

The effect of alogliptin on pulmonary function in obese patients with type 2 diabetes inadequately controlled by metformin monotherapy

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Abstract

Background: To observe the effect of alogliptin combined with metformin on pulmonary function in obese patients with type 2 diabetes inadequately controlled by metformin monotherapy (500 mg, bid po, for at least 3 months), and evaluate its efficacy and safety.

Methods: After a 2-week screening period, adult patients (aged 36–72 years) entered a 4-week run-in/stabilization period. Then, patients were randomly assigned to either the intervention group (n = 55) or the control group (n = 50) for 26 weeks. The patients in the control group were given metformin (1000 mg, bid po) and the patients in the intervention group were given metformin (500 mg, bid po) combined with alogliptin (25 mg, qd po). All the patients received counseling about diet and exercise from a nutritionist during run-in and treatment periods.

The primary endpoints were the between-group differences in the changes in pulmonary function parameters (vital capacity [VC]%, forced vital capacity [FVC]%, forced expiratory volume in 1 second (FEV1)%, peak expiratory force [PEF]%, maximal voluntary ventilation [MVV]%, total lung capacity [TLC]%, forced expiratory volume in 1 second/forced vital capacity [FEV1/FVC]%, diffusing capacity for carbon monoxide of lung [DLCO]%, and diffusing capacity for carbon monoxide of lung/unit volume [DLCO/VA%]) between pretherapy and posttreatment. The secondary endpoints were changes from baseline to week 26 in glycosylated hemoglobinA1c (HbA1c), FPG, 2hPG, homeostasis model assessment insulin resistance (HOMA-IR), waist circumference (WC), and BMI. The tertiary endpoints were the changes from baseline to week 26 in blood-fat (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides [TG]). The quartus endpoints were the changes from baseline to week 26 in systolic blood pressure (SBP) and diastolic blood pressure (DBP). The 5th endpoints were the changes from baseline to week 26 in oxidative/antioxidative parameters (reactive oxygen species [ROS], malondialdehyde [MDA], superoxide dismutase [SOD], and glutathione peroxidase [GSH-Px]). In addition, safety endpoints were assessed (AEs, clinical laboratory tests, vital signs, and electrocardiographic readings).

Results: Eighty-one patients completed our clinical trial: intervention group (n = 44) and control group (n = 37). At week 26, pulmonary function parameters (VC%, FVC%, FEV1%, PEF%, MVV%, TLC%, FEV1/FVC%, DLCO%, and DLCO/VA%) had increased significantly from pretherapy values in both groups ($P < 0.05$), and the pulmonary function tests were significantly greater ($P < 0.05$) in intervention group than in controls posttherapy. Pulmonary function (FVC%, FEV1%, PEF%, TLC%, FEV1/FVC%, DLCO%, and DLCO/VA%) was lower in the group with HbA1c levels ≥ 8.0 at 26 weeks, but VC%, FEV1%, MVV%, and TLC% were not significantly lower ($P > 0.05$). Pulmonary function parameters were positively correlated with GSH-Px and SOD and negatively correlated with ROS and MDA. Mean declines in HbA1c, FPG, 2hPG, HOMA-IR, and blood-fat (TC, HDL-C, LDL-C, and TG) were significantly greater ($P < 0.05$) in intervention group compared with the controls, but mean declines in BMI, WC, and BP (SBP, DBP) did not differ significantly between the 2 groups ($P > 0.05$). SOD and GSH-Px increased more ($P < 0.05$) in the intervention group, compared with the controls; ROS and MDA declined more ($P < 0.05$) in intervention group, as compared with the control group. The

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most common AEs were gastrointestinal events, headaches, skin-related AEs (mostly pruritic events), and hypoglycemia. The incidences of AEs did not differ significantly ($P > 0.05$) between the 2 groups except for the headache and skin-related adverse events (the incidence of headache was higher in the intervention group than in controls; $P < 0.05$). No patient died during the study.

Conclusion: In patients with type 2 diabetes mellitus (T2DM) inadequately controlled by metformin monotherapy, the addition of alogliptin contributed to clinically significant increases in pulmonary function through regulating glycemia and improving the imbalance of the oxidative-related substances in the serum, without increasing the incidence of hypoglycemia, dyslipidemia, dysarteriotony, and any notable increase in body weight.

Abbreviations: AE = adverse event, BMI = body mass index, BP = blood pressure, DBP = diastolic blood pressure, DLCO = diffusing capacity for carbon monoxide of lung, DLCO/VA = diffusing capacity for carbon monoxide of lung/unit volume, DPP-4 = dipeptidyl-peptidase-4, DR = diabetic retinopathy, FEV1 = forced expiratory volume in 1 second, FEV1/FVC = forced expiratory volume in 1 second/ forced vital capacity, FVC = forced vital capacity, GLP-1 = glucagon likepeptide-1, GSH-Px = glutathione peroxidase, HbA1c = glycosylated hemoglobinA1c, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment insulin resistance, IR = insulin resistance, LDL-C = low-density lipoprotein cholesterol, MDA = malondialdehyde, MVV = maximal voluntary ventilation, PEF = peak expiratory force, ROS = reactive oxygen species, SBP = systolic blood pressure, SOD = superoxide dismutase, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglycerides, TLC = total lung capacity, VC = vital capacity, WC = waist circumference.

Keywords: alogliptin, metformin, obesity, oxidative related substances, pulmonary function, type 2 diabetes mellitus

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide, particularly in Asian countries.^[1] Patients with T2DM develop abnormal glucose and lipid metabolism, which is associated with obesity and multiple organ dysfunction syndromes. Therefore, T2DM has been identified as an independent risk factor that accounts for a 2-fold increase in cardiovascular disease,^[2] and induces vascular complications, such as diabetic nephropathy and diabetic retinopathy (DR).^[3] Indeed, diabetic nephropathy and DR are leading causes of end-stage renal failure and acquired blindness, respectively.^[4] This vascular damage caused by diabetes and hyperglycemia increase intracellular reactive oxygen species (ROS) and malondialdehyde (MDA), decrease the activity of SOD and glutathione peroxidase (GSH-Px), and subsequently lead to apoptotic cell death, inflammation, and injury of endothelial cells.^[5,6]

More than 3 decades ago, researchers had already established that patients with T2DM had less alveolar gas exchange capacity than healthy subjects.^[7] Later clinical and experimental studies suggested that T2DM attenuated pulmonary function through vascular damage through oxidant/antioxidant imbalance.^[7-9] However, the pulmonary vascular injury induced by hyperglycemia has been overlooked in current treatment of T2DM. Smoking, obesity, vascular diseases, and the duration of diabetes also contributed notably to decreased lung function; however, current and ex-smokers manifested clinically significant chronic air flow obstruction,^[10] and the patients often had T2DM combined with obesity.^[1]

Glucagon likepeptide-1 (GLP-1), an incretin hormone, can prevent high-glucose-induced oxidative stress in cardiac microvascular endothelial cells, possibly through inhibition of activation of the Rho/ROCK pathway.^[11] By decreasing the GLP-1 level, dipeptidyl-peptidase-4 (DPP-4) inhibitors have become the new breakthrough diabetic therapy and been widely used in the diabetes mellitus treatment.^[12] In patients with T2DM,^[13] DPP-4 inhibitors stimulate release of glucose-dependent insulin and suppress glucagon production; DPP-4 inhibitors also slow gastric emptying, reduce appetite, decrease body weight, and potentially enhance preservation of β -cell function. However, little is known about whether DPP-4 inhibitors can improve pulmonary function by correcting oxidative/antioxidative imbalances and by protecting pulmonary vessels.

Alogliptin (alogliptin benzoate), the most recent DPP-4 inhibitor, entered the market in 2006. It is a potent and highly selective DPP-4 inhibitor with oral antidiabetic activity.^[14] Like others DPP-4 inhibitors (vildagliptin) alogliptin does not produce any notable increase in body weight.^[15] Metformin, a 1st-line drug, is most commonly prescribed worldwide for the treatment of T2DM. It functions by means of decreasing both hepatic glucose production and intestinal glucose absorption, and improving insulin sensitivity. Metformin as a safe and valid oral antidiabetic drug was recommended to the obese patients with a body mass index (BMI) >30 kg/m². It is of value in reducing or preventing weight gain and changes in metabolic parameters during treatment, and it can be combined with other antidiabetic drugs.^[16] In our research, we chose the initial dose (500 mg, bid po) of metformin and if the plasma sugar was inadequately controlled, the dose (1000 mg, bid po) of metformin was increased in the control group according to the guideline.^[16]

In the current study, we compared alogliptin combined with metformin with metformin alone to treat obese patients. Concerning T2DM patients inadequately controlled by metformin monotherapy, we examined the effect of alogliptin on pulmonary function, and evaluated its efficacy and safety. In updated guidelines released by the American Diabetes Association,^[17] metformin is recommended as the 1st-line drug for the treatment of T2DM because glycemic improvements and weight loss with metformin were rapid, sustained, and independent of age, race, and sex. For most patients, a combination of oral antidiabetic agents, with or without the use of insulin, is required to achieve and maintain treatment goals^[18]; extensive phase II and phase III clinical trial data support the use of alogliptin in combination with metformin. Therefore, we choose to study alogliptin combined with metformin.

The aims of our study were to assess the effect of alogliptin combined with metformin on pulmonary function in obese patients with type 2 diabetes inadequately controlled by metformin monotherapy with diet and exercise and to evaluate its efficacy and safety.

2. Patients and methods

2.1. Patients

We selected 120 obese patients with type 2 diabetes inadequately controlled by metformin monotherapy (500 mg, bid po,

Table 1
Baseline demographic and clinical characteristics.

Characteristics	Control group	Intervention group	t/χ ²	P
No. (n)	37	44	—	—
Sex, n, %				
Male	22 (59.5)	27 (61.4)	0.030	0.861
Female	15 (40.5)	17 (38.6)		
Age, years	53.41 ± 10.46	53.84 ± 9.53	0.196	0.845
BMI, kg/m ²	30.57 ± 1.46	31.07 ± 1.28	1.640	0.105
Diabetes duration, years	6.57 ± 6.19	6.60 ± 6.11	−0.022	0.983
WC, cm	93.65 ± 4.23	92.57 ± 3.72	1.295	0.199
FBG, mmol/L	8.79 ± 0.27	8.88 ± 0.27	−1.687	0.096
2hPBG, mmol/L	12.97 ± 1.28	12.95 ± 1.06	−0.008	0.994
HbA1c, %	8.22 ± 0.56	8.22 ± 0.54	0.013	0.990
Baseline HbA1c, n, %				
<8%	12 (32.43)	16 (36.36)	0.137	0.711
≥8%	25 (67.57)	28 (63.64)		
HOMA-IR (index)	2.93 ± 0.45	2.92 ± 0.53	0.291	0.783
TC, mg/dL	199.62 ± 17.99	200.75 ± 16.11	−0.298	0.767
HDL-C, mg/dL	44.08 ± 4.49	43.95 ± 4.71	0.123	0.902
LDL-C, mg/dL	120.30 ± 12.86	120.16 ± 10.70	0.053	0.958
TG, mg/dL	146.03 ± 12.29	146.98 ± 9.44	−0.393	0.695
Cholesterol-lowering drugs, n, %				
Use	12 (32.4)	16 (36.4)	0.137	0.711
No use	25 (67.6)	28 (63.6)		
SBP, mmHg	129.54 ± 6.72	130.45 ± 5.59	−0.668	0.506
DBP, mmHg	83.57 ± 3.91	83.95 ± 4.24	−0.424	0.673
Antihypertensive drugs, n, %				
Use	10 (27.0)	14 (31.8)	0.221	0.638
No use	27 (73.0)	30 (68.2)		

BMI=body mass index, DBP=diastolic blood pressure, FBG=fasting plasma glucose, HbA1c=glycosylated hemoglobinA1c, HDL-C=high-density lipoprotein cholesterol, HOMA-IR=homeostasis model assessment insulin resistance, 2hPBG=2-hour postprandial blood glucose, LDL-C=low-density lipoprotein cholesterol, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, WC=waist circumference.

≥3 months prior to screening) from the Department of Endocrinology and Metabolism in the Fourth People's Hospital of Shenyang. All patients were provided a diet and exercise program by professional nutritionists. Before the treatment period, the 2 groups did not differ significantly ($P > 0.05$) in sex ratio, the race ratio (all were Asians), age (range from 36 to 72 years), diabetes duration (range from 0.7 to 15 years), BMI (range from 28 to 33 kg/m²), waist circumference (WC), glycosylated hemoglobinA1c (HbA1c) (range from 7.0% to 10%), FPG, 2hPG, pulmonary function measures (vital capacity [VC]%, forced vital capacity [FVC]%, forced expiratory volume in 1 second [FEV1]%, peak expiratory force [PEF]%, maximal voluntary ventilation [MVV]%, total lung capacity [TLC]%, forced expiratory volume in 1 second/forced vital capacity [FEV1/FVC]%, and diffusing capacity for carbon monoxide of lung [DLCO]%, and diffusing capacity for carbon monoxide of lung/unit volume [DLCO/VA]%), blood-fat (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and TG) and blood pressure (BP) (Table 1), and oxidative/antioxidative parameters (ROS, MDA, SOD, and GSH-Px) (Table 3). T2DM was diagnosed according to the guidelines by the American Diabetes Association: ^[17] symptoms of diabetes (thirst, polydipsia, diuresis, and weight loss could not be interpreted; random plasma sugar (RPS) ≥11.1 mol/L or fasting plasma glucose (FPG) ≥7.0 mol/L or the outcome of oral glucose tolerance test: 2-hour postprandial plasma glucose (2hPG) ≥11.1 mol/L; or there were no symptoms of diabetes but RPS was ≥11.1 mol/L or FPG was ≥7.0 mol/L. The selection criteria were: aged from 36 to 72 years of either gender; BMI >28.0 kg/m², and WC >90 cm (male), or WC

>85 cm (female); the patients were diagnosed with T2DM according to the guidelines from the American Diabetes Association,^[17] and the symptoms and the serological outcome (7.0% < HbA1c < 10.0%) did not reach the therapeutic targets despite diet, exercise, and oral metformin monotherapy (500 mg, bid po, ≥3 months prior to screening); no smoking history, pulmonary disease nor pulmonary infection within a fortnight; no hepatopathy, nephropathy, and gastrointestinal disease; and likelihood to have good compliance and ability to visit our hospital for periodic assessments. The exclusion criteria were: T1DM, gestation and lactation; renal inadequacy, a serum creatinine >132 μmol/L (male), or a serum creatinine >123 μmol/L (female); hypohepatia, the liver enzyme was 2 times higher than normal; intensive care with insulin treatment; intolerance to alogliptin and metformin; New York Heart Association class III or IV heart failure, coronary bypass surgery, a history of coronary angioplasty, coronary stent placement, or myocardial infarction within 6 months; having received antidiabetic agents; inadequately controlled BP (systolic blood pressure [SBP] >140 mmHg and diastolic blood pressure [DBP] >90 mmHg) by antihypertensive drugs or severe uncontrolled hypertension (SBP >200 mmHg and DBP >100 mmHg); inadequately controlled blood-fat (TC >250 mg/dL, HDL-C <30 mg/dL, LDL-C >170 mg/dL, and TG >200 mg/dL) by cholesterol-lowering drugs; and use of weight loss drugs, bosentan or oral or systemically injected glucocorticoids within 3 months prior to randomization until the end of treatment. This trial was conducted in accordance with the Declaration of Helsinki. The clinical research was approved by the Medical Ethics Committee (Number ICE20140508). An independent ethics committee or

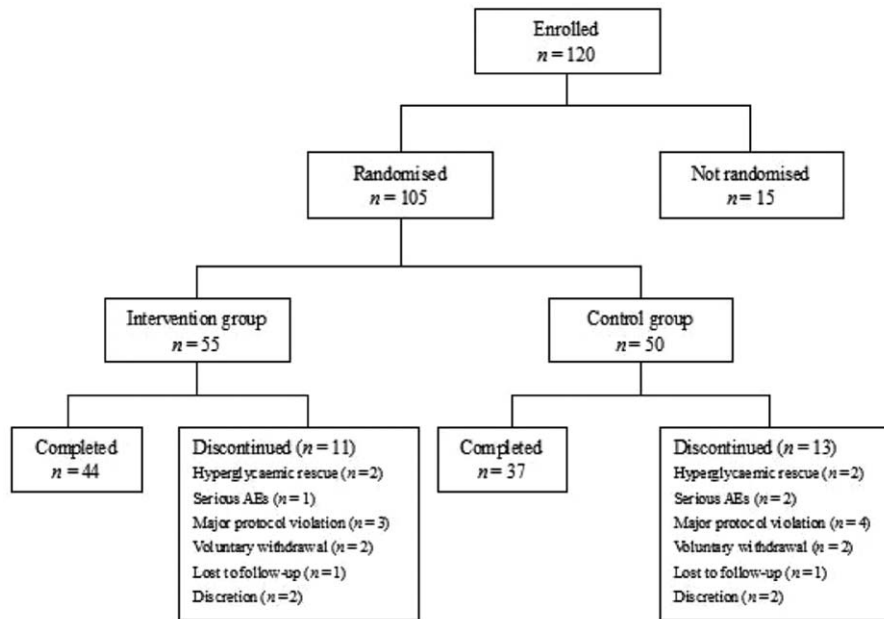


Figure 1. Flow diagram: participation of enrolled patients.

institutional review board at each research site reviewed the study protocol. Each patient and their family members gave written informed consent before randomization.

2.2. Major reagent and apparatus

Alogliptin was provided by Takeda Chemical industries Ltd in Japan (trade name: Nesina, 25 mg/tablet). Metformin was provided by Bristol Myers Squibb in America (trade name: Glucophage, 500 mg/tablet). Research kits for ROS, MDA, and SOD, GSH-Px were provided by Nanjing Jiancheng Bioengineering Institute in China. Research kits for TC, HDL-C, HDL-C, and TG were provided by Nanjing Jiancheng Bioengineering Institute in China. The spirometer used for pulmonary function tests was provided by Jaska Corporation in Japan, with model number: HI-101.

2.3. Study design

The research was divided into 3 stages: screening, run-in, and treatment period (Fig. 1). The screening period was 2 weeks (from -6 to -4 week); 120 eligible patients who met the study criteria were identified, screened, and enrolled. The run-in period was 4 weeks (from -4 to 0 week); during this period, the patients were treated with metformin monotherapy (500 mg, bid po). At the end of this period, 105 patients remained in the study; 15 participants were excluded due to inadequate compliance and for other reasons. Treatment period: after completion of the run-in period, 105 patients with HbA1c values of 7.5% to 10.0%; FPG <250 mg/dL (13.9 mmol/L); and $\geq 75\%$ compliance were eligible for the treatment period in light of their stable metformin dose for the past 8 weeks; 105 patients were assigned to the intervention or the control group. Finally, 81 patients (44 patients in the intervention group and 37 patients in the control group) completed our study. During the entire period, all the patients maintained the previous diabetes diet and exercise habits and telephone follow-up conversations once/week and outpatient

follow-up visits once every 2 to 4 weeks. Before and after the treatment period, 5 mL of venous blood was collected (following ≥ 8 hours of fasting) and pulmonary function tests were performed.

Visits included measurement of vital signs; clinical examination of skin and digits; review of diaries, adverse events (AEs), and glucometer readings; assessment of hematology and serum chemistry parameters; and dosing compliance. Patients were trained in glucometer use, instructed to recognize the signs and symptoms of hypoglycemia, and asked to maintain a diary of hypoglycemic events.

2.4. Study assessments and endpoints

Blood specimen collection and laboratory tests: venous blood was collected at 6 to 8 AM following a fast of ≥ 8 hours and used to measure FPG, HbA1c, homeostasis model assessment insulin resistance (HOMA-IR), ROS, MDA, SOD, GSH-Px, and blood-fat (TC, HDL-C, HDL-C, and TG). Plasma glucose levels were determined by the glucose oxidase method. The oral glucose tolerance test method used 75 g of oral glucose (50% anhydrous glucose solution 150 mL including 7.5 bottles added to 150 mL warm water). Venous blood was extracted to measure the 2hPG. In addition, 5 mL of venous blood was placed into a glass tube and left standing at least 10 minutes, centrifuged (3000 r/minutes) 10 minutes, and then to separate serum, which was kept in -70° C cryogenic refrigerator. TC, HDL-C, HDL-C, TG, ROS, MDA, SOD, and GSH-Px were measured according to the research kit instructions. All the specimens were measured within 1 week of collection. HOMA-IR was calculated as follows: fasting insulin (mU/mL) \times fasting glucose (mmol/L)/22.5.

BP measurement: SBP and DBP tests were performed using an electronic sphygmomanometer.

Measuring pulmonary function: pulmonary function tests (VC %, FVC %, FEV1 %, PEF %, MVV %, TLC %, FEV1/FVC %, DLCO %, and DLCO/VA %) were performed using a spirometer.

We used the ratio of measured values and the expected values, % of predicted value, to eliminate the influence of age, height, and weight. Before testing, the patient remained sitting at quiet rest for at least 30 minutes, pulmonary function tests were performed 3 times and the best of 3 acceptable readings was used in the analysis. Spirometry and analysis of pulmonary function were performed by trained professionals.

2.5. Decision criteria of AEs

During treatment, AEs (such as, hypoglycemia, gastrointestinal events, headache, and skin-related AEs) were recorded by patients or their family members. If the patients could not tolerate the adverse reactions or the AEs appeared severe, they were withdrawn from the study. If symptoms of hypoglycemia or hyperglycemia appeared, a glucometer was used to measure the blood glucose level promptly. Hypoglycemia was defined as blood glucose <60 mg/dL/3.9 mmol/L in the presence of symptoms or blood glucose <50 mg/dL/2.8 mmol/L with or without symptoms. A hypoglycemic event was considered severe (manifesting central nervous system symptoms) if the assistance from another person is required and, if measurement is allowed, blood glucose level was found to be <60 mg/dL/3.9 mmol/L. If a patient developed hypoglycemia, the metformin dose was reduced once on a weekly basis in increments of 250 mg until hypoglycemia was resolved. Rescue therapy for hyperglycemia was initiated if FPG was ≥ 275 mg/dL/15.3 mmol/L after more than 1 week of treatment but prior to the week 4 visit, if FPG was ≥ 250 mg/dL/13.9 mmol/L from the week 4 visit but prior to the week 8 visit, or if FPG was ≥ 225 mg/dL/12.5 mmol/L from the week 8 visit but prior to the week 12 visit, or if HbA1c was $\geq 8.5\%$ and was reduced by $\geq 0.5\%$ from baseline at week 12 or later.

2.6. Statistical analysis

Data were expressed as mean \pm standard deviation (SD). Statistical analysis was conducted using the SPSS statistical package (Version 17.0, SPSS Inc. Chicago, IL). Differences in categorical variables between the 2 groups were evaluated using the Chi-square test; differences in continuous variables between the 2 groups were evaluated using the independent-samples *t* test; before and after treatment within-group differences in continuous variables were assessed using the paired-sample *t* test. Changes in pulmonary function parameters according to HbA1c level at week 26 were tested using one-way ANOVA. The linear correlation between the pulmonary function parameters and oxidative/antioxidative parameters at week 26 were evaluated using Pearson correlation coefficient, *r*.

3. Results

3.1. Patient disposition and baseline characteristics

Of 120 enrolled patients, 105 were randomly assigned to a treatment group. Ultimately, 81 patients completed the study. The participation of patients through the study is summarized in Fig. 1. Four patients (3.8%) discontinued treatment because they needed hyperglycemic rescue, and 20 patients (19.0%) did not complete the treatment period for other reasons. The most common reasons were major protocol violations (intervention group: $n=3$, 5.45%; control group: $n=4$, 8.00%), which were mostly identified for personal reasons rather than AEs, lack of efficacy, or voluntary withdrawal.

Before the treatment period, similar baseline demographic and clinical characteristics were observed between the 2 groups (Table 1). The patients enrolled had a mean age of approximately 54 years, a mean HbA1c of approximately 8%, a mean FPG of approximately 9 mmol/L, a mean 2hPG of approximately 13 mmol/L, a mean TC of approximately 200 mg/dL, a mean HDL-C of approximately 44 mg/dL, a mean LDL-C of approximately 120 mg/dL, a mean TG of approximately 146 mg/dL, a mean SBP of approximately 130 mmHg, a mean DBP of approximately 83 mmHg, a mean BMI of approximately 31 kg/m², a mean WC of approximately 93 cm, and they were all Asians. Sex ratio in the 2 groups did not differ significantly ($P > 0.05$). The proportion of patients with a baseline HbA1c $\geq 8\%$ (53/81; 65.43%) was greater, as compared with patients with a baseline HbA1c $< 8\%$ (28/81; 34.57%); the proportion of patients using cholesterol-lowering drugs (28/81; 34.57%) was lower than that of patients without using cholesterol-lowering drugs (53/81; 65.43%), but the proportion of patients using cholesterol-lowering drugs in the 2 groups did not differ significantly ($\chi^2 = 0.137$, $P = 0.711 > 0.05$); the proportion of patients using antihypertensive drugs (24/81; 29.63%) was lower than that of patients without using antihypertensive drugs (57/81; 70.37%), but the proportion of patients using antihypertensive drugs in the 2 groups did not differ significantly ($\chi^2 = 0.221$, $P = 0.638 > 0.05$). (Table 1).

3.2. Comparison of HbA1c, FPG, 2hPG, BMI, and WC

By week 26, mean HbA1c and FPG decreased significantly more in the intervention group (-0.66% , $P < 0.05$; -2.42 mmol/L, $P < 0.05$, respectively) than in controls (-0.47% and -1.25 mmol/L, respectively); mean 2hPG changes were greater in the intervention group (-2.17 mmol/L) than in controls (-1.96 mmol/L) but did not differ significantly ($P > 0.05$); mean BMI declined more in the intervention group (-2.07 kg/m²) than in controls (-1.78 kg/m²) without significant difference ($P > 0.05$); mean declines in WC from baseline to week 26 were greater in the intervention group (-4.11 cm) than in the controls (-4.41 cm) without significant difference ($P > 0.05$). At week 26, the proportion of patients with HbA1c $\leq 7.0\%$ in the intervention group (8/44; 18.18%) was greater than in controls (4/37; 10.81%), and no significant difference was found ($P > 0.05$, Table 2).

3.3. Results of BP (SBP, DBP) and blood-fat (TC, HDL-C, HDL-C, and TG)

By week 26, mean TC decreased significantly more in the intervention group (-4.27 mg/dL; $P < 0.05$) than in controls (-1.59 mg/dL), whereas mean HDL-C raised significantly more in the intervention group (1.00 mg/dL; $P < 0.05$) than in controls (0.24 mg/dL). Both mean LDL-C and TG decreased significantly more in the intervention group (-2.36 mg/dL, $P < 0.05$; -6.23 mg/dL, $P < 0.05$, respectively) than in the control group (-0.16 and -2.78 mg/dL, respectively). However, the between group differences for BP (SBP, DBP) were not significant ($P > 0.05$) (Table 2).

3.4. Results of oxidative/antioxidative parameters (ROS, MDA, SOD, and GSH-Px)

By week 26, mean ROS and MDA decreased significantly more in the intervention group (-51.75 U/mL, $P < 0.05$; -8.98 nmol/mL; $P < 0.05$, respectively) than in controls (-16.97 U/mL and -5.54

Table 2

Mean change in HbA1c, FPG, 2hPG, HOMA-IR, BMI, WC, BP, and blood-fat from baseline to week 26.

Content	Item	Group		t/ χ^2	P
		Control group (n=37)	Intervention group (n=44)		
HbA1c, %	Baseline	8.22 ± 0.56	8.22 ± 0.54	0.013	0.990
	Week 26	7.75 ± 0.53	7.56 ± 0.53	1.603	0.113
	Change	-0.47 ± 0.11	-0.66 ± 0.08*	8.969	0.000
HbA1c, n, % at week 26	≤7.0% (n)	4 (10.81)	8 (18.18)	0.865	0.352
	>7.0% (n)	33 (89.19)	36 (81.82)		
FBG, mmol/L	Baseline	8.79 ± 0.27	8.88 ± 0.27	-1.687	0.096
	Week 26	7.54 ± 0.23	6.47 ± 0.18*	23.452	0.000
	Change	-1.25 ± 0.36	-2.42 ± 0.34*	15.109	0.000
2hPBG, mmol/L	Baseline	12.97 ± 1.28	12.95 ± 1.06	-0.008	0.994
	Week 26	11.01 ± 1.00	10.81 ± 1.02	0.897	0.372
	Change	-1.96 ± 1.00	-2.17 ± 0.81	1.017	0.312
HOMA-IR (index)	Baseline	2.93 ± 0.45	2.92 ± 0.53	0.291	0.783
	Week 26	2.72 ± 0.52	2.63 ± 0.34*	6.325	0.004
	Change	-0.21 ± 0.31	-0.29 ± 0.28*	19.325	0.000
BMI, kg/m ²	Baseline	30.57 ± 1.46	31.07 ± 1.28	1.640	0.105
	Week 26	28.78 ± 1.03	29.00 ± 1.24	-0.844	0.401
	Change	-1.78 ± 1.20	-2.07 ± 0.55	1.405	0.164
WC, cm	Baseline	93.65 ± 4.23	92.57 ± 3.72	1.295	0.199
	Week 26	89.24 ± 3.65	88.45 ± 2.49	1.151	0.253
	Change	-4.41 ± 1.98	-4.11 ± 1.24	-0.807	0.422
TC, mg/dL	Baseline	199.62 ± 17.99	200.75 ± 16.11	-0.298	0.767
	Week 26	198.03 ± 16.65	196.48 ± 12.77	0.474	0.637
	Change	-1.59 ± 3.55	-4.27 ± 5.33*	-2.607	0.011
HDL-C, (mg/dL)	Baseline	44.08 ± 4.49	43.95 ± 4.71	0.123	0.902
	Week 26	44.32 ± 3.84	44.95 ± 4.05	-0.714	0.477
	Change	0.24 ± 1.72	1.00 ± 1.63*	2.029	0.046
LDL-C, (mg/dL)	Baseline	120.30 ± 12.86	120.16 ± 10.70	0.053	0.958
	Week 26	120.14 ± 10.98	117.80 ± 8.69	1.219	0.227
	Change	-0.16 ± 3.11	-2.36 ± 3.56*	3.320	0.001
TG, mg/dL	Baseline	146.03 ± 12.29	146.98 ± 9.44	-0.393	0.695
	Week 26	143.24 ± 8.06	140.75 ± 7.53	1.437	0.155
	Change	-2.78 ± 5.51	-6.23 ± 7.89*	-2.235	0.028
SBP mmHg	Baseline	129.54 ± 6.72	130.45 ± 5.59	-0.668	0.506
	Week 26	128.57 ± 4.09	127.86 ± 5.07	0.678	0.500
	Change	-0.97 ± 4.63	-2.59 ± 4.40	-1.61	0.112
DBP mmHg	Baseline	83.57 ± 3.91	83.95 ± 4.24	-0.424	0.673
	Week 26	81.49 ± 2.66	82.45 ± 2.34	-1.742	0.085
	Change	-2.08 ± 4.63	-1.50 ± 3.64	0.705	0.483

BMI=body mass index, BP=blood pressure, DBP=diastolic blood pressure, FBG=fasting plasma glucose, HbA1c=glycosylated hemoglobinA1c, HDL-C=high-density lipoprotein cholesterol, HOMA-IR=homeostasis model assessment insulin resistance, 2hPBG=2-hour postprandial blood glucose, LDL-C=low-density lipoprotein cholesterol, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, WC=waist circumference.

* P<0.05, the difference between the 2 groups.

Table 3

Mean change in oxidative/antioxidative parameters from baseline to week 26 by treatment group.

Content	Item	Group		t	P
		Control group (n=37)	Intervention group (n=44)		
GSH-Px, μmol/L	Baseline	26.16 ± 2.87	25.70 ± 2.86	0.716	0.476
	Week 26	28.70 ± 2.11	31.36 ± 2.73*	-4.840	0.000
	Change	2.54 ± 2.96	5.66 ± 0.75*	-6.748	0.000
SOD, U/mL	Baseline	226.49 ± 14.26	228.32 ± 11.29	-0.645	0.521
	Week 26	239.38 ± 12.63	260.84 ± 15.68*	-6.696	0.000
	Change	12.89 ± 5.72	32.52 ± 17.57*	-6.508	0.000
ROS, U/mL	Baseline	651.92 ± 29.01	658.84 ± 27.40	-1.103	0.273
	Week 26	634.95 ± 24.34	607.09 ± 19.14*	5.764	0.000
	Change	-16.97 ± 36.36	-51.75 ± 33.73*	4.461	0.000
MDA, nmol/mL	Baseline	61.76 ± 3.16	61.30 ± 3.35	0.633	0.528
	Week 26	56.22 ± 3.04	52.32 ± 2.79*	6.020	0.000
	Change	-5.54 ± 1.83	-8.98 ± 1.42*	9.492	0.000

GSH-Px = glutathione peroxidase, MDA=malondialdehyde, ROS=reactive oxygen species, SOD=superoxide dismutase.

* P<0.05, the difference between the 2 groups.

Table 4
Mean change in pulmonary function tests from baseline to week 26 by treatment group.

Content	Item	Group		t	P
		Control group (n=37)	Intervention group (n=44)		
VC, L (% of predicted)	Baseline	79.78 ± 2.94	81.50 ± 2.17	-1.321	0.071
	Week 26	83.43 ± 2.48	88.34 ± 2.33*	-9.170	0.000
	Change	3.65 ± 1.57	6.84 ± 2.30*	-7.152	0.000
FVC, L (% of predicted)	Baseline	70.95 ± 3.61	71.18 ± 4.95	-0.241	0.810
	Week 26	72.65 ± 3.48	77.45 ± 4.76*	-5.097	0.000
	Change	1.70 ± 1.20	6.27 ± 1.04*	-18.352	0.000
FEV1, L (% of predicted)	Baseline	76.57 ± 4.35	75.80 ± 7.23	0.569	0.571
	Week 26	77.54 ± 5.27	83.43 ± 4.79*	-5.268	0.000
	Change	0.97 ± 6.83	7.63 ± 7.92*	-4.011	0.000
PEF, L/S (% of predicted)	Baseline	52.30 ± 3.94	52.75 ± 3.26	-0.566	0.573
	Week 26	55.00 ± 3.32	58.48 ± 3.33*	-4.690	0.000
	Change	2.70 ± 1.43	5.73 ± 1.47*	-9.341	0.000
MVV, L (% of predicted)	Baseline	87.08 ± 2.79	87.00 ± 3.35	0.117	0.907
	Week 26	90.14 ± 2.37	90.84 ± 2.58	-1.273	0.207
	Change	3.05 ± 0.91	3.84 ± 1.29*	-3.108	0.003
TLC, L (% of predicted)	Baseline	95.68 ± 3.86	95.70 ± 4.15	-0.032	0.974
	Week 26	99.24 ± 3.72	103.70 ± 5.00*	-4.481	0.000
	Change	3.57 ± 1.44	8.00 ± 2.39	-9.857	0.000
FEV1/FVC (% of predicted)	Baseline	74.27 ± 2.96	73.27 ± 4.12	1.229	0.223
	Week 26	76.86 ± 2.79	78.27 ± 4.07*	-1.782	0.079
	Change	2.59 ± 1.61	5.00 ± 1.43*	-7.126	0.000
DLCO, mL/min/mmHg (% of predicted)	Baseline	85.54 ± 3.78	85.45 ± 2.85	0.124	0.901
	Week 26	87.57 ± 2.81	89.82 ± 2.62*	-3.725	0.000
	Change	2.19 ± 1.61	4.36 ± 2.31*	-4.815	0.000
DLCO/VA, mL/min/mmHg (% of predicted)	Baseline	91.51 ± 2.39	90.02 ± 1.81	3.193	0.081
	Week 26	94.54 ± 2.02	95.50 ± 1.91*	-2.192	0.031
	Change	3.03 ± 1.28	5.48 ± 0.93*	-9.967	0.000

DLCO = diffusing capacity for carbon monoxide of lung, DLCO/VA = diffusing capacity for carbon monoxide of lung/unit volume, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, MVV = maximal voluntary ventilation, PEF = peak expiratory force, TLC = total lung capacity, VC = vital capacity.

* P < 0.05, the difference between the 2 groups.

nmol/mL, respectively). Mean increases in SOD and GSH-Px were significantly greater in the intervention group (32.52 U/mL, P < 0.05; 5.66 μmol/L; P < 0.05, respectively) than in controls (12.89 U/mL and 2.54 μmol/L, respectively) (Table 3).

3.5. Results of pulmonary function tests

By week 26, mean pulmonary function parameters (VC%, FVC%, FEV1%, PEF%, MVV%, TLC%, FEV1/FVC [%], DLCO%, and DLCO/VA [%]) increased remarkably more in the

intervention group (6.84, 6.27, 7.63, 5.73, 3.84, 8.00, 5.00, 4.36, and 5.48; P < 0.05) than in controls (3.65, 1.70, 0.97, 2.70, 3.05, 3.57, 2.59, 2.19, and 3.03) (Table 4). The pulmonary function of 3 categories of patients, based on HbA1c levels, were compared using ANOVA (Table 5): the group having HbA1c levels ≥ 8.0 had lower pulmonary function (FVC%, FEV1%, PEF%, FEV1/FVC [%], DLCO%, and DLCO/VA%), but the between category differences for VC%, FEV1%, MVV%, and TLC% were not significant (P > 0.05). Pulmonary function parameters were positively correlated with GSH-Px and SOD and negatively

Table 5
Comparison of pulmonary function parameters according to category of HbA1c level at week 26.

Content	HbA1c, %			F	P
	≥ 8.0 (n=25)	< 8.0 and > 7.0 (n=44)	≤ 7.0 (n=12)		
VC, L (% of predicted)	86.36 ± 3.37	85.93 ± 3.45	86.17 ± 3.71	0.124	0.883
FVC, L (% of predicted)	73.48 ± 5.63	75.98 ± 4.20	76.33 ± 4.68	2.563	0.023*
FEV1, L (% of predicted)	80.12 ± 5.94	81.02 ± 6.19	81.00 ± 1.16	0.204	0.087
PEF, L/S (% of predicted)	56.52 ± 4.06	56.57 ± 3.31	58.83 ± 4.22	1.956	0.013*
MVV, L (% of predicted)	90.28 ± 2.26	90.73 ± 2.63	90.25 ± 2.60	0.332	0.719
TLC, L (% of predicted)	101.36 ± 4.84	102.27 ± 4.75	100.27 ± 5.99	0.984	0.278
FEV1/FVC (% of predicted)	77.17 ± 2.66	77.52 ± 4.10	78.04 ± 3.05	0.278	0.022*
DLCO, mL/min/mmHg (% of predicted)	87.84 ± 7.32	88.61 ± 9.11	89.07 ± 2.86	0.378	0.007*
DLCO/VA, mL/min/mmHg (% of predicted)	95.08 ± 2.00	95.20 ± 2.00	96.65 ± 2.01	0.575	0.011*

DLCO = diffusing capacity for carbon monoxide of lung, DLCO/VA = diffusing capacity for carbon monoxide of lung/unit volume, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HbA1c = glycosylated hemoglobinA1c, MVV = maximal voluntary ventilation, PEF = peak expiratory force, TLC = total lung capacity, VC = vital capacity.

* P < 0.05, the difference between the 3 categories of HbA1c.

Table 6

Correlation between pulmonary function parameters and oxidative/antioxidative parameters at week 26.

Parameters	Content			
	GSH-Px, $\mu\text{mol/L}$	SOD, U/mL	ROS, U/mL	MDA, nmol/mL
VC, L (% of predicted)	$r=0.272$	$r=0.398$	$r=-0.396$	$r=-0.398$
<i>P</i>	0.014*	0.000*	0.000*	0.000*
FVC, L (% of predicted)	$r=0.333$	$r=0.229$	$r=-0.384$	$r=-0.295$
<i>P</i>	0.002*	0.040*	0.000*	0.008*
FEV1, L (% of predicted)	$r=0.140$	$r=0.326$	$r=-0.347$	$r=-0.320$
<i>P</i>	0.212	0.003*	0.001*	0.004*
PEF, L/S (% of predicted)	$r=0.120$	$r=0.193$	$r=-0.154$	$r=-0.120$
<i>P</i>	0.284	0.085	0.170	0.285
MVV, L (% of predicted)	$r=0.303$	$r=0.047$	$r=-0.063$	$r=-0.245$
<i>P</i>	0.048*	0.697	0.574	0.027*
TLC, L (% of predicted)	$r=0.213$	$r=0.291$	$r=-0.164$	$r=-0.304$
<i>P</i>	0.056	0.009*	0.143	0.006*
FEV1/FVC (% of predicted)	$r=0.118$	$r=0.051$	$r=-0.088$	$r=-0.118$
<i>P</i>	0.294	0.650	0.435	0.296
DLCO, mL/min/mmHg (%of predicted)	$r=0.326$	$r=0.293$	$r=-0.319$	$r=-0.249$
<i>P</i>	0.003*	0.008*	0.004*	0.025*
DLCO/VA (%of predicted)	$r=0.293$	$r=0.120$	$r=-0.131$	$r=-0.212$
<i>P</i>	0.008*	0.287	0.243	0.057

DLCO = diffusing capacity for carbon monoxide of lung, DLCO/VA = diffusing capacity for carbon monoxide of lung/unit volume, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GSH-Px = glutathione peroxidase, MDA = malondialdehyde, MVV = maximal voluntary ventilation, PEF = peak expiratory force, ROS = reactive oxygen species, SOD = superoxide dismutase, TLC = total lung capacity, VC = vital capacity.

* $P < 0.05$, the difference between the correlation coefficient, r , and 0.

correlated with ROS and MDA (Table 6). Consistent with improvements in glycemic control, better glycemic control could have led to improved oxidative/antioxidative balance and pulmonary function.

3.6. Hyperglycemic rescue and AEs

The overall incidence of AEs (39/105; 37.1%) and the proportion of patients who withdrew because of serious AEs (3/105; 2.9%) were similar between treatment groups. No patient died during the study. The proportion of patients with HbA1c $\leq 7.0\%$ in the intervention group (6/44; 13.64%) was higher than that in controls (2/37; 5.41%), but did not differ significantly ($P > 0.05$) (Table 2). Alogliptin (25 mg, qd po) combined with metformin (500 mg, bid po) did not increase the incidence of hyperglycemic rescues (3.6% vs 4.0%; $\chi^2 = 0.009$, $P = 0.923$).

The 25 mg dose of alogliptin was usually well tolerated. Most AEs were mild or moderate in intensity and well tolerated. Serious AEs were severe infections, less frequent in the intervention group (1.8%) than in controls (4.0%), but not significantly different between groups ($\chi^2 = 0.449$, $P = 0.503$). Gastrointestinal events, the most common AE, occurred less

often in the intervention group (7, 12.7%) than in controls (8, 16.0%). However, headaches occurred more frequently in the intervention group (7; 12.7%; $P < 0.05$) than in controls (1, 2.0%). In spite of strengthened surveillance for mild or moderate skin-related AEs, low overall incidence was documented in the intervention group (7, 12.7%), albeit significantly greater than in controls (2, 4.0%), mostly because of pruritic events. Serious cutaneous AEs, such as moderate subcorneal pustular dermatosis, moderate deterioration of contact dermatitis, and skin lesions similar to those from reports of other DPP-4 inhibitors, were not observed. Hypoglycemia was rare (4, 3.8%) in all the patients during the treatment period, and no hypoglycemic event was considered adverse or severe enough to require assistance. No clinically significant changes in laboratory test results, vital signs, or ECG recordings were observed (Table 7).

4. Discussion

The results of this study demonstrated that in obese patients with T2DM inadequately controlled with metformin monotherapy, once-daily treatment with a 25 mg dose of alogliptin significantly improved the imbalance of the oxidative-related substances

Table 7

Incidence of adverse events, by treatment group.

Subgroup	Group		
	Control group (n = 50)	Intervention group (n = 55)	The total incidence (n = 105)
Severe infection (serious AEs)	2 (4.0%)	1 (1.8%)	3 (2.9%)
Gastrointestinal events	8 (16.0%)	7 (12.7%)	15 (14.3%)
Headache	1 (2.0%)	7 (12.7%)*	8 (7.6%)
Skin-related AEs	2 (4.0%)	7 (12.7%)	9 (8.6%)
Hypoglycemia	2 (4.0%)	2 (3.6%)	4 (3.8%)
The total incidence	15 (30.0%)	24 (43.6%)	39 (37.1%)

AE = adverse event.

* $P < 0.05$, the difference between the 2 groups.

(GSH-Px, SOD, MDA, and ROS) and decreased HbA1c relative to metformin monotherapy; in the meantime, this dose did not increase body weight.

Our findings are in accordance with those in similar studies of other DPP-4 inhibitors in combination with sulfonylureas.^[19] HbA1c is an indicator of diabetes control. The higher the level of HbA1c, the poorer the diabetic control and the higher the circulating glucose concentration. If circulating glucose is constantly elevated for 3 months (as measured by HbA1c), it can lead to increased nonenzymatic glycosylation of tissue proteins. The consistency with other studies persists even though the current study enrolled patients with HbA1c levels as low as 7.0%, whereas other studies excluded patients with baseline HbA1c levels <7.5%. This distinction is important in that the efficacy of antidiabetic agents appears to be greater in patients with higher baseline HbA1c levels.^[15] Studies by Pratley et al^[19] showed that alogliptin lowered HbA1c to a greater degree in patients with higher baseline HbA1c than in those with lower baseline HbA1c. In our study, mean HbA1c, FPG, and 2hPG decreased significantly more in the intervention group ($P < 0.05$) than in controls by week 26 (Table 2). Proportionately more patients in the intervention group (8/44; 18.18%) achieved HbA1c levels $\leq 7.0\%$ at week 26 than those in the control group (4/37; 10.81%), which, however, was not significant ($P > 0.05$). In our study, the rate (8/44; 18.18%) of reaching this HbA1c standard was lower than that reported in Nauck et al's study (44%).^[19] Perhaps this was because our study population was too small; the mean HbA1c decreased by 0.66% in the intervention group, similar to Nauck et al's study (0.6%) too.^[20] The rate of reaching this HbA1c standard ($\leq 7.0\%$) was lower, but the FPG and 2hPG decreased significantly at week 26, and perhaps the glucose was inadequately controlled before treatment period. The glucose was adequately controlled before our research was ended. After treatment period, the patients in the control group can comply with the treatment of intervention group (metformin [500 mg, bid po] combined with alogliptin [25 mg, qd po]) for the purpose of controlling the glucose adequately.

The mean change of BMI and WC did not differ significantly between the 2 groups, but compared to baseline, they both decreased significantly by week 26 in both groups ($P < 0.05$). These results indicate that metformin alone can decrease body weight and the addition of alogliptin did not produce a weight increase. However, previous studies reported minor increases in mean weight when a DPP-4 inhibitor was added to sulfonylurea therapy.^[19] In the study by Nauck et al,^[20] mean body weight declined 0.3 kg, which accorded with the results in our intervention group by week 26.^[20] DPP-4 inhibitors monotherapy had a neutral effect on weight and did not increase the risk of gaining weight in previous studies.^[21] The mean change of blood-fat (TC, HDL-C, HDL-C, and TG) and HOMA-IR in the intervention group was more than control group ($P < 0.05$), and they all decreased by week 26 in both groups. In Rizzo et al's^[8] study the mean change of blood-fat (TC, HDL-C, HDL-C, and TG) and HOMA-IR in the sitagliptin group was similar to the vildagliptin group ($P > 0.05$) by week 12, but they both decreased significantly by week 12 in both groups ($P < 0.05$). But the between category differences for BP (SBP, DBP) were not significant ($P > 0.05$), which was in accordance with studies by Rizzo et al.^[8] Our results demonstrated that alogliptin combined with metformin could control the glucose adequately without increasing the incidence of hypoglycemia, dyslipidemia and dysarteriotony, and any notable increase in body weight, and can improve the insulin resistance (IR).

T2DM is often accompanied by IR that leads to hyperglycemia, and hyperglycemia generates ROS that in turn damage cells in many ways. Damage to the cells ultimately produces secondary complications in diabetes mellitus, and the weakened defense system of the body becomes unable to counteract enhanced ROS generation. This leads to an imbalance between ROS and their protection that leads to the predominant condition of oxidative stress.^[22] Oxidized lipids are able to produce MDA as a decomposition product; increased levels of MDA in diabetics suggest that peroxidative injury may be involved in the development of diabetic complications. Lipid peroxidation also indicates a decline in the defense mechanisms of enzymatic and nonenzymatic antioxidants. MDA can increase protein carbonyls as well as advanced oxidation protein products level in diabetic patients, which points to the importance of the protein conformational changes in the pathogenesis of diabetic nephropathy.^[23] GSH, a tripeptide, γ -L-glutamyl-L-cysteinylglycine, is present in all mammalian tissues at 1 to 10 mM concentrations (the highest concentration in the liver) as the most abundant nonprotein thiol that defends against oxidative stress. GSH can maintain SH groups of proteins in a reduced state, participate in amino acid transport, detoxify foreign radicals, act as coenzyme in several enzymatic reactions, and also prevent tissue damage.^[24] GSH plays important protective roles against cellular and histological damages produced by ROS. SOD is an antioxidant enzyme that catalyses the dismutation of superoxide anion into hydrogen peroxide and molecular oxygen.^[25] Here, we have described the oxidative stress-induced alterations in major biomolecules in the cell and the status of plasma antioxidant potential during type 2 diabetes. Our research showed that by week 26, mean ROS and MDA decreased significantly more in the intervention group (-51.75 U/mL, $P < 0.05$ and -8.98 nmol/mL, $P < 0.05$, respectively) than in controls (-16.97 U/mL and -5.54 nmol/mL, respectively), mean SOD and GSH-Px increased significantly more in intervention group (32.52 U/mL, $P < 0.05$ and 5.66 μ mol/L, $P < 0.05$, respectively) than in controls (12.89 U/mL and 2.54 μ mol/L, respectively) (Table 3). Consistent with improvements in glycemic control, better glycemic control could have led to improved oxidative/antioxidative balance. Our results indicate high-glucose-induced oxidative stress in our study population, and that glycemic control through metformin and alogliptin can improve oxidative/antioxidative imbalances through controlling hyperglycemia. Alogliptin can improve β -cell function, through this process imbalances of oxidative/antioxidative metabolism can be rectified.^[15]

Mechanisms of lung damage due to diabetes are indefinite, however, glycemic control seems to be associated with the relationship between reduced lung function. Convincingly, collagen is less susceptible to proteolysis due to the nonenzymatic glycosylation of proteins in the lungs and chest wall, contributing to its accumulation in lung connective tissue. Primarily triggered by hyperglycemia, this process is more pronounced in patients with poor metabolic control. In addition, the nonenzymatic glycosylation of proteins in the lungs decreases the compliance of lung.^[26] A large microvascular reserve is characteristic of the alveolar-capillary system, to which oxidative damage can be triggered, thus, the lung is damaged due to hyperglycemia.^[27] In clinical setting, the loss of microvascular reserve in the lung may be caused by increased risk of hypoxia in acute or chronic pathological lung conditions, such as pneumonia, asthma, chronic obstructive pulmonary disease, and congestive heart failure. Moreover, microvascular abnormalities frequently contribute to histological changes in the lung parenchyma, such

as nodular fibrosis.^[27] In addition, a very large surface area of the lungs, coupled with their ability to transport large amounts of oxygen to blood from the air, ensures a convenient portal for the entry of therapeutic agents.

Systemic inflammation is another concern in diabetic patients. Systemic inflammation attributed to oxidative stress is associated with endothelial dysfunction in diabetic patients.^[28–30] In addition, lung volume and mechanical function could be altered due to IR via mediators such as leptin.^[27] Moreover, IR may lead to airflow obstruction independently, in a manner similar to the way peripheral airway inflammation contributes to air flow obstruction in asthma.^[31] Lung CO transfer capacity is remarkably affected by the integrity of lung capillary endothelium, which supports increased attention to pulmonary vascular changes. There has been a growing concern the concept of the lung as an organ affected by diabetic microangiopathy. In terms of lung function tests in diabetic patients over the last 15 years, studies have focused predominantly on pulmonary microangiopathy but relatively few studies on pulmonary mechanical function. Specifically, lung function tests associated with pulmonary microangiopathy refer to pulmonary capillary blood volume and CO transfer capacity.^[32] Niranjana et al^[33] found significantly lower TLC, FVC, FEV1, and VC in type 1 diabetic patients than in healthy subjects. However, our study selected T2DM patients with diabetes duration from 8 to 96 months (<15 years) and the population was smaller than that in the studies by Niranjana et al^[33] we observed that pulmonary function increased significantly more in the intervention group (6.84, 6.27, 7.63, 5.73, 3.84, 8.00, 5.00, 4.36, and 5.48; $P < 0.05$) than in controls at week 26 (3.65, 1.70, 0.97, 2.70, 3.05, 3.57, 2.59, 2.19, and 3.03) (Table 4). HbA1c is an indicator of diabetes control; our results revealed that the pulmonary function differed by HbA1c level: many pulmonary function parameters were better in patients with lower HbA1c levels. However, not all the parameters were significantly higher in the lower category of HbA1c level (Table 5). In previous studies the correlations between the HbA1c and pulmonary function parameters were inconsistent; in 2 studies, the associations between HbA1c and spirometric measurements were weak or absent.^[34,35] Another cross-sectional population study revealed negative correlation between plasma glucose level and FVC and/or FEV1.^[36] Correlation analysis found that the pulmonary function parameters were positively correlated with GSH-Px and SOD, but negatively correlated with ROS and MDA had (Table 6). Our results were similar to a previous report.^[22] In this study, we could not observe the microangiopathy in the lung, but the pulmonary function improved in parallel with improvement in oxidative/antioxidative balance. However, it is noteworthy that good glycemic control and regular treatment positively affected functional lung parameters in T2DM patients.

AEs rates reported for alogliptin (24/55; 43.6%) in the present study were lower than those in similar studies of sitagliptin (56%),^[37] vildagliptin (50.3%),^[15] and alogliptin (63%).^[19] The incidence of hyperglycemic rescues was lower in the intervention group (2/55; 3.6%) than in the control group (2/50; 4.0%), without significant difference ($\chi^2 = 0.009$, $P = 0.923$). The result that alogliptin (25 mg, qd po) combined with metformin (500 mg, bid po) did not increase the incidence of hyperglycemic rescues, was in agreement with Pratley and Nauck et al's study.^[19,20] Serious AEs were severe infections, which were less frequent in the intervention group (1/55; 1.8%) than in controls (2/50; 4.0%), but not significantly different ($\chi^2 = 0.449$, $P = 0.503$). Gastrointestinal events, the most common AE, occurred less often

in the intervention group (7/55; 12.7%) than in controls (8/50; 16.0%) and the total incidence of gastrointestinal events (15/105; 14.3%) was similar to DeFronzo et al's study (12.1–14.3%).^[14] Headache occurred more frequently in the intervention group (7/55; 12.7%; $P < 0.05$) than in controls (1/50; 2.0%). This finding, that alogliptin could increase the incidence of headache, was similar to DeFronzo et al's study.^[14] Despite strengthened surveillance for mild or moderate skin-related AEs, their overall incidence was low in the intervention group (7/55; 12.7%), albeit significantly greater than in controls (2/50; 4.0%), mostly because of pruritic events. Serious cutaneous AEs, such as moderate subcorneal pustular dermatosis, moderate exacerbation of contact dermatitis, and skin lesions similar to those from studies of other DPP-4 inhibitors, were not observed. DeFronzo et al's study^[14] reported that 2 patients discontinued treatment owing to skin-related AEs: 1 AE was possibly associated with the study drug (25 mg, moderate subcorneal pustular dermatosis). Hypoglycemia was infrequent (4/105; 3.8%) and was not serious. Overall, the addition of alogliptin to metformin led to additive therapeutic effects without any notable increase in body weight, hypoglycemic events, major cardiac events, or other AEs relative to metformin monotherapy and did not trigger clinically meaningful changes in vital signs, electrocardiograms, hematology, urinalysis, or serum chemistry.

There are several problems that will be resolved in the future. First, we could not observe the morphological changes in alveolar tissue and did not identify the protein that induced the damage to alveolar tissue. Because all the patients did not accept biopsy of the lung, we will adopt an animal model to study alveolar tissue. Second, the lung volume and mechanical function could be altered by IR through such mediators as leptin,^[27] we could not measure the leptin level in serum. Third, several longitudinal studies revealed an accelerated decline in lung function, a significant time-related effect of lung injury caused by diabetes, has been observed in longitudinal studies. However, findings about this topic are not completely in agreement: 2 other longitudinal studies, based on follow-up periods of 5 and 15 years, have revealed a similar decrease in FVC and FEV1 in diabetics and nondiabetics.^[38,39] Therefore, we will evaluate long-term therapy to observe the time-related effect of alogliptin combined with metformin on pulmonary function. Fourth, alogliptin and metformin have been found to boost circulating total GLP-1 levels in both nondiabetic and T2DM patients,^[40] but previous study did not report the total GLP-1 levels in T2DM patients treated by metformin combined with alogliptin; we plan to measure the total GLP-1 levels in the future. Fifth, with an increased use of traditional Chinese medicine (TCM) in T2DM, the complementary TCM therapy might decrease the risk of stroke in T2DM.^[41] In the future, we will observe the effect of TCM on pulmonary function in obese patients with T2DM. Finally, lung damage in T2DM will affect quality of life. Therefore, clinicians and patients are recommended to monitor lung damage in T2DM similar to monitoring for diabetic nephropathy and DR.

In conclusion, alogliptin provides significant improvements in pulmonary function, imbalance of the oxidative related substances, and glycemic control when added to metformin in T2DM patients who did not adequately respond to metformin monotherapy, with good safety and low risk of hypoglycemia and weight gain and without increasing the incidence of dyslipidemia and dysrhythmia. This indicates that patients and doctors should monitor lung function during treatment and that alogliptin is a viable treatment option for

patients with T2DM failing on metformin who require a 2nd antihyperglycemic agent and are not candidates for an insulin therapy.

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