reported a correlation ($r = 0.86$) between consumption of unfermented milk proteins and incidence of diabetes.

Ecological studies such as this really only suggest hypotheses that need to be tested by other study designs. There is a well-established geographical IDDM incidence gradient from north to south, and in addition to differences in milk consumption, there are many other environmental and cultural factors that will distribute in the same way and therefore correlate with IDDM, i.e., a similar study of coffee consumption explained 53% of the geographic variation of IDDM incidence (10). Furthermore, in twins, only 35% are concordant for IDDM, whereas in siblings only 3–5% are concordant for IDDM, and in general, diet within families does not vary much. However, little is known about intrafamilial variability of milk consumption.

Therefore, our findings need to be interpreted with great caution. Cows' milk is an important element of childrens' food, and elimination of milk from the diet may cause more harm than benefit. However, the results may generate further research to define more precisely possible triggering factors for IDDM.

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Received for publication 29 November 1990 and accepted in revised form 15 May 1991.

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Effect of New Oral Antidiabetic Agent CS-045 on Glucose Tolerance and Insulin Secretion in Patients with NIDDM

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Objective: To study the effects of CS-045, a newly developed thiazolidine analogue, on glucose tolerance and insulin response to oral glucose load in patients with non-insulin-dependent diabetes mellitus (NIDDM). Research Design and Methods: Nineteen NIDDM patients (mean ± SD age 48.9 ± 9.4 yr) whose previous glycemic control on diet and/or sulfonylurea (SU) therapy was judged stable but unsatisfactory (>7.8 mM) were selected for this study. CS-045 (400 mg/day p.o.) was given alone or together with the previous SU drugs for 12 wk. A 75-g oral glucose tolerance test (OGTT) was performed before and after CS-045 treatment. Results: The following results were found after CS-045 treatment. *1*) Fasting plasma glucose (FPG) and HbA_{1c} decreased ($n = 19$, FPG, 11.0 ± 2.4 vs. 8.4 ± 2.7 mM [before vs. after], $P < 0.001$; HbA_{1c}, 8.0 ± 1.1 vs. 7.4 ± 1.3%, $P < 0.005$), and glucose tolerance markedly improved. *2*) Fasting insulin (immunoreactive insulin [IRI]) and insulin response during OGTT decreased ($n = 19$, fasting IRI, 77.4 ± 49.8 vs. 56.5 ± 24.6 pM [before vs. after], $P < 0.05$; area under the curve of IRI, 540.3 ± 350.5 vs. 426.4 ± 216.3 pM · h, $P < 0.05$). Conclusions: CS-045 is effective in improving glucose tolerance without stimulation of insulin secretion in NIDDM, suggesting an effect in improving insulin sensitivity. *Diabetes Care* 14:1083–86, 1991

A newly developed antidiabetic agent, (±)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-thiazolidinedione (CS-045), exhibited an antihyperglycemic effect in various animal models of insulin-resistant non-insulin-dependent diabetes mellitus (NIDDM) (1,2). Previous studies in animals revealed that CS-045 increases insulin

sensitivity and has a triglyceride (TG)-lowering effect (2). A phase 1 study in nondiabetic men revealed few adverse effects (unpublished observations). In this study, we examined the effects of CS-045 on glucose tolerance and insulin response during oral glucose tolerance tests (OGTTs) in patients with NIDDM.

RESEARCH DESIGN AND METHODS

Nineteen NIDDM patients (9 men, 10 women, mean ± SD age 48.9 ± 9.4 yr) attending the outpatient clinic of our hospital whose glycemic control was judged unsatisfactory (fasting plasma glucose [FPG] >7.8 mM) on diet alone and/or sulfonylurea (SU) were the subjects of this clinical trial. This study was approved by the Institutional Review Board of Jichi Medical School. The purpose and protocol of this trial were explained to patients, and those willing to participate were selected.

After an 8-wk observation period, CS-045 (Sankyo, Tokyo) was administered orally in a daily dose of 400 mg (200 mg twice daily) for 12 wk. Throughout this trial and an observation period, the previous treatment, diet and/or SU drug, was kept unchanged. FPG and HbA_{1c} levels were measured every 4 wk. A 75-g OGTT was performed before and 12 wk after CS-045 treatment, and plasma glucose and serum immunoreactive insulin (IRI) levels were determined. IRI was determined by solid-phase radioimmunoassay. Results were expressed as means ± SD unless stated. Statistical differences were calculated with paired or Student's *t* tests.

RESULTS

Patients were divided into two groups according to treatment. Eight patients were treated with CS-045 alone and 11 with CS-045 plus SU. Table 1 shows the baseline clinical characteristics and changes in metabolic parameters after CS-045 treatment in each group and total subjects. At baseline, FPG and HbA_{1c} levels in CS-045 alone group were lower than in the CS-045 plus SU group.

In all subjects, FPG and HbA_{1c} levels were stable before CS-045 administration and began to fall after starting CS-045. The fall of FPG levels was significant at 4 wk and decreased throughout the drug administration. At 20 wk, 8 wk after cessation of CS-045, FPG levels increased again (data not shown). Glycemic parameters fell similarly in each group of the patients treated with CS-045 alone and with CS-045 plus SU, although the levels of each parameter were different between the two groups.

Figure 1 shows glucose and IRI levels during 75-g OGTT before and after 12 wk of CS-045 treatment in each group of patients. After CS-045 treatment, plasma

TABLE 1
Baseline clinical characteristics of patients and changes in body weight and other metabolic parameters after CS-045 treatment

	Treatment		
	CS-045 alone	CS-045 plus SU	Total
n (M/F)	3/5	6/5	9/10
Age (yr)	46.9 ± 8.8	50.4 ± 9.9	48.9 ± 9.4
Body weight (kg)			
Before	62.4 ± 6.6	66.8 ± 7.6	64.9 ± 7.4
After	63.4 ± 6.6	67.9 ± 7.8	66.0 ± 7.5
Fasting plasma glucose (mM)			
Before	9.7 ± 1.9	12.0 ± 2.3*	11.0 ± 2.4
After	7.2 ± 1.1†	9.3 ± 3.2†	8.4 ± 2.7‡
Fasting serum insulin (pM)			
Before	61.9 ± 30.2	88.7 ± 59.1	77.4 ± 49.8
After	57.7 ± 25.1	55.6 ± 25.5§	56.5 ± 24.6§
HbA_{1c} (%)			
Before	7.4 ± 0.9	8.5 ± 1.0*	8.0 ± 1.1
After	6.7 ± 0.7‖	7.9 ± 1.5	7.4 ± 1.3†
AUC of plasma glucose (mM · h)			
Before	53.5 ± 8.4	57.8 ± 7.9	56.0 ± 8.2
After	39.5 ± 6.7†	48.5 ± 11.8‖	44.7 ± 10.8‡
AUC of serum insulin (pM · h)			
Before	528.9 ± 241.5	548.6 ± 424.4	540.3 ± 350.5
After	463.8 ± 164.3	399.2 ± 251.7§	426.4 ± 216.3§

Values are means ± SD. SU, sulfonylureas; AUC, area under curve during 75-g oral glucose tolerance test.
*$P < 0.05$ vs. CS-045 alone (Student's *t* test).
†$P < 0.005$, ‡$P < 0.001$, §$P < 0.05$, ‖$P < 0.01$, vs. before (paired *t* test).

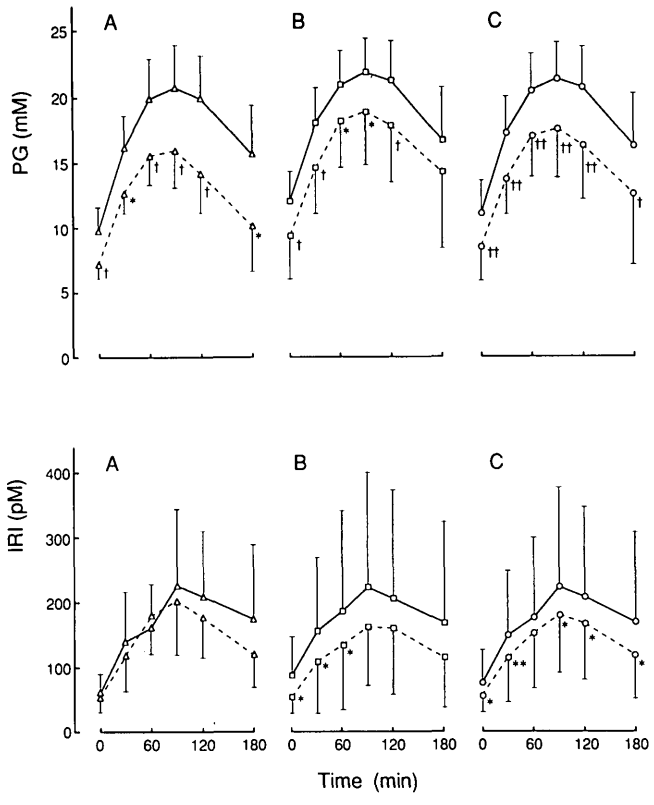

FIG. 1. Profiles of plasma glucose (PG) and immunoreactive insulin (IRI) during 75-g oral glucose tolerance test before (wk 0; *solid lines*) and after (wk 12; *dashed lines*) CS-045 treatment in patients with non-insulin-dependent diabetes mellitus. *A*: patients treated with CS-045 alone (n = 8); *B*: patients treated with CS-045 plus SU (n = 11); *C*: total subjects (n = 19). Data are means ± SD. *$P < 0.05$, **$P < 0.01$, †$P < 0.005$, ††$P < 0.001$, vs. before treatment.

glucose levels during OGTT decreased significantly except at 180 min in the CS-045 plus SU group, and area under the curve (AUC) of plasma glucose during OGTT decreased significantly in each group of patients (Table 1). After CS-045 treatment, fasting IRI and AUC of IRI during OGTT significantly decreased in the CS-045 plus SU group and in all subjects, but they did not change in the group treated with CS-045 alone (Table 1; Fig. 1).

CONCLUSIONS

Impaired insulin secretion and insulin resistance are major characteristic features in NIDDM (3,4). Improvement of metabolic abnormalities in NIDDM can be achieved by stimulating insulin secretion, reducing insulin resistance, or both, and the development of oral antidiabetic drugs to reduce insulin resistance has been attempted (5–9).

CS-045 is a hindered phenolic compound with a thiazolidine ring and is structurally similar to ciglitazone (6). Its structure contains both lipid peroxide–lowering and hypolipidemic and/or hypoglycemic moieties (1,9). Fujiwara et al. (2) reported that a single administration of the drug (50 mg/kg p.o.) in KK mice caused a remarkable fall in FPG levels for up to 18 h, and oral administration for 10 days (200–250 mg/kg) caused a marked decrease in plasma glucose and IRI. In *ob/ob* mice, another model of NIDDM with hyperinsulinemia and obesity, the drug also improved hyperglycemia and hyperinsulinemia when given orally for 15 days (2).

Fujiwara et al. (2) showed that CS-045 (150 mg/day p.o.) improved glucose tolerance and reduced insulin response after oral glucose load in Zucker fatty rats. These animals had characteristic features of insulin resistance. The effect of the drug seemed to be mediated by improving insulin sensitivity. Fujiwara et al. also found that CS-045 administration caused an increase in insulin binding by increasing insulin-receptor number in adipocytes and both insulin sensitivity and responsiveness (2).

Previously, Kosaka et al. (10) showed that insulin responsiveness of NIDDM patients with overt fasting hyperglycemia increased after treatment of diabetes independent of the mode of treatment. In this study, both fasting insulin and insulin response during OGTT decreased significantly after CS-045 treatment in the CS-045 plus SU group and in all subjects. Glucose tolerance was markedly improved despite the decrease in insulin response or without increasing insulin response. The observation in this study is at variance with the previous report by Kosaka et al. (10), but it is inconsistent with previous data on diabetic animals (2), suggesting that the drug improved glucose metabolism by increasing insulin sensitivity. Change in body weight and improvement of obesity may cause a considerable change in glucose tolerance and should always be taken into account. In this study, mean body weight did not change after CS-045 treatment, suggesting that the improvement of glucose tolerance was not due to body weight loss in the patients.

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Received for publication 15 October 1990 and accepted in revised form 1 May 1991.

ACKNOWLEDGMENTS

We are grateful to Sankyo for supplying CS-045. We thank Fusako Aoki and Rie Suzuki for assistance in manuscript preparation.

This study was presented as an abstract at the 50th annual meeting of the American Diabetes Association, Atlanta, Georgia, 14–19 June 1990.

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Visceral Afferent Neuropathy in Diabetic Gastroparesis

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Objective: To determine whether a lack of symptoms in diabetic patients with gastrointestinal motility disorders is associated with visceral afferent neuropathy. Research Design and Methods: We investigated cerebral evoked potentials (EPs) after esophageal stimulation in 10 patients with motor dysfunction of the gastrointestinal tract and in 10 healthy control subjects. All patients had insulin-dependent diabetes mellitus (5 men, 5 women, age range 31–60 yr, diabetes duration 8–36 yr, 10 of 10 with polyneuropathy, 6 of 10 with cardiac autonomic neuropathy). Their esophageal and gastric motor disorders had been diagnosed by scintigraphy, and gastrointestinal stenosis had been excluded by gastroscopy. Only 2 patients had severe symptoms, whereas 6 patients complained of minor discomfort (distension, bloating), and 2 patients were symptom free. Results: EPs were recorded after electrical stimulation of the esophagus (32 cm from the incisors) at intensity just above the perception threshold. All control subjects exhibited regular EPs at 0.1 ms/30 mA stimulation intensity. In 6 diabetic patients, no EPs were detected at 0.1 and 0.3 ms/30 mA, and the perception thresholds were significantly elevated. In 4 patients with normal perception threshold, EPs of regular shape but decreased amplitude were recorded. These patients had mild or severe gastroparetic complaints. Conclusions: These data show for the first time an association between a lack of symptoms in diabetic gastrointestinal motility disorders and visceral afferent neuropathy.
***Diabetes Care* 14:1086–89, 1991**

Abnormal autonomic nervous system function is a common complication of long-standing diabetes mellitus (1) that frequently may affect the gastrointestinal tract (2). However, a lack of symptoms has been reported in diabetic patients with proven gastrointestinal motility disorders, suggesting that a reduced sensitivity of afferent pathways may be associated with autonomic diabetic neuropathy (3,4). However, specific nerve damage of gastrointestinal afferents in humans has not been subject to diagnostic evaluation because specific research tools were not available. It has been shown that cerebral evoked potentials (EPs) can be recorded after stimulation of the esophagus in healthy subjects (5). This technique provides the opportunity to assess nerve conduction of afferent pathways from the gut to the brain. We applied this technique in the investigation of diabetic patients with proven motor dysfunction of the gut.

RESEARCH DESIGN AND METHODS

Ten patients with insulin-dependent diabetes mellitus (IDDM) were studied. These included five men and five women with an age range of 31–60 yr and diabetes duration of 8–36 yr. All patients had brittle diabetes. Blood glucose concentration ranged from 5.5 to 10 mM before testing (13). Esophageal and gastric motility dys-