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ORIGINAL ARTICLE

Differential Responses to Acarbose Between Obese and Non-obese Patients with Type 2 Diabetes Mellitus

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To investigate the responses in terms of body weight, glycemic control, metabolic control, and the side effects to acarbose add-on therapy in obese and non-obese type 2 diabetes patients with inadequately controlled by sulfonylureas and metformin.

Materials and Methods: Forty obese (BMI ≥27) and 80 sex- and age-matched non-obese patients with type 2 diabetes mellitus were enrolled in this 3-month, open-label, case-controlled trial for acarbose add-on therapy. Totally 111 (73 non-obese and 38 obese) patients completed 3-month acarbose add-on therapy. This study adopted a 2-center open-label parallel group design. After a 4-week run-in period, acarbose was added (titrated up to 100 mg t.i.d.) to the current sulfonylureas and metformin combined therapy of subjects. Both obese patients (9.3±1.3% vs. 8.3±1.6%, p<0.0001) and non-obese patients (9.4±1.2% vs. 8.4±1.2%, p<0.0001) showed decreased HbA1c after therapy. While obese patients showed a significant serum alanine aminotransferase (ALT) (61±26 vs. 49±18, p<0.0001) and triglyceride reduction (242±127 vs. 187±71, p<0.01) after add-on therapy, non-obese patients did not. Neither obese (74.8±9.2 vs. 74.4±9.8 kg, N.S.) nor non-obese patients (61.9±7.9 vs. 61.6±7.7 kg, p=0.0579) show significant decrease in body weight.

Conclusion: Both obese patients and non-obese patients showed decreased HbA1c after acarbose therapy. Obese patients had an additional benefit of a decrease in their previoulsly elevated ALT and triglyceride levels after acarbose therapy.

Key words: Type 2 diabetes mellitus, Acarbose, Obesity

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Introduction

The United Kingdom Prospective Diabetes Study (UKPDS) has shown that intensive blood-glucose control reduces risk of complications in patients with type 2 diabetes mellitus.[1] However, the untoward weight gain effect associated with the therapy in patients with type 2 diabetes is considered serious.[2] In addition, in the long term majority of patients

need multiple therapies to attain these glycemic target levels. Even with sulfonylurea and metformin combination therapy, most patients end up with secondary failure and a third agent is needed to achieve HbA1c target values.[3] Results of recent evidence-based clinical studies, acarbose, indicate that an α-glucosidase inhibitor, has a beneficial effect on glycemic control without weight gain effect in type 2 diabetes mellitus[4].

Acarbose delays glucose absorption and thus attenuates postprandial rises in blood glucose and insulin. In addition, it also significantly improves insulin sensitivity. Acarbose therapy has been shown to improve long-term glycemic control[4, 5]. It is a suitable add-on therapy for patients with poorly controlled type 2 diabetes mellitus under traditional therapy. Some reports have confirmed the effectiveness of acarbose add-on therapy in patients inadequately controlled with metformin monotherapy.[6-8] In addition, acarbose add-on therapy to sulfonylurea and metformin combination therapy has also been demonstrated.[9,10]

Acarbose was reported to be beneficial for glycemic control in normal weight,[11] overweight[7] and obese[12] type 2 diabetes patients, but differential responses to acarbose add-on therapy in obese and non-obese type 2 diabetes patients were not reported. Because most Asian people consume more carbohydrate than westerners, whether or not acarbose therapy has additional effects for Asian was considered. Weight reducing effects with acarbose monotherapy have been reported in an Asian multi-center study[13]. This study was conducted as an investigation into the differential responses to acarbose add-on therapy in obese and non-obese Taiwanese patients with type 2 diabetes patients.

Materials and Methods

Subjects

According to the definition of obesity as BMI ≥ 27 for Taiwanese, by the Department of Health, we recruited 40 obese patients (18 men and 22 women, mean age 59.5±9.0 years) and 80 sex- and age-matched non-obese patients with type 2 diabetes mellitus (36 men and 44 women, average age 60.0 ±10.4 years) for this 3-month, open-label, case-controlled, parallel-group trial for add-on acarbose therapy. These patients were regularly treated at the out-patient clinic of 2 major medical centers in southern Taiwan and the study was approved by the Human Research Committee. After the purpose of the tests was explained and informed consent was obtained, patient histories were taken and physical examinations conducted.

A diagnosis of type 2 diabetes mellitus was based on clinical characteristics, including the absence of ketoacidosis, age > 20 years at diagnosis of diabetes, treatment with oral hypoglycemic agents, or a fasting C-peptide level > 0.90 ng/ml. The patients, who were treated with sulfonylurea and metformin at a tolerable maximal dose, all had HbA1c ≥ 8.0% before acarbose add-on therapy.

All the patients had been treated with one of the following sulfonylureas: gliclazide 320 mg/day, glibenclamide 20mg/day, glipizide 30mg/day, or glimepiride 6mg/day. The doses of metformin ranged from 1000 to 3000 mg daily. The baseline characteristics of both groups are listed on Table 1.

After at least a two-month follow-up, 120 patients who had poorly controlled plasma glucose levels received a 3-month acarbose add-on treatment in addition to their existing traditional treatment of sulfonylurea and metformin. All patients were routinely educated about lifestyle modifications of diabetes mellitus. Before starting acarbose, the patients were informed of the action of acarbose and educated in brief about hypoglycemia during acarbose add-on therapy. Following this, all patients were given acarbose (50mg/tablet) 1 tablet with meals thrice daily during the initial 4 weeks, the dose then being increased to 2 tablets with meals thrice daily for the following 8 weeks. After adding acarbose, they were regularly followed up at 4-week intervals for 3 months.

Table 1. Baseline characteristics of obese and non-obese patients with type 2 diabetes mellitus

	Non-obese (n=80)	Obese (n=40)
Age (years)	60.0±10.4	59.5±9.0
Sex (Men/Women)	36/44	18/22
Duration of disease (years)	10.4±5.2	9.7±6.0
Body height (cm)	160.3±7.8	159.0±9.3
Sulfonyureas (glibenclamide, glipizide, gliclazide, glimepiride)	59/1/16/4	32/0/8/0
Metformin doses (1000mg/ 1500mg/ 2000mg/ 2250mg/ 3000mg per day)	7/32/26/7/8	5/14/9/4/8
Hyperlipidemia (with antihyperlipidemic agents)	32 (32)	21 (21)
Hypertension (with antihypertensive agents)	36 (36)	27 (25)
Body weight (kg)	61.5±8.4	74.3±9.3*
BMI (kg/m^2)	24.0±2.1	29.4±2.5*
Systolic pressure (mmHg)	133±15	134±16
Diastolic pressure (mmHg)	79±9	81±9
Fasting plasma glucose (mg/dL)	230±52	234±47
Postprandial plasma glucose (mg/dL)	302±51	297±65
HbA1c (%)	9.5±1.2	9.4 ± 1.3
C-peptide (ng/mL)	2.4±1.2	3.3±1.3†
Creatinine (mg/dL)	1.1±0.2	1.0±0.2
Cholesterol (mg/dL)	205±40	214±48
Triglyceride (mg/dL)	159±75	242±127*
HDL-cholesterol (mg/dL)	42±10	38±10
ALT (U/L)	33±22	61±26*

*p<0.0001 in comparison with non-obese patients; † p<0.01.

Body height (BH) was measured to the nearest 0.5 cm without shoes, and body weight (BW) was measured to the nearest 0.1 kg with indoor clothing. Body mass index (BMI) was derived as follows: BMI = 10000 x body weight (in kg) /body height^2 (in cm). Blood pressure was measured in sitting position with a standard clinical mercury baumanometer after resting for at least 10 minutes.

Venous blood sampling

Blood samples were collected in the morning after overnight fasting for 12 hours, from all patients qualified to be included. Blood was drawn from the antecubital vein with the patient in a seated position, for serum creatinine, alanine aminotransferase (ALT), total and HDL cholesterol (HDL-C), triglycerides, glucose, HbA1c, and C-peptide before and after a 3-month acarbose add-on therapy. Each patient was then given a standard meal consisting of 260 g skimmed milk and a sandwich. The energy content of the test meal was 282 kcal (including skimmed milk 46 kcal and sandwich 236 kcal). It contained 30% of calories from fat, 55% from carbohydrates, and 15% from protein. Venous blood for postprandial plasma glucose (PPG) was taken 2-h after a standard meal. The meal tolerance test was performed before and after a 3-month acarbose add-on therapy.

Plasma glucose, serum creatinine, cholesterol, triglyceride, and HDL-cholesterol (HDL-C) levels were measured with a Hitachi 747 analyzer. HbA1c was measured with the boronate affinity HPLC method (PRIMUS affinity HPLC, CLC385; coefficient of variation (CV) was 1.1% at a mean HbA1c value of 5.28% and 0.8% at a mean HbA1c value of 10.2%) during the period of the study. C-peptide was determined by radioimmunoassay (C-Peptide Kit "Daiichi" III; Intra-assay CV 2.9-4.8%, Inter-assay CV 2.3-4.7 %).

Statistical Analysis

All of data are expressed as mean±SD. The software package of JMPIN (SAS Institute, Cary, NC, USA) was used to analyze the data. The differences in fasting plasma glucose, postprandial plasma glucose, HbA1c, and body weight before and after acarbose add-on therapy were analyzed for significance using paired t-test. The differences between groups were analyzed for significance using unpaired t-test. P level < 0.05 was considered statistically significant.

Results

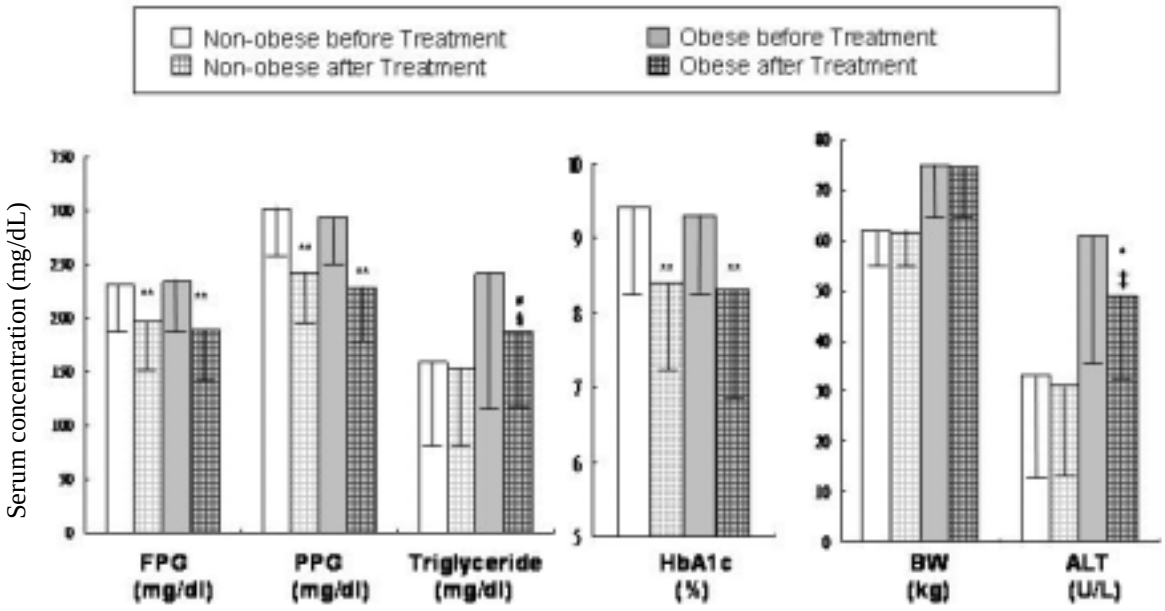
Nine patients (7 non-obese and 2 obese) did not complete the 3-month study. The causes of withdrawal included abdominal pain-2, poor glycemic control-5, and unwillingness to continue-2. Of the 111 (73 non-obese and 38 obese) patients completing the trial, 53 did so without adverse effects, 38 with flatus (24 non-obese and 14 obese), 9 (5 non-obese and 4 obese) with abdominal fullness, 4 (3 non-obese and 1 obese) with diarrhea, 2 (0 non-obese and 2 obese) with abdominal pain, and 5 (2 non-obese and 3 obese) with constipation.

After the 3-month acarbose add-on therapy, both obese (9.3±1.2% vs. 8.3±1.6%, p<0.0001) and non-obese patients (9.4±1.1% vs. 8.4±1.3%, p<0.0001) showed decreased HbA1c. Ten of 73 (13.7%) non-obese and 8 of 38 (21.1%) obese patients reached the target goal of HbA1c < 7% (no statistical significance). Both groups showed significant decreases in FPG, PPG, and HbA1c. They both showed decrease in systolic blood pressure, whereas only the non-obese group reach statistic significance (Table 2).

Table 2. Differential effects on BW and metabolic parameters after 3-month Acarbose Therapy Add-on Therapy

	Non-obese (n =73)		Obese (n=38)		Total (n=111)	
	Before	**After**	**Before**	**After**	**Before**	**After**
BW (Kg)	61.9±7.9	61.6±7.7	74.8±9.2	74.4±9.8	66.3±10.4	66.0±10.4*
SBP (mmHg)	133±15	131±14*	136±14	134±15	134±15	132±13†
DBP (mmHg)	80 ± 9	79 ± 9	82 ± 9	81 ± 9	80 ± 9	80 ± 8
FPG (mmol/L)	231±50	196±54‡	234±48	189±61‡	232±49	193±56‡
PPG (mmol/L)	301±51	243±52‡	294±65	228±61‡	299±56	238±56‡
HbA1c (%)	9.4±1.1	8.4±1.2‡	9.3±1.2	8.3±1.6‡	9.4±1.2	8.4±1.4‡
C-peptide (ng/dL)	2.4±1.2	1.8±0.9‡	3.3±1.3	2.5±1.0‡	2.7±1.3	2.1±1.0‡
Creatinine (mg/dL)	1.1±0.2	1.0±0.2	1.0±0.2	1.0±0.2	1.0±0.2	1.0±0.2
Cholesterol (mg/dL)	205± 40	199± 43	214± 48	214± 44	208± 43	204± 44
TG (mg/dL)	159 ± 75	153± 73	242± 127	187± 71†§	187± 104	164± 74†
HDL-c (mg/dL)	42± 10	41± 9	38± 10	38± 9	41± 10	40± 9
ALT (U/L)	33± 22	31± 18	61± 26	49± 17¶ ‖	43± 27	37± 19¶

* p<0.05, in comparison with before add-on therapy; † p<0.01; ‡ p<0.0001; § p<0.01; ¶ p<0.001; ‖ p<0.0001, the changes before and after acarbose therapy are significantly different between non-obese and obese groups



** p<0.0001; ∗ p<0.001; # p<0.01; φ p<0.05, in comparison with before add-on therapy.; § p<0.01; ‡ p<0.0001, the changes before and after acarbose therapy are significantly different between non-obese and obese groups

Fig. 1. After a 12-week acarbose therapy, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c decreased in both non-obese patients and obese patients with type 2 diabetes. The higher basal serum ALT and triglyceride levels in the obese patients decreased after acarbose therapy. Body weight (BW) did not significantly change in both groups.

Neither obese (74.8±9.2 kg vs. 74.4±9.8 kg, *NS*) nor non-obese patients (61.9±7.9 kg vs. 61.6±7.7 kg, *p*=0.0579) show significant decrease in body weight, but total patients had a significant decrease in body weight after treatment (66.3±10.4 kg vs. 66.0±10.4 kg, p<0.05). In addition, obese patients showed a significant ALT (61±26 vs. 49±18, p<0.001) and a triglyceride reductions (242±127 vs. 187±71, p<0.01) after therapy, but not in non-obese patients. Comparing the changes before and after acarbose therapy between non-obese and obese groups, showed decreases in serum ALT (p<0.0001) and triglyceride levels (p<0.01) to be significantly higher in the obese group (Fig. 1). In other parameters, no changes between groups were observed (Table 2).

Discussion

In this study, acarbose treatment reduced both fasting and post-loading plasma glucose, and HbA1c in both obese and non-obese patients with type 2 diabetes mellitus. The results obtained are consistent with the previous clinical studies.[6-10] A previous Asian multi-center clinical trial demonstrated an additional weight-reducing effect of acarbose therapy for patients with type 2 diabetes.[13] However, our study, which is an add-on therapy and is considered be close to clinical practice, revealed that the weight-reducing effect of acarbose therapy is minimal in both non-obese and obese groups.

We found that decreases in triglyceride and ALT levels after acarbose therapy are only noted in the obese patients with type 2 diabetes mellitus. Most obese patients with in-

creased basal triglyceride and ALT levels were diagnosed with fatty liver (data not shown). The results are compatible with the medical hypothesis that acarbose is a promising agent for the treatment of patients with nonalcoholic steatohepatitis (NASH).[14]

The lowering serum triglyceride effect of acarbose was reported in abdominally obese, normal weight, type 2 diabetic patients,[11] obese hypertensive subjects with normal glucose tolerance,[15] and type 2 diabetic patients with hypertriglyceridaemia.[16] Our study demonstrated that the major effect on triglyceride levels was caused by reducing the relatively high basal triglyceride levels in the obese patients.

Although a increase in serum hepatic transaminases has never been reported,[10] decrease in the mean value of serum hepatic transaminases after an 8-week acarbose therapy has however been reported in patients with chronic hepatitis or liver cirrhosis and overt diabetes mellitus.[17] Our study showed that acarbose therapy might have some beneficial effects on the elevated serum ALT levels in obese diabetic patients. As the obese patients had higher levels of serum C-peptide than the non-obese ones, they were more insulin-resistant. In those with IGT, acarbose has been demonstrated to improve insulin secretion and insulin sensitivity.[18,19] Serum proinsulin and C-peptide were examined for some patients before and after acarbose therapy and both serum proinsulin and C-peptide decreased more markedly after acarbose therapy in obese patients (not shown). So, we suggest that the ALT-decreasing effect, which implied a beneficial effect for fatty liver, must be caused by the improvement in insulin sensitivity. Our finding is compatible with the recent clinical study that delineated the relationship between C-peptide and fatty liver in type 2 diabetes.[20] Finally, we would like to mention the possibility of acarbose-induced toxicity.[21] In such a rare condition, the serum ALT levels will increase more than ten fold of the upper normal limit.

A limitation of the current study, is that the numbers of obese patients studied are relatively small and the duration is relatively short. A study of larger numbers for a longer period may be needed to elucidate the possible effect of acarbose on carbohydrate metabolism. Finally, it should be emphasized that these studies were performed in Taiwanese patients who take rice as their major source of carbohydrate and may not be applicable to other ethnic groups.

In conclusion, acarbose effectively improves both plasma glucose and HbA1c in both obese and non-obese patients with type 2 diabetes mellitus. Obese patients had an additional benefit of lowering of the higher basal ALT and the higher basal triglyceride levels after acarbose therapy.

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