Efficacy of *Ipomoea batatas* (Caiapo) on Diabetes Control in Type 2 Diabetic Subjects Treated With Diet

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OBJECTIVE — To investigate the tolerability, efficacy, and mode of action of Caiapo, an extract of white sweet potatoes, on metabolic control in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 61 type 2 diabetic patients treated by diet were given 4 g Caiapo ($n = 30$; mean age 55.2 ± 2.1 years; BMI 28.0 ± 0.4 kg/m^2) or placebo ($n = 31$; mean age 55.6 ± 1.5 years; BMI 27.6 ± 0.3 kg/m^2) once daily for 12 weeks. Each subject underwent a 75-g oral glucose tolerance test (OGTT) at baseline and after 1, 2, and 3 months to assess 2-h glucose levels. Additionally, fasting blood glucose, HbA_{1c}, total cholesterol, and triglyceride levels were measured.

RESULTS — After treatment with Caiapo, HbA_{1c} decreased significantly ($P < 0.001$) from 7.21 ± 0.15 to 6.68 ± 0.14%, whereas it remained unchanged ($P = 0.23$) in subjects given placebo (7.04 ± 0.17 vs. 7.10 ± 0.19%). Fasting blood glucose levels decreased ($P < 0.001$) in the Caiapo group (143.7 ± 1.9 vs. 128.5 ± 1.7 mg/dl) and did not change in the placebo group (144.3 ± 1.9 vs. 138.2 ± 2.1 mg/dl; $P = 0.052$). A decrease in body weight was observed in both the placebo group ($P = 0.0027$) and in the Caiapo group ($P < 0.0001$), probably due to a better-controlled lifestyle. In the Caiapo group, body weight was related to the improvement in glucose control ($r = 0.618$; $P < 0.0002$). Two-hour glucose levels were significantly ($P < 0.001$) decreased in the Caiapo group (193.3 ± 10.4 *vs.* 162.8 ± 8.2 mg/dl) compared with the placebo group (191.7 ± 9.2 *vs.* 181.0 ± 7.1 mg/dl). Mean cholesterol at the end of the treatment was significantly lower in the Caiapo group (214.6 ± 11.2 mg/dl) than in the placebo group (248.7 ± 11.2 mg/dl; $P < 0.05$). No significant changes in triglyceride levels or blood pressure were observed, and Caiapo was well tolerated without significant adverse effects.

CONCLUSIONS — This study confirms the beneficial effects of Caiapo on plasma glucose as well as cholesterol levels in patients with type 2 diabetes. For the first time, the long-term efficacy of Caiapo on glucose control was demonstrated by the observed decrease in HbA_{1c}. Thus, the neutraceutical Caiapo seems to be a useful agent in the treatment of type 2 diabetes.

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The pathogenesis of type 2 diabetes involves insulin resistance and impaired insulin secretion (1,2). When diet therapy and exercise remain ineffective, medications such as oral hypoglycemic drugs or insulin must be used (3,4). In addition to insulin and drugs that stimulate insulin release, new compounds that improve insulin sensitivity are currently under investigation or are already in clinical use (4–7). Recently, attention has also been directed to evaluate the efficacy of natural and neutraceutical products on diabetes control (8–10). As noted in a recent meta-analysis on neutraceuticals in management of diabetes, few compounds have shown efficacy in randomized trials (11). However, in the absence of thoroughly controlled studies on effectiveness and potential risks, these neutraceuticals cannot be unanimously recommended for management of diabetes (12,13).

A variety of white sweet potato cultivated in a mountainous region of Kagawa Prefecture, Japan, has been eaten raw for many years in the belief that it is effective therapy for anemia, hypertension, and diabetes. Caiapo (*Ipomoea batatas*) is commercialized in Japan without medical prescription as a food additive (neutraceutical) for the prevention and care of type 2 diabetes (14,15). In a previous study, we evaluated the efficacy and tolerability of two doses (2 and 4 g/day) of Caiapo versus placebo given orally for 6 weeks to 18 male Caucasian patients with type 2 diabetes treated only by diet (16). Those results showed that Caiapo at the dose of 4 g/day for 6 weeks lowered total and LDL cholesterol levels, as well as blood glucose, by increasing insulin sensitivity without affecting insulin secretion.

The low number of subjects and the short duration of the prior study prevented us from evaluating the effect of Caiapo on parameters of long-term glucose control such as HbA_{1c}. Thus, it seemed of clinical and scientific interest to verify those findings in a wider comparative trial. The aim of the present study was, therefore, assessment of the efficacy and tolerability of Caiapo (4 g/day) compared with placebo when administered for 12 consecutive weeks to type 2 diabetic patients with mild fasting hyperglycemia who were advised to keep body weight, physical activity, and diet under control during the entire study period.

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Abbreviations: OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of the subjects at baseline*

Variable	Caiapo	Placebo
Sex (male/female)	15/15	19/12
Age (years)	55.2 ± 2.1	55.6 ± 1.5
BMI (kg/m^2)	28.0 ± 0.4	27.6 ± 0.3
Systolic blood pressure (mmHg)	138.7 ± 1.9	139.3 ± 2.4
Diastolic blood pressure (mmHg)	82.4 ± 1.2	83.2 ± 1.5

Data are means ± SE. No statistically significant difference was detected.

RESEARCH DESIGN AND METHODS

This investigation was performed in a total of 61 clinically stable type 2 diabetic patients treated by diet only and recruited from the offices of general practitioners. In five patients, the respective antidiabetic medication (metformin, glibenclamide, glimepiride) was withdrawn 2 weeks before the start of the study. All of these patients gave informed consent to participate in this study, which was approved by the Ethics Committee of the Swiss Federal Authorities (IKI). All patients had no relevant history of renal, hepatic, cardiovascular, hematological, respiratory, autoimmune, or neurological diseases. Apart from diabetes, no other endocrine dysfunction that could interfere with the study was detected. Subjects were instructed to follow a weight-maintaining diet (28–32 kcal/kg body wt) consisting of 55% carbohydrates, 30% fat, and 15% proteins. Drinking alcohol and smoking cigarettes were allowed if patients were in the habit of doing so, but alcohol consumption was limited to 60 g/day for men and 40 g/day for women and smoking was limited to 10 cigarettes/day. Each subject was advised to maintain usual physical activity at a constant level throughout the entire period of the study.

The study was placebo-controlled, randomized, and double-blinded. Patients were randomly divided into two groups: group 1 ($n = 30$) consumed Caiapo 4 g/day, and group 2 ($n = 31$) consumed placebo. After disclosure of the randomization code, data of both groups showed no differences in baseline parameters, except for glucose levels measured 2 h after dinner (Tables 1 and 2). Both Caiapo and placebo were taken orally once daily, in the morning before breakfast. Each subject underwent a 75-g oral glucose tolerance test (OGTT) in the clinic at baseline and after 1, 2, and 3 months. Fasting and 2-h glucose levels were measured from venous samples (15 ml) by the glucose oxidase method. Subjects measured their blood glucose levels at home using a blood glucose test system (Glucotrend; Boehringer Mannheim, Mannheim, Germany). All patients were instructed regarding use of the glucometer, and the subjects' ability to correctly use the glucometer, as well as instrument precision and calibration, were frequently checked. Blood glucose levels were monitored three times per week: on Monday before breakfast, on Wednesday 2 h after beginning lunch, and on Friday 2 h after beginning dinner. These measurements were averaged over 1 month. HbA_{1c} was measured by immunoassay (IMX; Abbott, North Chicago, IL); cholesterol and triglyceride levels were measured by routine laboratory methods.

Statistics

Changes in blood glucose, total cholesterol, triglyceride, and HbA_{1c} values after treatment were analyzed between groups by ANOVA using corresponding baseline values and BMI as covariates. Comparisons versus baseline were assessed within groups with the appropriate Student's *t* test corrected by Bonferroni adjustment. Coefficient of correlation was calculated for changes in HbA_{1c} versus changes in weight. Unless otherwise specified, data are reported as means ± SE.

Tolerability and safety

Tolerability scores were compared between groups using χ^2 test. The safety analysis was performed in all randomized patients to assess the nature, severity, and frequency of adverse effects, including laboratory values outside the normal range that may suggest a clinically relevant abnormality. The equivalence between the two groups concerning occurrence of adverse effects was assessed using χ^2 test.

RESULTS

HbA_{1c}

After treatment with Caiapo, HbA_{1c} significantly decreased after 2 and 3 months (Table 2); no change was observed in the placebo group ($P = 0.08$ after 2 months and $P = 0.23$ after 3 months versus baseline). At both 2 and 3 months, HbA_{1c} values in the Caiapo group were lower than the corresponding values of the placebo group ($P < 0.001$). Because both groups exhibited significant weight loss (Table 2), we tested the hypothesis that the de-

Table 2—*Results after 2 and 3 months of treatment*

	Caiapo			Placebo		
Variable	Baseline	2 months	3 months	Baseline	2 months	3 months
Fasting blood glucose (mg/dl)	143.7 ± 1.9	132.3 ± 1.8*	128.5 ± 1.7*	144.3 ± 1.9	138.8 ± 2.2†	138.2 ± 2.1
Glucose 2 h after OGTT (mg/dl)	193.3 ± 10.4	164.9 ± 6.9*	162.8 ± 8.2*	191.7 ± 9.2	187.5 ± 7.3	181.0 ± 7.1
Glucose 2 h after lunch (mg/dl)	169.5 ± 4.5	156.5 ± 4.0*	150.6 ± 2.6*	167.1 ± 6.2	156.6 ± 3.8	157.8 ± 4.0
Glucose 2 h after dinner (mg/dl)	172.9 ± 5.1	159.9 ± 3.2*	155.0 ± 3.0*	163.5 ± 4.2	158.5 ± 3.8	155.0 ± 3.7‡
HbA_{1c} (%)	7.21 ± 0.15	6.94 ± 0.14*	6.68 ± 0.14*	7.04 ± 0.17	7.05 ± 0.19	7.10 ± 0.19
Body weight (kg)	78.9 ± 1.7	75.8 ± 1.4§	75.2 ± 1.4§	77.2 ± 2.0	76.1 ± 1.8‖	76.2 ± 1.7¶
Total cholesterol (mg/dl)	225.1 ± 10.1	NA	214.6 ± 11.2	240.9 ± 10.4	NA	248.7 ± 11.2†
Triglycerides (mg/dl)	211.6 ± 14.3	NA	205.4 ± 17.0	216.1 ± 15.2	NA	219.7 ± 15.2

Data are means ± SE. *$P < 0.001$, †$P < 0.05$, ‡$P < 0.01$, §$P < 0.0001$, ‖$P < 0.03$, ¶$P < 0.003$; all versus baseline. NA, not assessed.

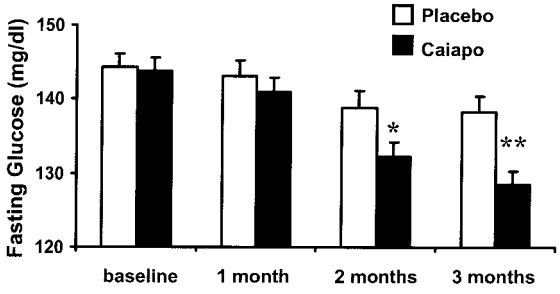

Figure 1— *Changes in fasting glucose concentration in the two treatment groups during the study period. Asterisks indicate significant differences for Caiapo versus placebo (*P < 0.05; **P < 0.001). See RESULTS for additional statistics.*

crease in HbA_{1c} in the Caiapo group was related to the changes in body weight by using ANOVA with body weight as a covariate. The *P* value was 0.041, indicating that a possible influence of the change in body weight on the improvement of HbA_{1c} cannot be excluded. Accordingly, body weight and HbA_{1c} changes correlated significantly ($r = 0.618$; $P < 0.0002$).

Fasting, OGTT, and postprandial glucose

Fasting blood glucose (Table 2, Fig. 1) decreased at 2 months in both groups (Caiapo group: $P < 0.001$; placebo group: $P < 0.05$), but the decrease was greater in the Caiapo group ($P = 0.0289$ versus the placebo group). No further decrease was observed in the placebo group afterward, where fasting glucose levels in the Caiapo group continued to decrease (at 3 months: $P < 0.001$ versus the placebo group). The frequency of achieving mean fasting blood glucose levels below the upper normal limit (126 mg/dl) after 3 months of treatment was evaluated: there were 48.3% responders in the Caiapo group versus 7.7% in the placebo group ($P < 0.0005$, χ^2 test).

Figure 2 shows the differences between the Caiapo and placebo groups in regard to glucose values measured 2 h after oral administration of glucose (Table 2). No significant changes from baseline were observed in the placebo group at 2 and 3 months. In the Caiapo group, a progressive decrease occurred ($P < 0.005$ at 1 and 2 months; $P = 0.001$ at 3 months versus the placebo group). Within the Caiapo group, the differences from baseline were statistically significant at any data point ($P < 0.001$).

Blood glucose levels measured 2 h after lunch decreased significantly in the Caiapo group after 2 and 3 months (Table 2). In the placebo group, a nonsignificant decrease was observed until 2 months ($P > 0.14$), but there was no further change after that time. Blood glucose levels measured 2 h after dinner at baseline were more elevated in the Caiapo group than in the placebo group ($P < 0.05$, Table 2). They became virtually identical after 2 and 3 months; however, when evaluating the progressive decrease in blood glucose levels versus baseline, we observed a statistical significance within the Caiapo group after 2 and 3 months, whereas in the placebo group, the difference compared with baseline was significant only at 3 months.

Body weight, blood pressure, and lipid levels

Body weight was similar at baseline ($P = 0.8$) and decreased significantly in both groups at 3 months, but the decrease was more pronounced in the Caiapo group (Table 2). In fact, despite similar body weight at 3 months ($P = 0.67$), the difference versus baseline was higher in the Caiapo group (3.7 ± 0.3 vs. 1.0 ± 0.3 kg, $P = 0.0004$). Overall, 26 subjects in the Caiapo group and 18 subjects in the placebo group lost weight during the study. Blood pressure did not change; at the end of the study, the mean blood pressure was 136.2 ± 2.0/81.6 ± 1.2 mmHg in the Caiapo group and 137.2 ± 2.1/81.7 ± 1.0 in the placebo group ($P > 0.15$ versus baseline, Table 1). Mean cholesterol at baseline was similar in the two groups ($P = 0.276$); at 3 months, it was significantly higher, as at baseline, in the placebo group, whereas it was slightly decreased in the Caiapo group, without reaching statistical significance ($P = 0.08$). At the end of the treatment period, cholesterol levels in the Caiapo group were lower than those in the placebo group ($P < 0.05$). There were no significant differences in triglyceride levels neither between nor within the groups; *P* values ranged from 0.2 to 0.8.

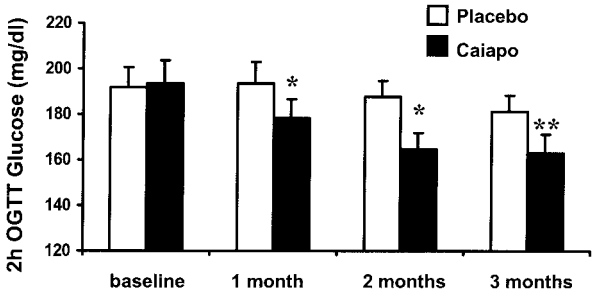

Figure 2— *Changes in glucose concentration measured 2 h after a 75-g oral glucose load in the two treatments during the study period. Asterisks indicate significant differences for Caiapo versus placebo (*P < 0.005; **P < 0.001). See RESULTS for additional statistics.*

Tolerability and safety

At the end of the study, the patients expressed their opinions about gastrointestinal tolerability (poor, acceptable, good, excellent). Tolerability was very good in the Caiapo group, in which only three subjects reported a negative opinion. Similarly, no negative opinions were expressed by the subjects in the placebo group ($P = 0.8181$ Caiapo versus placebo). Regarding adverse events, 16 were reported in the Caiapo group and 14 were reported in the placebo group. In six subjects in the Caiapo group and two subjects in the placebo group, a relation with the medication could not be excluded. These adverse events were mainly of gastrointestinal nature (constipation, gastric pain, meteorism) and of mild intensity.

CONCLUSIONS — In this study, we confirmed the beneficial effects of Caiapo on glucose and serum cholesterol levels in type 2 diabetic patients treated by diet (16) after 3 months of administration. This effect was observed in improved fasting blood glucose levels as well as improved glucose levels during an OGTT and in the postprandial state. In addition, we demonstrated for the first time an improvement in long-term glucose control as expressed by the significant decrease in HbA_{1c}.

The glucose-lowering potency of Caiapo has long been recognized, and over the past decades, it has been commercial-

ized in Japan as an antidiabetic medication. However, publications on the efficacy and safety of this compound consisted mainly of case reports and uncontrolled studies. We have recently performed a pilot study in 18 type 2 diabetic patients over a period of 6 weeks and reported a significant decrease in plasma glucose levels (16). The duration of the study, however, was too short to allow an evaluation of long-term parameters of glucose control, such as HbA_{1c}. Therefore, the present study was designed to address this issue and to further extend the knowledge about the safety of Caiapo. Regarding glucose control, the data of the pilot study were confirmed, and Caiapo can be regarded as an effective compound in the treatment of type 2 diabetes. After 3 months of treatment, 48.3% of patients in the Caiapo group had fasting blood glucose levels <126 mg/dl, which is diagnostic for diabetes.

HbA_{1c} was lowered by 0.5%, and thus, the glucose-lowering potency of Caiapo is in the range or even beyond that of compounds such as acarbose (17) or nateglinide (18). Furthermore, baseline glucose control was fairly good, as indicated by an HbA_{1c} of 7–7.2%, and one could speculate whether Caiapo would have proven more efficient if patients with higher HbA_{1c} levels had been studied. The improvement of glucose control comprised fasting as well as postprandial blood glucose levels and raises a question regarding of the mode of action of Caiapo.

In a previous study, we investigated the effect of Caiapo by performing oral and intravenous glucose tolerance tests in type 2 diabetic patients (19). The study showed an improvement in insulin sensitivity as the responsible mechanism for the amelioration of glucose tolerance, while any effect on glucose absorption or insulin secretion was excluded. These findings were in accordance with a study in obese Zucker fatty rats (14), in which glucose tolerance increased in response to 100 mg/kg of Caiapo powder per day. The effects, demonstrated by an enhanced [^{14}C]glucose uptake in isolated adipocytes, were comparable to treatment with 50 mg/kg of troglitazone per day in a pair-fed group. Contrary to troglitazone, no weight gain could be seen after Caiapo treatment in those animals. Whereas the active substance responsible for the glucose-lowering effect in this extract of white-skinned potatoes is not entirely known, an acidic glycoprotein has been identified as possible candidate (15) and is currently under thorough investigation.

Unlike in animals and in our pilot study, we observed a decrease in body weight in both groups; however, this decrease was more pronounced in the Caiapo group. After further analyzing the HbA_{1c} data by using body weight change as a covariate, a possible influence of weight loss on the improvement in glucose control was shown for the Caiapo group. We cannot, however, quantify the exact contribution of weight loss on the effects observed. In both groups, the decrease in body weight may be due partly to a change in lifestyle under the conditions of a controlled study. However, reduction of body weight was definitely more sustained in the Caiapo group, and this raises a question about a possible mechanism of Caiapo in decreasing body weight. This issue, however, remains unclear and requires further investigation. At this stage, malabsorption can be excluded by analysis of safety laboratory parameters. Because the tolerability of Caiapo was considered very good, with only three subjects reporting a negative opinion, a potential gastrointestinal side effect is unlikely to be responsible for the reduction of body weight. From the time course of weight loss and improvement of glucose control, however, we hypothesize that the continuing decrease in glucose at a stable body weight during the last month supports an intrinsic action of Caiapo beyond weight loss, presumably by means of those effects seen in previous studies, e.g., by increasing insulin sensitivity.

Finally, we found in this, as well as in the pilot study (16), a beneficial effect of Caiapo on serum cholesterol levels. Although we have not determined LDL or HDL cholesterol levels in the present investigation, the pilot study showed that this effect was confined only to LDL cholesterol. Because the improvement in insulin sensitivity exerted by Caiapo is not expected to alter cholesterol levels, a second compound, which is not yet identified, could be responsible for this effect. Weight loss in these patients could also contribute to the lowering of cholesterol levels; however, the amount of this reduction exceeds the extent expected from a weight loss of 3.7 kg. No change in the main safety parameters (blood pressure and other laboratory measurements) was observed with Caiapo, and the tolerability was considered good, as also indicated by the very low number of adverse events. These were similar between the respective groups, with only a slightly higher number of mild gastric problems during administration of Caiapo.

In conclusion, this study confirms the beneficial effects of Caiapo on fasting and postprandial plasma glucose levels, as well as cholesterol, in patients with type 2 diabetes. For the first time, we demonstrated the long-term efficacy of Caiapo on glucose control by the observed reduction of HbA_{1c}. Thus, the neutraceutical Caiapo seems to be a useful agent in the management of type 2 diabetes.

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Preliminary results of this study have been presented at the Scientific Sessions of the American Diabetes Association (ADA) Annual Meeting, New Orleans, Louisiana, June 2003.

Caiapo is a registered product name by Fuji Sangyo (FJI-120).

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