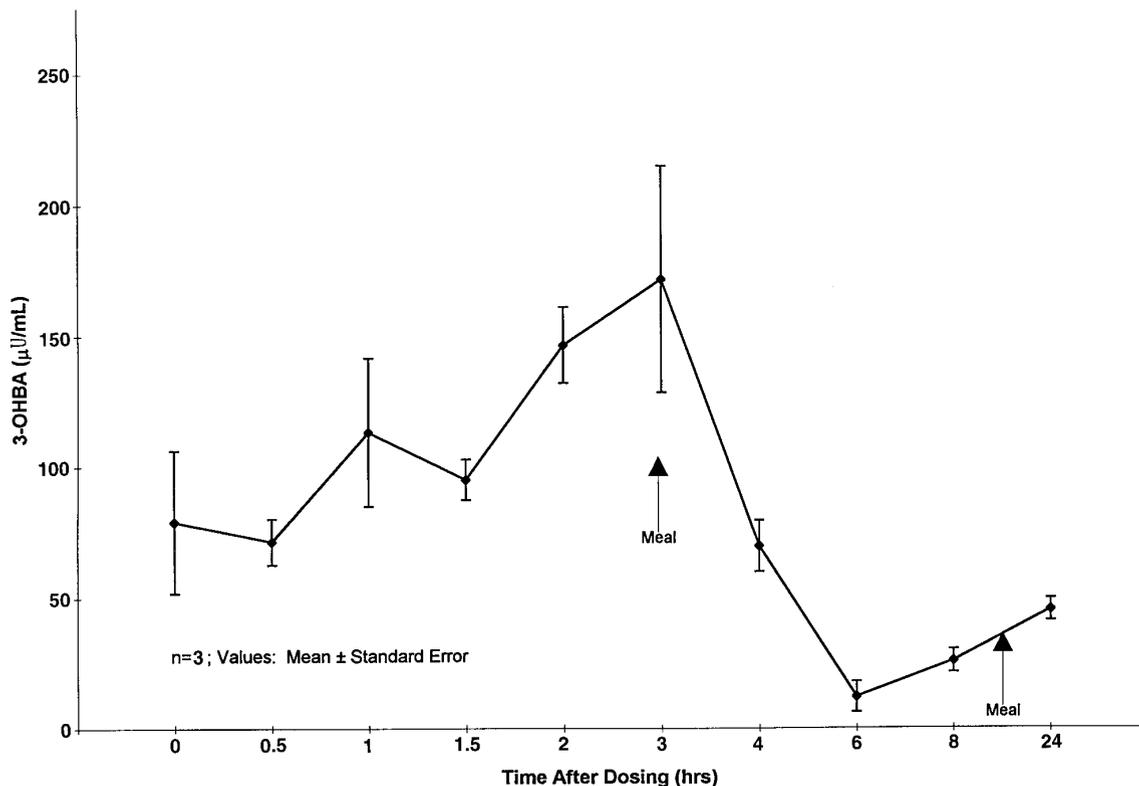


FIG. 4. Change in blood 3-hydroxybutyric acid (3-OHBA) concentration after a single oral dose of 20 g erythritol in diabetics.

No changes were observed in blood glucose and insulin from 0.5 to 3 hr, compared to preadministration levels (baseline). Food was taken between 3 and 4 hr, and the blood glucose level rose to 233.8 ± 44.0 mg/dl at 4 hr, compared to a preload level of 123.8 ± 15.5 mg/dl (Fig. 1). Insulin rose significantly after ingestion of food to a level of 26.4 ± 9.0 μ U/ml, compared to a baseline level of 6.4 ± 3.3 μ U/ml (Fig. 2).

NEFA did not change significantly 3 hr after administration, compared to a baseline level of 0.6 ± 0.2 mEq/liter, but decreased to 0.2 ± 0.1 mEq/liter after ingestion of food (Fig. 3). 3-OHBA tended to increase over 3 hr from a value of 79.0 ± 54.6 μ M/liter before administration, but dropped to 11.9 ± 11.9 μ M/liter after ingestion of food (Fig. 4).

The peak serum erythritol concentration (649.4 ± 37.4 μ g/ml) was achieved 1 hr after administration. Most of the erythritol ($81.99 \pm 3.7\%$) was eliminated in the urine within 24 hr (Fig. 5). The percentage rose to almost 90% at 72 hr (Table 1).

Fourteen-Day Ingestion Test

Body weight dropped in three of seven subjects and remained constant in the other four. As a result, the group average body weight was nonsignificantly decreased from a preadministration mean of 60.8 ± 11.6

kg to a postdosing mean of 58.1 ± 9.5 kg (mean weight of seven individuals, $n = 7$). Single-day FBS readings pretest and posttest indicated maintenance of serum glucose in four of nine subjects and changes in five of nine subjects (three decreasing and two increasing); group average FBS decreased from a predosing mean of 181 ± 60 mg/dl to a postdosing mean of 165 ± 57 mg/dl ($n = 9$), but this change was not significant. The decrease was due to large drops in individuals with initially high FBS levels. HbA1c readings remained at pretest levels for 4 of 11 subjects, decreased in 6 of 11 subjects, and increased in 1 of 11 subjects; the group mean HbA1c levels declined significantly ($P < 0.05$) from a predosing mean of $8.5 \pm 1.5\%$ to a postdosing mean of $7.5 \pm 1.6\%$ ($n = 11$), but, again, most of this decrease was due to large decreases in a few individuals. Two-week administration of erythritol, therefore, had no adverse effect on body weight or blood glucose control.

BUN, an index of renal function, showed no significant postdosing changes, either in one patient whose predosing levels were higher than the normal levels of 21 mg/dl or in four patients with normal levels. The predosing group mean of 15.3 ± 5.0 mg/dl ($n = 5$) did not significantly differ from the postdosing mean of 14.0 ± 7.3 mg/dl. Similarly, changes in creatinine levels were not judged to be significant. The predosing group

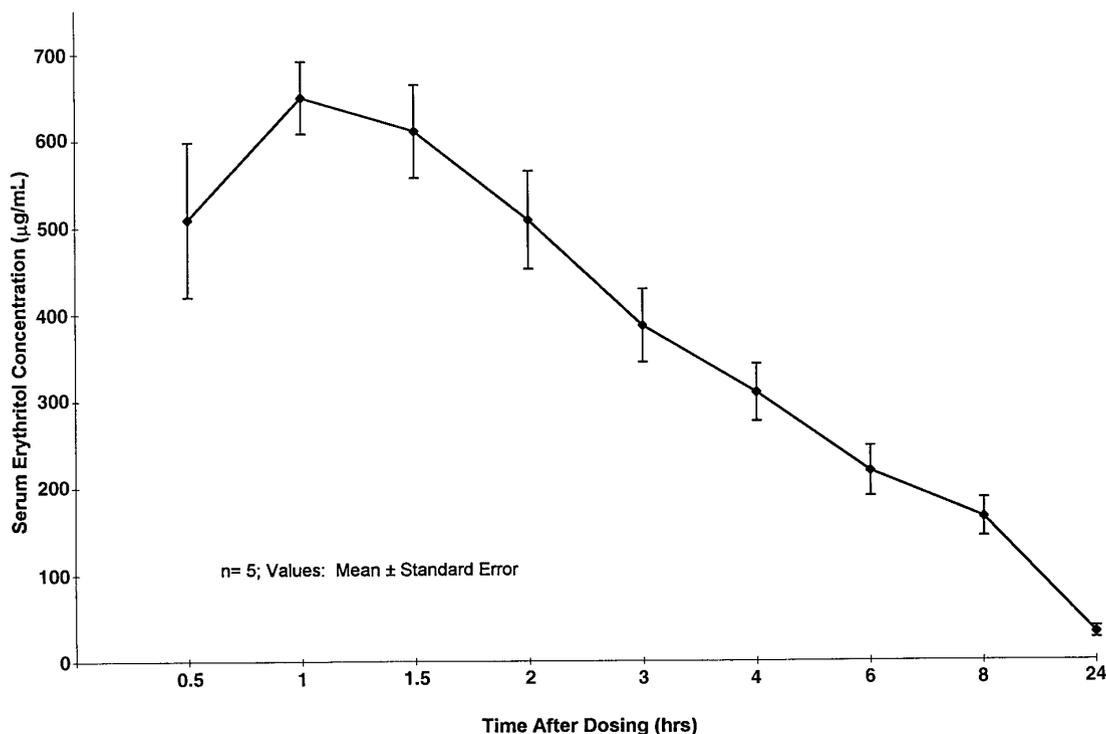


FIG. 5. Change in serum erythritol concentration after a single oral dose of 20 g erythritol in diabetics.

mean creatinine level was 0.9 ± 0.2 mg/dl ($n = 5$), virtually unchanged from the postdosing mean of 0.8 ± 0.2 mg/dl. Levels of β 2-MG did not change significantly in four patients ($n = 4$) who had predosing levels higher than 1.9 mg/liter. Likewise, there were no postdosing changes in urinary proteins. The indices of renal functions in diabetes patients thus showed no significant changes after daily administration of 20 g erythritol for 14 days.

DISCUSSION AND CONCLUSIONS

The single dose study suggests that erythritol exerts no effect on the metabolic system of diabetic patients. No significant changes were observed in blood glucose and insulin until ingestion of food. The increases in

NEFA and 3-OHBA after erythritol administration followed by decreases after ingestion of food probably occurred because no energy was supplied under erythritol load, placing the subjects in a state of hunger.

The results are similar to those from a study in which single doses of 0.3 g/kg body wt erythritol or glucose were ingested in one dose by five healthy males (Noda *et al.*, 1994). Only slight changes in serum glucose or insulin levels were observed on ingestion of erythritol, in contrast to ingestion of glucose. NEFA did not significantly rise after erythritol ingestion but did decline after a meal was taken at 3 hr. Erythritol did not induce any significant effects on serum levels of total cholesterol, triacylglycerol, Na, K, and Cl. The Noda *et al.* study also showed a cumulative urinary erythritol excretion level of about 90%.

TABLE 1
Cumulative Urinary Excretion^a of Erythritol in Diabetic Patients after a Single Oral 20-g Dose

Time (hr)	Case 1	Case 2	Case 3	Case 4	Case 5	Mean	SE
24	80.43	90.27	86.04	84.48	68.72	81.99	3.7
48	85.85	96.88	91.21	88.19	76.85	87.90	3.3
72	86.50	97.89	91.80	88.60	77.92	88.54	3.3

^a Expressed as a percentage of the total dose.

Daily (14-day) administration of erythritol had no significant effect on blood glucose levels, nor were there any significant effects observed on renal function. The significant decline in HbA1C, which provides an integrated index of the glycemic state, is an indication that erythritol may be helpful in long-term glucose control.

The findings of the current study and those of the Noda *et al.* study suggest that the sweetener erythritol

may safely be a part of the diet of diabetics when used at these levels.

REFERENCE

Noda, K., Nakayama, K., and Oku, T. (1994). Serum glucose and insulin levels and erythritol balance after oral administration of erythritol in healthy subjects. *Eur. J. Clin. Nutr.* **48**, 286–292.