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Post-meal β-cell function predicts the efficacy of glycemic control in patients with type 2 diabetes inadequately controlled by metformin monotherapy after addition of glibenclamide or acarbose

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Abstract

Background: This study aimed to explore parameters which will predict good control of HbA_{1c} after adding a second anti-diabetic drug in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with metformin monotherapy.

Methods: Fifty-one patients (M/F: 25/26, mean age: 53.7 ± 8.2 years, mean glycated hemoglobin [HbA_{1c}] 8.4 ± 1.2%) with T2DM inadequately controlled with metformin were randomized to add-on glibenclamide or acarbose for 16 weeks. Before and after combination therapy, the subjects underwent a 2-hour liquid mixed meal tolerance test to determine insulin secretion (HOMA-β, insulinogenic index, and disposition index [DI]) and insulin sensitivity (HOMA-IR and Matsuda insulin sensitivity index).

Results: At baseline, there was a significant inverse relationship between DI_{120} and HbA_{1c} ($p = 0.001$) in all subjects. The addition of glibenclamide and acarbose improved HbA_{1c} significantly from 8.6 ± 1.6% to 7.4 ± 1.2% ($p < 0.001$), and from 8.2 ± 0.8% to 7.5 ± 0.8% ($p < 0.001$), respectively. In the glibenclamide group, DI_{120} significantly increased from 51.2 ± 24.2 to 74.9 ± 41.9 ($p < 0.05$), and in the acarbose group, from 62.5 ± 31.4 to 91.7 ± 36.2 ($p < 0.05$), respectively. Multiple regression analyses showed that both baseline HbA_{1c} and DI_{120} independently predicted reduction of HbA_{1c} as well as final HbA_{1c} after combination therapy.

Conclusions: In patients with T2DM inadequately controlled with metformin, add-on oral anti-diabetic agent with glibenclamide or acarbose resulted in the significant HbA_{1c} reduction and improvement of β-cell function. Subjects with greater baseline β-cell function reserve displayed better glycemic response in the combination therapy of metformin with glibenclamide or acarbose.

Trial registration: This study was registered in the ClinicalTrials.gov with registration number of NCT00417729.

Keywords: Beta-cell function, Disposition index, Glycated hemoglobin, Glycemic control, Metformin

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Background

Impaired insulin secretion and insulin sensitivity are the main pathogenic defects in type 2 diabetes mellitus (T2DM), and can lead to either fasting or postprandial hyperglycemia [1]. The United Kingdom Prospective Diabetes Study (UKPDS) reports that at the diagnosis of T2DM, the pancreatic β-cell function is already half reduced, and then declines continuously despite the allocated therapy [2]. However, insulin insensitivity generally remains stable for years following the diagnosis [3]. Data from our group demonstrated that the contribution of PPG to glycemic control is equal to or greater than that of FPG across different ranges of HbA_{1c} [4], and that this is partly accounted by the impaired early secretory defect of β-cell function in Asians, resulting in a greater contribution of PPG to overall glycemic control [5,6].

In patients with T2DM, metformin therapy is generally recommended as the first line medication for glycemic control [7]. If the patients are unable to achieve or maintain their glycemic goal, other anti-diabetic agents are usually required, but which class of drug is more suitable remains a matter of debate. It has been reported that addition of sulfonylurea or acarbose can improve glycemic control in diabetic patients who fail to reach their HbA_{1c} target with metformin alone, but limited data are available guiding the add-on class of oral anti-diabetic drug (OAD) in patients with T2DM inadequately controlled with metformin [7]. At present, few data are available to study the factors that influence the glycemic response after addition of glibenclamide and acarbose in patients with type 2 diabetes inadequately controlled by metformin monotherapy. Because β-cell dysfunction plays an important role in the progression of glycemic control in T2DM, it was hypothesized that underlying β-cell dysfunction may affect the glycemic control efficacy of the secondary added-on medication. Therefore, this study aimed to compare the clinical efficacy of addition of glibenclamide and acarbose and evaluate whether β-cell function could predict glycemic control (indicated as HbA_{1c}) in patients with T2DM poorly controlled with metformin.

Methods

Study design

This was a 24-week, randomized, open-label, parallel study conducted at Taichung Veterans General Hospital and Changhua Christian Hospital, Taiwan. Some of the results of this study were published before [8]. In brief, outpatients with T2DM, who were 30 to 70 year-old and treated by mono- or dual- OAD therapy for above 3 months with a HbA_{1c} value of 7.0 to 11.0%, were eligible. Total 51 subjects (mean age, 54 years; females, 51%; mean body mass index (BMI), 25.6 kg/m^2; mean HbA_{1c}, 8.4% were randomized when they were inadequately controlled by metformin monotherapy (500 mg 3 times daily) for 8 weeks. Anthropometric data, FPG, HbA_{1c}, and lipid profiles were measured at baseline (randomization visit) and at the end of the study after a 16-week treatment with dual oral hypoglycemic agents. Patients were excluded if they were treated with insulin or drugs that promote weight loss, had impaired renal (serum creatinine concentration >1.5 mg/dL) or liver (aspartate aminotransferase or alanine aminotransferase 2.5 times greater than the normal range) function, had a history of hemoglobinopathy or chronic anemia, or were women of child-bearing potential without adequate contraception. During the 16-week period of dual therapy, dosages were 50 mg TID for acarbose and 2.5 mg TID for glibenclamide for the first 4 weeks. For the following 12 weeks, dosages were doubled in each group, if the subjects could tolerate [8]. The present report further analyzed the relationship between HbA_{1c} and insulin secretion/sensitivity indices, and examined whether beta-cell function and insulin sensitivity were correlated with glycemic control after add-on glibenclamide or acarbose. Prior to randomization, a liquid mixed meal tolerance test (LMTT) was conducted after a 10-hour overnight fast. The liquid mixed meal contained 355.5 ml and 399 kcal (caloric contribution: 64% carbohydrate, 14% fat, and 22% protein). Blood samples were collected for measurement of serum glucose and insulin concentration at pre-meal (0 min) and at the 10^{th} min, 20^{th} min, 30^{th} min, 60^{th} min, 90^{th} min, 120^{th} min, and 180^{th} min via an indwelling venous catheter. AUC_{glu} was determined as the sum of the basal area and incremental area from 0 min to 120 min. Insulin sensitivity was estimated by homeostasis model assessment of insulin resistance (HOMA-IR) [9] and the Matsuda insulin sensitivity index (MISI) [10]. Insulin secretion was estimated by homeostasis model assessment of β-cell function (HOMA-β) [9] and the insulinogenic index calculated as the ratio of incremental insulin to glucose during the first 30 min of the LMTT (Δinsulin to Δglucose = I_{30} - I_0/G_{30} – G_0) [11]. In addition, because the response of insulin secretion from β-cells to hyperglycemia is modulated by the severity of insulin resistance, we also used the disposition index (DI), which is calculated as the product of insulin sensitivity and insulin secretion [12-14]: early-phase disposition index, $DI_{30} = [AUC_{ins\ 30}/AUC_{glu\ 30}] \times MISI$ and total disposition index, $DI_{120} = [AUC_{ins\ 120}/AUC_{glu\ 120}] \times MISI$. After a 16-week therapy of dual oral hypoglycemic agents, a second LMTT was performed with all patients. The study was approved by the Institutional Review Board of Taichung Veterans General Hospital and Changhua Christian Hospital, Taiwan, and all subjects provided informed consent.

Laboratory measurements

Plasma glucose was measured by the glucose oxidase–peroxidase method (Advia 1800; Siemens Healthcare Diagnostics Inc., Deerfield, Illinois). The inter- and

intra-assay%CV for glucose were both <1.5%. Serum insulin was determined using electrochemiluminescence immunoassay (Elecsys 2010; Roche Diagnostics, Indianapolis, Indiana). The inter- and intra-assay%CV for insulin were 1.8% and 2.5%, respectively. HbA_{1c} was measured by cation-exchange HPLC (HLC-723 G7; Tosoh Bioscience Ltd., Worcestershire, United Kingdom). The inter- and intra-assay%CV for HbA_{1c} were both <4.0%.

Statistical analyses

Data are presented as the mean ± standard deviation for continuous variables and percentage for categorical variables. The Chi-square test and Mann–Whitney *U* test were used for between-group comparison. Linear regression analyses were used to determine the relationship between any one index of insulin sensitivity or secretion and glucose control parameters, such as baseline HbA_{1c}, FPG, or (AUC_{glu}) in 120 min after adjustment of age, gender, baseline BMI, and disease duration. The Wilcoxon signed rank test was used to analyze the differences in BMI, FPG, HbA_{1c}, HOMA-IR, HOMA-β, insulinogenic index, MISI, and DI_{120} from baseline to the end of the study. In addition, simple correlation and multiple regression analysis were conducted to evaluate the independent relationship between either HbA_{1c} level or the magnitude of HbA_{1c} reduction after combination therapy and background factors as well as baseline insulin secretion/sensitivity indices. A *p-value* of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois).

Results

The CONSORT flow diagram of this study was shown in the Figure 1. All of the 51 subjects enrolled in the present study were treated with metformin (500 mg 3 times daily) for the first 8 weeks as a washout period. After this period, 28 subjects were treated with metformin and acarbose while another 23 were treated with metformin and glibenclamide for 16 weeks. There was no significant difference in the clinical characteristics of each group before randomization (Table 1). Multiple linear regression analyses were performed to test the association between glucose control parameters and insulin secretion/sensitivity indices after metformin monotherapy and before randomization. It was shown DI_{120} was the only parameter inversely associated with HbA_{1c} after adjustment of age, gender, disease duration, and baseline BMI. Both DI_{120} and HOMA-β significantly correlated with other glucose control parameters, FPG or AUC_{glu}. As for indices of insulin sensitivity or

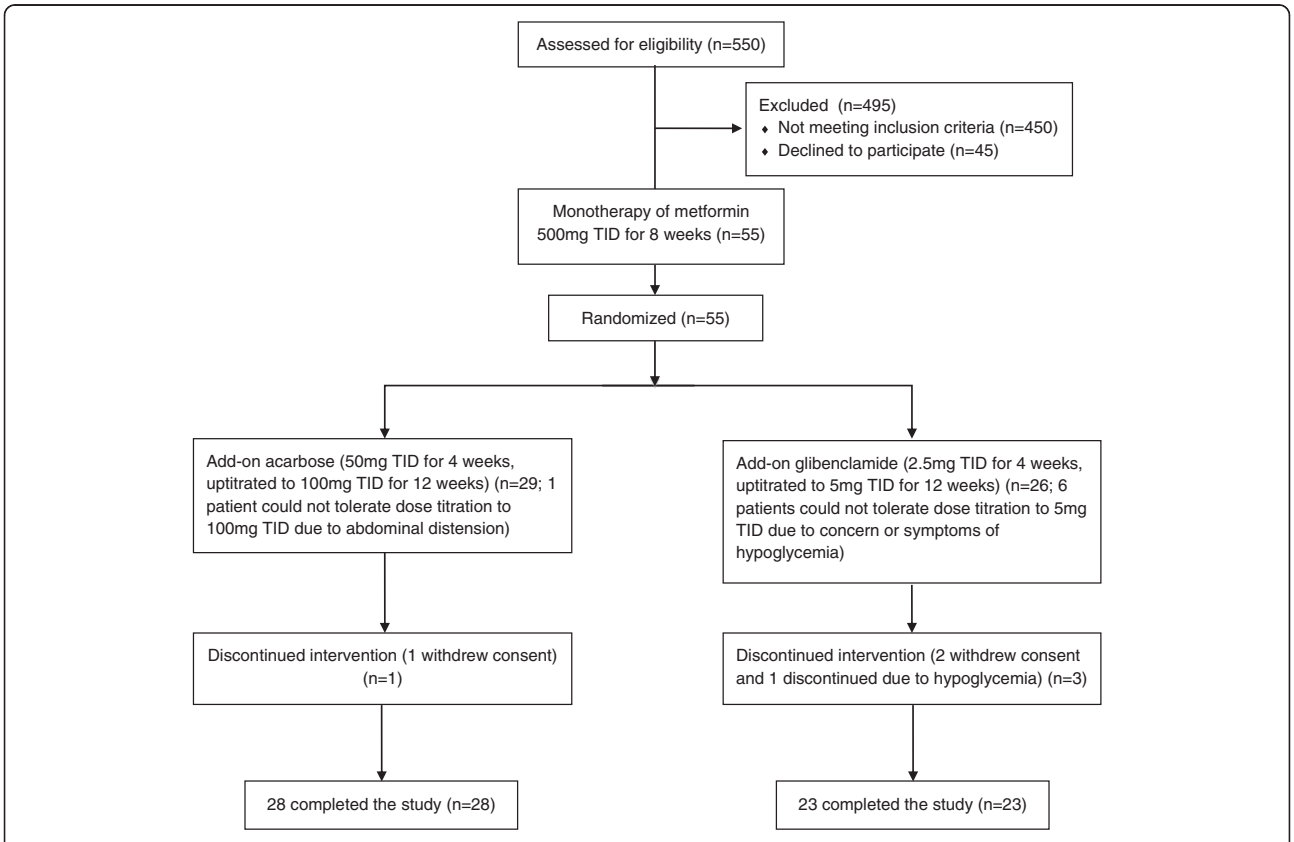

Figure 1 CONSORT flow diagram.

Table 1 Baseline characteristics of participants by treatment at randomization

	All (n = 51)	Glibenclamide (n = 23)	Acarbose (n = 28)	*P* value
Gender (female, %)	51.0%	56.5%	46.4%	0.477
Age (years)	53.7 ± 8.2	54.7 ± 8.3	52.8 ± 8.2	0.378
Disease duration (years)	6.9 ± 4.6	6.0 ± 4.7	7.6 ± 4.5	0.106
BMI (kg/m^2)	25.6 ± 3.3	25.3 ± 3.8	25.9 ± 3.0	0.334
HbA_{1c} (%)	8.4 ± 1.2	8.6 ± 1.6	8.2 ± 0.8	0.691
Fasting plasma glucose (mmol/l)	8.5 ± 2.3	9.0 ± 3.0	8.2 ± 1.3	0.538
DI_{30}	41.1 ± 25.0	36.8 ± 19.1	44.7 ± 29.0	0.247
DI_{120}	57.3 ± 28.6	51.2 ± 24.2	62.5 ± 31.4	0.289
HOMA-IR	3.7 ± 2.9	4.7 ± 3.9	2.9 ± 1.5	0.316
MISI	3.4 ± 1.8	3.2 ± 1.7	3.6 ± 1.8	0.321
HOMA-β (%)	44.9 ± 40.4	52.3 ± 49.7	38.9 ± 30.4	0.248
Insulinogenic $index_{30}$ (pmol/mmol)	42.1 ± 63.4	35.0 ± 37.2	47.9 ± 79.0	0.416

Chi-square test. Mann–Whitney *U* test. Data are presented as mean ± standard deviation or percentage of participants.
DI, disposition index; HOMA-β, homeostasis model assessment β-cell function index; HOMA-IR, homeostasis model assessment insulin resistance index; MISI, Matsuda insulin sensitivity index.

resistance, only HOMA-IR was significantly associated with FPG (Table 2).

After 16 weeks of dual-OAD therapy, there was a significant decrease in FPG and HbA_{1c} values in both groups (Table 3), and eighteen of the 51 subjects (35.3%) achieved good glycemic control of $HbA_{1c} < 7.0\%$ (9 subjects, 32.1% in acarbose group and 9 subjects, 39.1% in glibenclamide group, respectively, $p = 0.603$). Although there was no difference in HbA_{1c} between the 2 groups after add-on therapy, the mean HbA_{1c} reduction in the glibenclamide arm (1.2%) was greater than in acarbose arm (0.7%), that was compatible with the general concept that sulfonylurea has a more potent effect upon the magnitude of HbA_{1c} reduction than acarbose [7]. In addition, the insulin secretion marker, DI_{120}, improved in both groups, but there was no significant difference in these insulin secretion/sensitivity surrogates, and their change before and after combination therapy between the 2 treatment groups. Multiple linear regression analyses were performed to test the relationship between baseline DI_{120} and HbA_{1c} in all subjects after combination therapy of metformin with glibenclamide or acarbose (Table 4). By using the 3 analysis models to adjust OAD classes and other possible bias factors, including age, gender, disease duration, baseline BMI, and other insulin secretion/sensitivity indices, both baseline HbA_{1c} and DI_{120} were significantly associated with HbA_{1c} after add-on therapy. Likewise, a significant association was also found between baseline DI_{120} and the magnitude of HbA_{1c} reduction after add-on therapy (Table 5). In each subgroup, simple correlation analysis showed that there was a negative correlation between baseline DI_{120} and HbA_{1c} after dual therapy in acarbose group ($r = -0.439$, $p = 0.022$), and in glibenclamide group ($r = -0.584$, $p = 0.003$), respectively.

Discussion

The main finding from the present study was that in those patients with T2DM inadequately controlled by metformin, residual β-cell function, expressed by DI_{120}, independently predicted glycemic response after adding a 2nd OAD, either glibenclamide or acarbose.

Table 2 Multiple linear regression analysis between insulin sensitivity and secretion indices and glucose control parameters before randomization

	HbA_{1c}			Fasting plasma glucose			AUC_{glu}		
	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*
DI_{120}	−0.784	(−0.053,-0.014)	0.001*	−0.426	(−1.053,-0.148)	0.011*	−0.525	(−14.088,-2.496)	0.006*
HOMA-β (%)	0.005	(−0.010,0.011)	0.979	−0.507	(−0.752,-0.262)	<0.001*	−0.348	(−7.040,-0.759)	0.016*
Insulinogenic $index_{30}$ (pmol/mmol)	0.341	(−0.001,0.014)	0.075	0.211	(−0.038,0.303)	0.124	0.016	(−2.074,2.296)	0.919
HOMA-IR	−0.068	(−0.223,0.165)	0.764	0.484	(2.168,11.302)	0.005*	0.128	(−38.411,78.513)	0.492
MISI	0.270	(−0.111,0.488)	0.210	0.037	(−6.204,7.882)	0.811	−0.021	(−95.634,84.672)	0.903

Adjusted for age, gender, body mass index, and disease duration. *$P < 0.05$.
AUC_{glu}, area under curve of glucose in 120 min; DI, disposition index; HOMA-β, homeostasis model assessment β-cell function index; HOMA-IR, homeostasis model assessment insulin resistance index; MISI, Matsuda insulin sensitivity index.

Table 3 Comparison of glucose control parameters, insulin secretion and sensitivity surrogates before and after treatment in both groups

	Acarbose (n = 28)			Glibenclamide (n = 23)		
	Before	**After**	***P*-values vs. baseline**	**Before**	**After**	***P*-values vs. baseline**
BMI (kg/m^2)	25.9 ± 3.0	25.5 ± 3.3	0.005*	25.3 ± 3.8	25.5 ± 4.0	0.072
Fasting plasma glucose (mmol/l)	8.2 ± 1.2	7.3 ± 1.2	0.002*	9.0 ± 3.0	7.2 ± 2.1	0.001*
HbA_{1c} (%)	8.2 ± 0.8	7.5 ± 0.8	<0.001*	8.6 ± 1.6	7.4 ± 1.2	<0.001*
HOMA-IR	3.0 ± 1.4	3.1 ± 2.9	0.682	4.8 ± 3.9	3.5 ± 2.7	0.101
HOMA-β (%)	40.3 ± 30.0	49.4 ± 40.2	0.021*	53.7 ± 50.5	47.0 ± 83.4	0.153
Insulinogenic $index_{30}$ (pmol/mmol)	47.9 ± 79.0	50.6 ± 42.0	0.080	35.0 ± 37.2	36.1 ± 24.5	0.191
MISI	3.6 ± 1.8	4.6 ± 2.8	0.124	3.2 ± 1.7	4.1 ± 2.9	0.176
$AUC_{ins\ 120}/AUC_{glu\ 120}$[§](pmol/mmol)	2.9 ± 2.3	3.8 ± 3.1	0.003*	2.7 ± 1.4	3.3 ± 1.7	0.121
DI_{120}	62.5 ± 31.4	91.7 ± 36.2	0.002*	51.2 ± 24.2	74.9 ± 41.9	0.003*

Wilcoxon signed rank test; Data are presented as mean ± standard deviation.
*P <0.05: § total area under curve of insulin within 120 minutes divided by total area under curve of glucose within 120 minutes.
DI, disposition index; HOMA-β, homeostasis model assessment β-cell function index; HOMA-IR, homeostasis model assesment insulin resistance index; MISI, Matsuda insulin sensitivity index.

It is well recognized that pancreatic β-cell dysfunction is a key pathogenetic factor involved in T2DM [1]. In 1981, Bergman et al. [15] postulated the product of insulin sensitivity and insulin secretion was a constant, namely, the disposition index (DI). This index represents the responsiveness of β-cells in compensating for insulin sensitivity [16]. In general, DI_{120} represents the overall insulin response to insulin sensitivity during oral glucose tolerance test [12]. In addition, DI_{120} derived from LMTT also has a predictive power analogous to that calculated from intravenous glucose tolerance test [13,14]. In clinical studies, DI has been shown to decrease with progression from normal glucose tolerance to diabetes mellitus, and can be used to predict the development of diabetes over a long period in a population without diabetes [17]. Of note, our study also demonstrated that before randomization, there was a significant negative association between DI_{120} and $HbA_{1c,}$ but not HOMA-β, insulinogenic index, HOMA-IR, or MISI. These observations were supported by our previous report that PPG was an important contributor to glycemic control [4] and indicated that β-cell dysfunction relative to insulin sensitivity was a major determinant of HbA_{1c} in Asians.

There was a significant decrease in FPG and HbA_{1c} values after 16 weeks of dual-OAD therapy in both groups.

Table 4 Multiple linear regression models of HbA_{1c} after combination therapy

	Model 1		Model 2		Model 3	
	β	***P***	**β**	***P***	**β**	***P***
Drug group (0 = glibenclamide; 1 = acarbose)	0.089	0.410	0.152	0.127	0.145	0.126
Gender (0 = female; 1 = male)	−0.163	0.110	-	-	-	-
Age (years)	−0.106	0.307	-	-	-	-
Disease duration (years)	0.105	0.313	-	-	-	-
BMI (kg/m^2)	0.172	0.179	-	-	-	-
HbA_{1c} (%)	0.677	<0.001*	0.687	<0.001*	0.703	<0.001*
MISI	0.162	0.391	0.217	0.234	-	-
HOMA-IR	−0.305	0.080	−0.210	0.148	−0.244	0.085
HOMA-β (%)	−0.030	0.864	0.029	0.835	-	-
Insulinogenic $index_{30}$ (pmol/mmol)	−0.072	0.734	-	-	-	-
$AUC_{ins\ 120}/AUC_{glu\ 120}$[§](pmol/mmol)	0.301	0.258	0.302	0.150	0.158	0.249
DI_{120}	−0.801	0.045*	−0.743	0.031*	−0.552	0.030*
DI_{30}	0.456	0.226	0.329	0.176	0.284	0.142

Multiple linear regression models with HbA_{1c} after combination therapy as the dependent variable. All independent variables were collected before randomization of the second-line OADs.
*$P < 0.005$; § total area under curve of insulin within 120 minutes divided by total area under curve of glucose within 120 minutes.
DI, disposition index; HOMA-β, homeostasis model assessment β-cell function; HOMA-IR, homeostasis model assessment insulin resistance index; Incremental AUC, incremental area under curve during liquid mixed meal tolerance test; MISI, Matsuda insulin sensitivity index.

Table 5 Multiple linear regression models of magnitude of HbA_{1c} reduction after combination therapy

	Model 1		Model 2		Model 3	
	β	*P*	β	*P*	β	*P*
Drug group (0 = glibenclamide; 1 = acarbose)	−0.113	0.410	−0.192	0.127	−0.183	0.126
Gender (0 = female; 1 = male)	0.206	0.110	-	-	-	-
Age (years)	0.134	0.307	-	-	-	-
Disease duration (years)	−0.132	0.313	-	-	-	-
BMI (kg/m^2)	−0.217	0.179	-	-	-	-
HbA_{1c} (%)	0.730	<0.001*	0.718	<0.001*	0.698	<0.001*
MISI	−0.204	0.391	−0.273	0.234	-	-
HOMA-IR	0.384	0.080	0.265	0.148	0.308	0.085
HOMA-β (%)	0.037	0.864	−0.036	0.835	-	-
$Insulinogenic\ index_{30}$ (pmol/mmol)	0.091	0.734	-	-	-	-
$AUC_{ins\ 120}/AUC_{glu\ 120}$§(pmol/mmol)	−0.379	0.258	−0.380	0.150	−0.199	0.249
DI_{120}	1.009	0.045*	0.936	0.031*	0.696	0.030*
DI_{30}	−0.574	0.226	−0.414	0.176	−0.358	0.142

Multiple linear regression models with HbA_{1c} reduction after combination therapy as the dependent variable. All independent variables were collected before randomization of the second-line OADs.
*$P < 0.005$; § total area under curve of insulin within 120 minutes divided by total area under curve of glucose within 120 minutes.
DI, disposition index; HOMA-β, homeostasis model assessment β-cell function; HOMA-IR, homeostasis model assessment insulin resistance index; Incremental AUC, incremental area under curve during liquid mixed meal tolerance test; MISI, Matsuda insulin sensitivity index.

It was shown that baseline HbA_{1c} was significantly associated with the magnitude of HbA_{1c} reduction after add-on therapy. Several factors, including higher baseline HbA_{1c}, longer disease duration, younger age, and higher BMI have been reported to be associated with poorer glycemic control in patients with T2DM [18-20]. However, in the present study, only baseline HbA_{1c}, but not age, disease duration, BMI, or gender, independently predicted good glycemic control after adding glibenclamide or acarbose to metformin therapy. It was speculated that a small sample size, short follow-up duration, and limited OAD classes might be causes of inconsistent results.

In addition to decreased HbA_{1c} after add-on second OAD, the insulin secretion marker, DI_{120}, also improved in both groups. It is proposed that ameliorating hyperglycemia in subjects with type 2 diabetes might also have a helpful effect on β-cell failure by attenuating so-called glucose toxicity effect [21]. Particularly, our study also found that baseline DI_{120} was an independent predictor of glycemic control after adding glibenclamide or acarbose in the subjects inadequately controlled by metformin monotherapy. It has been reported that β-cell dysfunction can relate to HbA_{1c} in newly diagnosed T2DM [22,23], or in already OAD-treated adults with T2DM [24-26]. However, some of these studies were limited in that they disclosed only the cross-sectional relationship between β-cell function and glycemic parameters. Our study findings would extend the role of β-cell function in predicting the therapeutic response of HbA_{1c} levels. This result may be particularly important in Asian people with diabetes because it is proposed that β-cell dysfunction plays a major role in the pathogenesis of T2DM in this group of patients [5], and thus can determine HbA_{1c} response after use of oral hypoglycemic agents.

Several studies have reported that the addition of sulfonylurea or acarbose improved glycemic control in patients with T2DM unable to achieve or maintain glycemic control with metformin monotherapy alone [7,27]. It is generally accepted that sulfonylureas exert their hypoglycemic effect in part through direct action on pancreatic β-cells, which augments insulin secretion, although improvements in insulin sensitivity have also been reported in some, but not all studies [28-30]. Based on the anti-hyperglycemic mechanisms of sulfonylurea, it seemed reasonable that patients with higher baseline DI_{120} would have a better treatment response after adding glibencalmide, as seen in our patients.

Alpha-glucosidase inhibitors, such as acarbose, act via inhibiting disaccharide hydrolyzing enzymes in the small intestine, thereby decreasing glucose absorption and improving control over postprandial hyperglycemia. Acarbose has also been found to improve both insulin resistance and secretion indirectly in obese patients with T2DM [31,32]. It is postulated that insulin secretion and sensitivity might have improved at least in part through a decrease in glucose toxicity, because α-glucosidase inhibitors do not have a direct effect on insulin secretion or sensitivity. It was speculated that the improvement in HbA_{1c} in the patients in the acarbose group was a result of cooperative improvement of insulin sensitivity and secretion after

an amelioration of glucose toxicity, and thus residual β-cell function still played a role in the regulation of glycemic response after acarbose [33].

The strength of our study is the collection of insulin secretion or insulin sensitivity parameters during LMTT, which is not easily done in clinical studies. However, this LMTT was limited by that some subjects still used the investigational medication (e.g. sulfonylurea) in the evening before the 2nd LMTT, and thus the DI_{120} derived from the 2nd LMTT may reflect drug-stimulated rather than endogenous residual β-cell function. Second, our study enrolled small sample size of patients a single ethnic population, which might influence statistical power to analyze whether DI_{120} was a significant predictor of HbA_{1c} after combination therapy of metformin with glibenclamide or acarbose. Third, this study had short washout period, that might make the baseline HbA_{1c} at inclusion underestimated in patients taking sulfonylurea in comparison to those selected after metformin monotherapy failure. Finally, we did not evaluate the other choices of add-on medication. Further prospective studies with more patients and longer follow-up are needed to determine the association between DI_{120} and good glycemic control, especially in connection with different OADs.

Conclusions

Addition of glibenclamide or acarbose resulted in the significant HbA_{1c} reduction and improvement of DI_{120} in patients poorly controlled with metformin, and post-meal DI_{120} predicted the change in HbA_{1c} in each group after addition of glibenclamide or acarbose. It is suggested that residual β-cell function reserve may help to predict glycemic control response of combination of these agents.

Abbreviations

AUC_{glu}: Area under curve of glucose; AUC_{ins}: Area under curve of insulin; BMI: Body mass index; DI: Disposition index; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostasis model assessment insulin resistance index; HOMA-β: Homeostasis model assessmentβ-cell function index; LMTT: Liquid mixed meal tolerance test; MISI: Matsuda insulin sensitivity index; OAD: Oral anti-diabetic drug; PPG: Postprandial glucose; T2DM: Type 2 diabetes mellitus; UKPDS: United Kingdom prospective diabetes study.

Competing interests

I-T Lee received grants from MSD and Bayer Schering Pharma. S-T Tu has been a consultant for MSD, Bayer Schering Pharma, Eli Lilly, Astra-Zeneca, and BMS, and received honoraria from MSD, Bayer Schering Pharma, Eli Lilly, BMS, and Novo-Nordisc; he has also received grants from Bayer Schering Pharma. Wayne H-H Sheu has been a consultant for MSD, Roche, Bayer Schering Pharma, Eli Lilly, Astra-Zeneca, and BMS, and received honoraria from MSD, Roche, Bayer Schering Pharma, Eli Lilly, Astra-Zeneca, BMS, and Novo-Nordisc; he has also received grants from MSD and Bayer Schering Pharma. The other authors whose names are listed above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest, and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Authors' contributions

P-HC interpreted the data and wrote the manuscript; Y-TT interpreted the data and wrote the manuscript; J-SW conducted the study and performed the data collection; S-DL conducted the study; W-JL conducted the study and performed the data collection; S-LS conducted the study; I-TL conducted the study and performed data collection; S-TT conducted the study; Y-HT conducted the study; WH-HS conducted the study and interpreted the data; S-YL conducted the study, interpreted the data, and wrote the manuscript. All authors read and approved the final manuscript.

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