

The Mushroom *Agaricus blazei* Murill in Combination with Metformin and Gliclazide Improves Insulin Resistance in Type 2 Diabetes: A Randomized, Double-Blinded, and Placebo-Controlled Clinical Trial

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Background: Complementary and alternative medicine use in adults with type 2 diabetes is popular. Although most of the herbs and supplements appear to be safe, there is still insufficient evidence that demonstrates their definitive beneficial effects. This study was done to determine whether the supplement of *Agaricus blazei* Murill extract improves insulin resistance in type 2 diabetes.

Materials and Methods: This study was a clinical randomized, double-blind, placebo-controlled trial. Of a population of 536 registered diabetes patients with 72 subjects (1) aged between 20 and 75 years, (2) being Chinese, (3) having type 2 diabetes for more than 1 year, and (4) having been taking gliclazide and metformin for more than 6 months were enrolled in this study. The enrolled patients were randomly assigned to either receiving supplement of *Agaricus blazei* Murill (ABM) extract or placebo (cellulose) 1500 mg daily for 12 weeks. Homeostasis model assessment for insulin resistance (HOMA-IR) was used as the major outcome measurement.

Results: At the end of the study, subjects who received supplement of ABM extract ($n = 29$) showed significantly lower HOMA-IR index (3.6[standard deviation, 2.5] versus 6.6[standard deviation, 7.4], $p = 0.04$) than the control group ($n = 31$). The plasma adiponectin concentration increased 20.0(standard deviation, 40.7)% in the ABM group after 12 weeks of treatment, but decreased 12.0(20.0)% among those taking the placebo ($p < 0.001$).

Conclusions: Supplement of ABM extract improves insulin resistance among subjects with type 2 diabetes. The increase in adiponectin concentration after taking AMB extract for 12 weeks might be the mechanism that brings the beneficial effect. Studies with longer periods of follow-up should be conducted in the future.

INTRODUCTION

Type 2 diabetes represents a heterogeneous group of disorders characterized by increased insulin resistance.¹ Lifestyle, diet, obesity, and family history of diabetes have been associated with the development of insulin resistance, although the molecular pathway remains unknown.² Thiazolidinediones (TZD) have been found to improve peripheral insulin resistance and has been employed for treating type 2 diabetes.^{3,4} However, some adverse side effects on liver function have also been reported.⁵ Hence, it is desir-

able to find a natural herbal medicine that can help boost insulin resistance but has less undesirable side effects.

The mushroom *Agaricus blazei* Murill (ABM) is a natural food, which has been used as a health care product for the prevention of a range of illness including cancer, diabetes, arteriosclerosis, and chronic hepatitis. It has been reported that ABM has beneficial effects in fighting cancer,⁶⁻¹⁰ virus,¹¹ and *Streptococcus pneumoniae* infection in mice¹² as well as enhancing antibody production of vaccine.^{13,14} Rich polysaccharides such as β -glucans are found to be the main compounds of ABM.¹⁴⁻¹⁷ β -Glucans from

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ABM have demonstrated antidiabetic activity.¹⁷ An animal model study and a pilot study have both indicated its beneficial effect in type 2 diabetes. Hence, we conducted this clinical trial to examine whether ABM extract given as a supplement can improve insulin resistance in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population

The trial was conducted from July 1, 2005 through December 31, 2005 in the Taipei Hospital, Taiwan. Of a population of 536 registered patients with diabetes, 72 subjects met with the inclusion criteria: (1) aged between 20 and 75 years; (2) being Chinese; (3) having type 2 diabetes for more than 1 year; and (4) having been taking gliclazide and metformin for more than 6 months were enrolled in this study; and exclusion criteria were as follows: (1) aminotransferases aspartate or aminotransferases alanine >80 IU/L, serum creatinine >2.0 mg/dL; (2) prolactin or pregnant women, heart failure, acute myocardial infarct, stroke, and heavy injuries; and (3) any other conditions not suitable for trial as evaluated by the physician. The protocol was approved by the Human Ethics Committee of our hospital. Informed consent was obtained from all the enrolled patients. The patients were instructed to maintain an isocaloric diet and their previous eating habits during the study period. All subjects were free to withdraw at any time during the course of the study.

Preparation of sample and treatment

ABM is a health care product popularly used in Taiwan. Our ABM extract samples, obtained from Eng Chiao Bio-Technology Co. Ltd., Taiwan, were extracted from dried fungal bodies of ABM according to the preset standard procedures with certificate of analysis given. The placebo given to the control group comprised pure microcrystalline cellulose. The subjects were asked to take one capsule containing 500 mg of either ABM extract or cellulose three times each day for 12 weeks. The capsule was taken with gliclazide 30 minutes before eating and metformin was taken 30 minutes after eating. During the study period, the subjects should keep taking the same dose of gliclazide and metformin except when hypoglycemia occurs, in which case the dose of gliclazide or metformin should be reduced immediately.

Randomization and blindness

All subjects were randomly assigned to one of the two groups. A random number between 0.0 and 0.99 would be generated by the computer for each patient. Patients with a random number between 0.0 and 0.49 were assigned to the group with ABM extract given, whereas those with a ran-

dom number between 0.50 and 0.99 would be assigned to the placebo group with cellulose given. The same opaque capsules containing either dried powdered ABM extract or placebo (cellulose) were administered to the subjects by a research assistant blinded to the contents in the capsules. All patients were treated in the same fashion.

Assessment

Homeostasis model assessment for insulin resistance (HOMA-IR) [fasting glucose (mmol/L) \times fasting insulin (UI/L)/22.5] was used as the major outcome measurement.^{18,19} At baseline and after 12 weeks of treatment, anthropometric measurements, blood pressure, fasting glucose, hemoglobin A1C% (HbA1C), insulin, adiponectin and plasma lipoproteins (triglyceride, cholesterol, cholesterol-high-density lipoprotein, and cholesterol-low-density lipoprotein) of both groups were measured. The change (%) in concentration of adiponectin after the 12-week treatment was also evaluated.

All measurements were made at 8 AM to 9 AM after an overnight fast using standardized methods. A sample of whole blood was drawn and centrifuged at 4°C, and a 1-mL aliquot of serum was rapidly frozen (-80°C) for subsequent hormone analysis. The plasma adiponectin concentration was measured by a radioimmunoassay kit (Linco Research, Inc., St. Charles, Missouri). This kit employs the double-antibody/polyethylene glycol technique using ¹²⁵I-labeled adiponectin and a multispecies adiponectin rabbit antiserium. Plasma insulin levels were measured using a commercially available radioimmunoassay (Linco Research Inc.). The intra- and interassay coefficients of variation were 3.1% and 4.9%, respectively. The limit of sensitivity is 0.5 ng/mL.

Statistical analysis

The data were analyzed with SPSS software (version 11.5, SPSS Software, Inc., Chicago, IL). Paired *t* tests were used to examine differences within-group at 0 to 12 weeks. Student *t* test was used to examine the main outcome, demographic data, and other measurements between group means. Chi-square test was employed for gender comparison between groups. All *p* values were two-tailed, and the α level of significance was set at 0.05. We estimated in power 0.8 that each group required 28 subjects.

RESULTS

Demographics

Seven subjects of the ABM extract group and five subjects of the placebo group withdrew because of personal reasons. In the end, 60 patients completed the study. Table 1 shows the demographic data, fasting serum glucose meta-

TABLE 1. CHARACTERISTICS OF SUBJECTS AT BASELINE

	Agaricus blazei Murill extract (n = 29)	Placebo control (cellulose) (n = 31)	p value
Basic data			
Gender (male/female)	14/15	13/18	0.41
Age (years)	57.0 (9.4)	56.4 (12.0)	0.83
Time since diagnosis of diabetes (y)	57.0 (9.4)	56.4 (12.0)	0.83
Daily dose of gliclazide (mg)	9.1 (7.5)	8.2 (6.6)	0.65
Daily dose of metformin (mg)	171.0 (28.1)	175.5 (43.4)	0.64
Body mass index (kg/m ²)	1658.6 (557.3)	1690.3 (646.7)	0.84
Waist circumflex (cm)	25.5 (3.1)	27.4 (5.7)	0.11
Systolic blood pressure (mm Hg)	131.3 (16.7)	138.9 (14.8)	0.08
Diastolic blood pressure (mm Hg)	78.3 (10.6)	82.8 (9.8)	0.10
Fasting serum glucose metabolic factors			
Glucose (mg/dL)	181.0 (66.9)	194.6 (57.6)	0.40
HbA1c (%)	8.9 (1.3)	9.1 (1.5)	0.55
Insulin (IU/L)	10.6 (6.6)	12.8 (17.8)	0.55
HOMA-IR index	4.8 (3.5)	6.3 (9.2)	0.40
Adiponectin (ng/mL)	15.8 (7.3)	18.4 (7.8)	0.20
Plasma lipoprotein			
Fasting triglyceride (mg/dL)	160.5 (114.4)	229.6 (224.3)	0.14
Fasting cholesterol (mg/dL)	181.3 (42.5)	187.5 (50.2)	0.61
HDL-cholesterol (mg/dL)	43.9 (7.3)	42.7 (8.7)	0.58
LDL-cholesterol (mg/dL)	116.6 (38.2)	107.0 (38.1)	0.51
Other fasting serum factors			
Aminotransferases, aspartate (IU/L)	32.4 (19.7)	29.5 (15.6)	0.53
Aminotransferases, alanine (IU/L)	24.5 (11.6)	24.5 (10.2)	1.0
Creatinine (mg/dL)	0.9 (0.2)	1.0 (0.2)	0.08

HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

bolic factors, plasma lipoprotein, and clinical profiles of the groups at the time of entry. As can be seen, there were no significant differences in all the baseline measurements between the ABM extract group and the placebo group.

Within-group comparison at 12 weeks

Table 2 shows the within-group comparisons at baseline and after the 12-week treatment. According to the analysis of the fasting serum glucose metabolic factors, the ABM extract group showed a significant difference in reduced HbA1C, insulin concentration, and homeostasis model assessment for insulin resistance (HOMA-IR) index as well as increased concentration of adiponectin, compared with the initial values, whereas the placebo group showed significant difference only in reduced adiponectin level compared with the initial values.

Between-group comparison at 12 weeks

At the end of 12 weeks (Table 2), there were no significant differences between the two groups in all the measurements except insulin concentration and HOMA-IR index ($p = 0.05$ and 0.04). Figure 1 shows a significant difference between the ABM extract group and the placebo group ($p < 0.001$) in terms of change (%) in plasma adiponectin concentrations after 12 weeks of treatment.

Adverse effects

Three subjects of the ABM extract group had hypoglycemia-like symptoms; 2 patients had the dose of oral hypoglycemia agent (OHA) reduced, whereas 1 patient withdrew. One subject of the placebo group also developed hypoglycemia-like symptoms. The dose of OHA was reduced and he stayed on in the study.

Two subjects of the ABM extract group developed skin itching, 1 subject of the placebo group had skin allergy with papules, and another had nausea and fullness sensation. All 4 of them withdrew. No major adverse effects were noticed.

DISCUSSION

This study shows the benefits of ABM extract supplement for reducing the HOMA-IR index in subjects with type 2 diabetes treated with gliclazide and metformin.

Insulin resistance, a common cause of type 2 diabetes, implies impairment of insulin signaling in target tissues. It has been reported that some OHA might influence insulin resistance.^{4,5,17,20-22} To avoid existing confounders and bias, we examined a homogenous Chinese cohort who had had type 2 diabetes for more than 1 year and had been taking gliclazide and metformin for more than 6 months.

TABLE 2. CHARACTERISTICS OF SUBJECTS AFTER 12-WEEK TREATMENT

	Agaricus blazei Murill extract (n = 29)	Placebo control (cellulose) (n = 31)	p value
Basic data			
Daily dose of gliclazide (mg)	168.3 (32.7)	175.5 (43.4)	0.47
Daily dose of metformin (mg)	1634.9 (570.4)	1706.5 (635.1)	0.65
Body mass index (kg/m ²)	25.6 (3.0)	27.7 (5.7)	0.08
Waist circumflex (cm)	88.0 (8.4)	92.9 (14.0)	0.11
Systolic blood pressure (mm Hg)	131.2 (16.5)	139.7 (15.4)	0.06
Diastolic blood pressure (mm Hg)	77.2 (10.8)	83.2 (10.4)	0.07
Fasting serum glucose metabolic factors			
Glucose (mg/dL)	182.3 (52.9)	197.9 (55.9)	0.27
HbA1c (%)	8.3 (1.8)*	8.9 (1.7)	0.24
Insulin (IU/L)	7.8 (4.9)*	13.5 (7.8)	0.05
HOMA-IR index	3.6 (2.5)*	6.6 (7.4)	0.04
Adiponectin (ng/mL)	18.8 (10.9)*	16.3 (8.3)*	0.33
Plasma lipoprotein			
Fasting triglyceride (mg/dL)	141.8 (73.5)	215.5 (207.3)	0.07
Fasting cholesterol (mg/dL)	200.5 (44.7)	192.7 (31.0)	0.44
HDL-cholesterol (mg/dL)	44.4 (7.1)	41.8 (8.8)	0.22
LDL-cholesterol (mg/dL)	136.4 (46.8)	121.1 (34.8)	0.16
Other fasting serum factors			
Aminotransferases, aspartate (IU/L)	31.4 (23.4)	31.5 (15.3)	0.99
Aminotransferases, alanine (IU/L)	24.0 (10.9)	26.9 (14.0)	0.37
Creatinine (mg/dL)	0.9 (0.2)	1.0 (0.2)	0.09

Data are means (SD).

* $p < 0.05$ from baseline to the end (12 weeks) with paired t tests.

HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

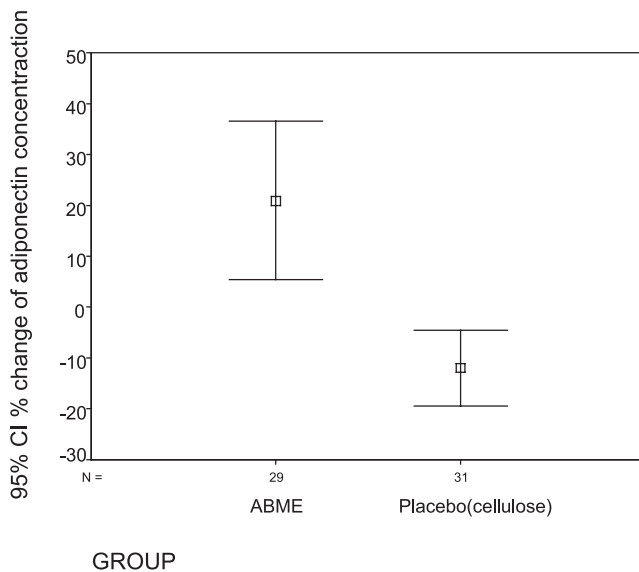


FIG. 1. Change (%) in plasma adiponectin concentrations after 12-week treatment in *Agaricus blazei* Murill extract (ABME) group and placebo (cellulose) group ($p < 0.001$). CI, confidence interval.

Many animal model studies have demonstrated the anti-diabetic activity of ABM.¹⁷ After an animal model study in 2003 and a pilot study had showed its beneficial effect in patients with type 2 diabetes, we conducted this clinical trial to examine whether the supplement of ABM extract improves insulin resistance in patients with type 2 diabetes. We also evaluated the adiponectin concentration using many fasting serum glucose metabolic factors to further examine the possible mechanism of its beneficial effects.

In this study, subjects who received the supplement of ABM extract showed a significant reduction in HOMA-IR index (from 4.8 to 3.6), which was much lower than that observed among the control subjects (from 6.3 to 6.6).

It is interesting to note that the subjects who had taken a supplement of ABM extract for 12 weeks showed a significant increase in plasma adiponectin concentrations compared with the placebo (cellulose) group ($p < 0.001$) (Fig. 1). Many previous studies have reported that the adiponectin level might be a major modulator of insulin resistance²³ and predict the development of type 2 diabetes.^{24–26} Circulating adiponectin levels in human is positively correlated with insulin sensitivity.^{23,27} The level of adiponectin appeared to play a very important role in the regulation of insulin acting and energy homeostasis.^{27,28} We observed a 20% increase in adiponectin level after 12 weeks of treatment with

ABM extract supplement. This might account for the effect of improving insulin resistance in the ABM extract group.

Our finding reveals that after the 12-week treatment, subjects receiving ABM extract had a 6.7% reduction of HbA1C (from 8.9 to 8.3) and those taking cellulose had a 2.4% reduction (from 9.1 to 8.9). Although both supplements showed a similar effect on reducing HbA1C with no statistical difference, the results still had clinical implications. In the AMB extract group, the decrease in HbA1C could be attributed to the improved insulin resistance, whereas that in the control group might be caused by loss of appetite or reduced food intake. Although the initial results showed no statistical difference in HbA1C, treatment of longer duration might result in significant statistical difference.

As mentioned in our study design, all the subjects should maintain the same dose of gliclazide and metformin during the study period unless hypoglycemia occurs. During the 12-week treatment, 3 subjects of the ABM extract group developed hypoglycemia-like symptoms; 2 patients had the dose of OHA reduced and stayed in the study whereas the other patient withdrew. Although at the end of study there was no significant difference in the dose of OHA received, the supplement of ABM extract might have the effect of reducing the current OHA dose for type 2 diabetes, which is beneficial to diabetes control. Hence, future studies on effects of ABM should be alert for hypoglycemia-like symptoms.

Although many positive effects of ABM have been reported, most of them were from *in vitro* or animal studies.^{6–17} To our knowledge, this is the first randomized clinical ABM study. Our results reveal improvement in insulin resistance by ABM. Although TZD can enhance insulin sensitivity,^{3,4,29} its toxicity affects the liver.⁵ Hence, ABM can be a possible supplement that has no major adverse effects and does not result in liver function impairment, as noted in this study. Attention must be paid to the 2 subjects of the ABM extract group who developed skin itching. Clinical observation of other possible side effects should be made in future.

Complementary and alternative medicine use in adults with type 2 diabetes is popular.^{30–32} Although most of the herbs and supplements appear to be safe, there is still insufficient evidence that demonstrates their definitive beneficial effects.³¹ The ABM extract was obtained from dried fungal bodies of ABM, which has been widely taken as a health care product in Taiwan and Japan for years. The effect of insulin resistance improvement attributed to taking supplement of ABM extract was demonstrated in our studies. The beneficial effects of AMB are worth further exploration in detailed clinical studies.

Despite the encouraging results, our work still had limitations, such as short period of study. Future research should be performed with a longer follow-up period and other well-designed protocols.

In conclusion, this study demonstrated that supplementa-

tion with ABM extract improves insulin resistance in type 2 diabetes. The increase in adiponectin concentration after 12-week treatment with ABM extract supplement might be the mechanism that brings beneficial effect. Studies with a longer period of follow-up should be made in the future.

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