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ORIGINAL ARTICLE

Factors predicting therapeutic efficacy of combination treatment with sitagliptin and metformin in type 2 diabetic patients: the COSMETIC study

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Summary

Objective We assessed the predictive parameters for therapeutic efficacy of initial combination therapy with sitagliptin and metformin in drug-naïve type 2 diabetic patients.

Design, Patients, and Measurements In this 52-week treatment study, 150 patients (mean age, 54·9 ± 12·5 years) with type 2 diabetes and HbA1c of 7·0–10% were treated with sitagliptin 100 mg once and metformin 500 mg twice daily. To assess the predictive parameters for therapeutic efficacy, a multivariate regression analysis was performed with baseline fasting glucose, insulin, C-peptide, and glucagon levels, homoeostasis model assessment-insulin resistance (HOMA-IR) and β-cell function (HOMA-B), insulinogenic index (IGI, defined as 30–0 min insulin/30–0 min glucose), and area under the curve for glucose, insulin, and C-peptide obtained after 75-g oral glucose tolerance test.

Results After 52 weeks, mean HbA1c levels and fasting and postload 2-h glucose were significantly decreased from 8·7 ± 1·4% to 7·2 ± 1·3%, 9·2 ± 3·0 to 7·2 ± 1·8 mM, and 17·5 ± 5·1 to 10·9 ± 3·6 mM, respectively ($P < 0·01$). HOMA-B and IGI increased significantly from 50·3 ± 33·5 to 75·1 ± 32·8 and from 11·3 ± 1·3 to 35·0 ± 6·3 at 52 weeks, respectively ($P < 0·01$). Multivariate regression analysis indicated that the reduction in HbA1c was significantly associated with high baseline HbA1c, low IGI, and short duration of diabetes after adjusting for age, sex, body mass index, blood pressure, triglycerides, creatinine, high-sensitivity CRP, glucagon, C-peptide, HOMA-B, and HOMA-IR. No severe adverse events were observed.

Conclusion These results suggest that drug-naïve type 2 diabetic patients with low β-cell function would benefit the most from early initial combination therapy of sitagliptin and metformin.

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Introduction

It has been well established that inhibition of dipeptidyl peptidase-4 (DPP-4) reduces blood glucose levels in both fasting and postprandial states[1–3] and preserves pancreatic β-cell function in patients with type 2 diabetes.[4,5] The mechanism of action of DPP-4 inhibitors is to increase the levels of active incretin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP), which stimulate insulin secretion as well as insulin biosynthesis while inhibiting glucagon release from pancreatic islets.[6] DPP-4 inhibitors also have better safety and tolerability profiles (e.g., weight neutrality and less hypoglycaemia) compared with other hypoglycaemic agents. When considering combination therapy with DPP-4 inhibitors, metformin is the most commonly used agent, which has been shown to be effective and well tolerated from previous studies. Besides the glucose-lowering effect by reducing hepatic glucose output and improving insulin resistance, metformin without inhibiting DPP-4 activity[7,8] also increases active GLP-1 concentrations by 1·5- to 2-fold following an oral glucose load in obese, nondiabetic subjects.[9] Accordingly, this effect of metformin may provide a unique benefit when combined with DPP-4 inhibitors through a substantial enhancement of the incretin axis, which provides effective and potentially additive glycaemic improvement.[10,11]

Because of its favourable pharmacological properties, combination of a DPP-4 inhibitor and metformin has been increasingly used to achieve rapid glycaemic goal with low risk of hypoglycaemia and no weight gain and to delay the need for subsequent regimen changes.[10] DPP-4 inhibitors block DPP-4 enzyme and preserve endogenous incretins, whereas metformin increases the active form of GLP-1,[9] both of which may enhance the secretory function of pancreas. However, the response to DPP-4 inhibitors and metformin combination therapy may be different in individuals according to their pancreatic function and insulin resistance

status. In fact, previous studies with DPP-4 inhibitors showed different potency in glycaemic controls depending on various patient characteristics including the severity of diabetes and the use of other antidiabetic drug.[1,3,10,12–14] Consequently, it would be clinically important to identify the most appropriate candidate for this combination therapy. However, there has been little knowledge about the predictive factors for therapeutic efficacy of initial combination therapy with DPP-4 inhibitors and metformin.

In this study, we investigated the parameters that can predict the therapeutic efficacy of combination of sitagliptin, a DPP-4 inhibitor, and metformin in drug-naïve type 2 diabetic patients.

Subjects and methods

Study subjects

We screened 174 patients with type 2 diabetes mellitus (DM) from the diabetes clinic at Seoul National University Bundang Hospital, Seongnam, Korea, from June to December 2009. Patients aged 20–80 years with HbA1c of 7·0–10% and not on antidiabetic medications were eligible to participate. We excluded those with type 1 diabetes, gestational diabetes, or diabetes with secondary causes, significant renal impairment (estimated creatinine clearance <60 ml/min), or elevated (more than twofold the upper limit of normal) alanine aminotransferase or aspartate aminotransferase. Patients with acute or chronic diseases and who were on medications known to affect glycaemic control were also excluded. Eligible patients (n = 150) received sitagliptin 100 mg once daily and metformin 500 mg twice a day for 52 weeks and were followed up at weeks 12, 24, 36, and 52 for efficacy and safety assessments (Fig. S1). Compliance with medication was assessed by pill count at every visit. Of those enrolled, 136 patients (90·7%) completed the 52-week treatment. The protocol was reviewed and approved by the institutional review board of Seoul National University Bundang Hospital (No. B-0909/083-008) and performed in accordance with the Declaration of Helsinki. All patients gave written informed consent. This study was performed under the registration to the ClinicalTrial.gov (NCT00969566).

Measurement of anthropometric and biochemical parameters

Height and body weight were measured to the nearest 0·1 cm and 0·1 kg, respectively. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the narrowest point between the lower limit of the ribcage and the iliac crest, to the nearest 0·1 cm. Blood pressure was recorded three times between 07:00 and 09:00 h, after the subjects had been in a relaxed state for at least 10 min and a 5-min resting period was given between each measurement. Family history of diabetes was also obtained. After 14 h of overnight fast, venous blood samples were drawn from the antecubital vein between 07:00 and 09:00 h. Plasma was separated by centrifugation (1006 ***g***, 20 min, 4 °C), and biochemical measurements were conducted immediately. For the evaluation of glucose metabolism, plasma glucose, insulin, C-peptide, and glucagon levels were measured at fasting status; 75-g oral glucose tolerance test (OGTT) was carried out, and fasting and postload 30- and 120-min glucose levels were measured. Plasma glucose levels were measured by Hitachi 747 chemistry analyser (Hitachi, Tokyo, Japan), and plasma insulin, C-peptide, and glucagon concentrations were measured by radioimmunoassay (Linco, St. Louis, MO, USA). HbA1c was measured by immunoturbidimetric assay with a Cobra Integra 800 automatic analyser (Roche Diagnostics, Basel, Switzerland). The fasting plasma concentrations of total cholesterol, triglyceride, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were measured using the Hitachi 747 chemistry analyser. Serum high-sensitivity CRP (hsCRP) levels were measured by high-sensitivity automated immunoturbidimetric method (Denka Seiken CRP II Latex X2, Tokyo, Japan). Urinary albumin levels were measured by turbitimer assay (A&T 502X; A&T, Tokyo, Japan), and urine creatinine levels were measured by the Jaffe method (Hitachi 7170; Hitachi) to calculate spot urine albumin-to-creatinine ratio.

Measurement of pancreatic β-cell function and insulin resistance

Pancreatic β-cell function and insulin resistance were calculated using the homoeostasis model assessment (HOMA) and insulinogenic index (IGI).[15,16] The IGI, as an estimate of early insulin secretion, was calculated by dividing the increment in insulin during the first 30 min by the increment in glucose over the same period [30–0 min insulin (pM)/30–0 min glucose (mM)]. Area under the curve for glucose, insulin, and C-peptide ($AUC_{glucose}$, $AUC_{insulin}$, and $AUC_{C\text{-}peptide}$) was calculated by a trapezoidal method.

Efficacy

Changes in HbA1c from baseline to 24 and 52 weeks were measured for primary efficacy of initial combination with sitagliptin and metformin in this study. Changes in fasting plasma glucose (FPG), insulin, C-peptide, glucagon, postload 2-h glucose (2-h PG), homoeostasis model assessment-insulin resistance (HOMA-IR), homoeostasis model assessment β-cell function (HOMA-B), IGI, lipids profiles, hsCRP, urine albumin-to-creatinine ratio, BMI, and WC at weeks 24 and 52 from baseline were also evaluated.

Predictors for response to combination of sitagliptin and metformin

To assess the predictive parameters for therapeutic efficacy of initial combination with sitagliptin and metformin, correlation analysis between changes in HbA1c and various related parameters was performed. Multiple regression analyses with age, sex, BMI, blood pressure, lipid profiles, kidney function, hsCRP, and various markers for pancreatic beta-cell function or insulin resistance were performed with HbA1c change as the dependent variable.

Safety assessment

Data were collected on clinical and laboratory adverse experiences, physical examinations, vital signs, and body weight throughout the

52-week treatment period. Patients were educated to measure and record their blood glucose concentration whenever they experienced a hypoglycaemic symptom. Severe hypoglycaemia was defined by blood glucose <2·8 mM (50 mg/dl) with hypoglycaemic symptoms. Hypoglycaemia was defined by blood glucose <3·9 mM (70 mg/dl) with or without hypoglycaemic symptoms. These entries were transcribed in the adverse event form by the study nurses. Patients were discontinued for the lack of efficacy based on glycaemic control status: FPG >15·0 mM (270 mg/dl) or HbA1c >10·0% at week 12 and FPG >13·3 mM (240 mg/dl) or HbA1c >9·0% from week 24 to week 52. All adverse experiences were assessed by investigators for their relationship to study drugs. Clinical adverse experiences of interest included hypoglycaemia and gastrointestinal adverse symptoms such as nausea, vomiting, abdominal discomfort, and diarrhoea. Liver function and kidney function were also monitored for the assessment of adverse effects.

Statistical analysis

All continuous variables with normal distributions were expressed as means ± SD, and categorical data were expressed as percentages. Paired *t*-test was used to compare the continuous variables between pre- and post-treatment. Pearson's correlation analysis was used to determine the relationship between change in HbA1c and various parameters. To assess the multicollinearity of the regression model, we checked for the variance inflation factor. A variance inflation factor >10 suggests an erroneous model and was not included in the models. To evaluate the independent relationship between the change in HbA1c and baseline glucose homoeostasis, we established four separate multivariate regression models. First, we examined the adjusted effects of baseline C-peptide level on the change in HbA1c adjusted for age, sex, BMI, blood pressure, HbA1c, triglycerides, creatinine, hsCRP, glucagon, HOMA-IR, and duration of diabetes (Model 1); model 2 was adjusted for HOMA-B instead of C-peptide; model 3 was adjusted for IGI instead of C-peptide or HOMA-B. In model 4, C-peptide, HOMA-B, and IGI were all included. A level of $P < 0{\cdot}05$ was considered statistically significant. All analyses were performed using the SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Among 150 patients, 59·3% were men ($n = 89$) and 40·7% were women ($n = 61$; Table 1). Mean age was 54·8 ± 12·5 years, and the mean duration of diabetes was 6·1 ± 6·4 years. Mean BMI was 25·3 ± 3·4, which was comparable to data from large Asian cohorts.[17] Systolic and diastolic blood pressures were <140/90 mmHg, and lipid profiles were within the acceptable range. On average, patients in this study were moderately hyperglycaemic [mean HbA1c = 8·7 ± 1·4%, FPG = 9·2 ± 3·0 mM (166·3 ± 54·8 mg/dl), and 2-h PG = 17·5 ± 5·1 mM (315·6 ± 92·4 mg/dl), respectively, at baseline]. C-peptide levels were above 0·2 nM (0·6 ng/ml) in all patients. After enrolment, 136 patients (90·7%) completed the 52 weeks of treatment.

Effects of initial combination of sitagliptin and metformin on glycaemic control and other metabolic and anthropometric parameters

Initial combination therapy of sitagliptin and metformin significantly reduced the HbA1c level by 1·6% (from 8·7 ± 1·4 to 7·1 ± 1·2, $P < 0{\cdot}01$) at week 24% and 1·5% (from 8·7 ± 1·4 to 7·2 ± 1·3, $P < 0{\cdot}01$) at week 52 (Table 1). Additional decrease in HbA1c of 0·3% from week 12 to week 24 was also statistically significant ($P < 0{\cdot}01$), but from week 24 and thereafter, HbA1c levels were stable (Fig. 1). FPG and 2-h PG were also significantly decreased over 52 weeks (Table 1 and Fig. 1).

The combination therapy of sitagliptin and metformin has significantly increased plasma insulin level, HOMA-B, and IGI, which are the parameters of pancreatic β-cell secretory function but did not change C-peptide level. Total cholesterol and triglyceride concentrations were also reduced significantly over 52 weeks. There were no changes in BMI, waist circumference, and blood pressures (Table 1).

Correlation between reduction in HbA1c over 52 weeks and various parameters at baseline

Reduction in HbA1c positively correlated with FPG, 2-h PG, $AUC_{glucose}$, and HOMA-IR at baseline (Table S1). There were negative correlations between reduction in HbA1c and age, DM duration, creatinine levels, $AUC_{C\text{-}peptide}$, HOMA-B, and IGI.

Reduction in HbA1c according to various parameters for glucose homoeostasis

Reductions in HbA1c were evaluated according to the baseline quartiles of C-peptide, IGI, HOMA-B, and HOMA-IR over the 52-week treatment of sitagliptin and metformin combination (Fig. 2). The magnitude of HbA1c reduction was greatest in the lowest quartile group of IGI (*vs* other three quartiles, $P < 0{\cdot}01$). A similar trend was found in HOMA-B but not in C-peptide quartiles. There was no difference in HbA1c reduction according to quartiles of HOMA-IR.

Phenotype comparison between patients with greatest and least response to combination treatment with sitagliptin and metformin

Patients' phenotype was compared according to the changes in their HbA1c (ΔHbA1c) during the 52-week treatment with sitagliptin and metformin (Table 2). Patients in the highest quartile of ΔHbA1c [median (range) = 3·3 (2·5–5·4)] were younger and had diabetes for shorter duration, higher fasting and postload 2-h glucose concentration, higher baseline HbA1c level, and lower creatinine level than those in the lowest quartile of ΔHbA1c [0·3 (0·2–0·7)]. HOMA-B, IGI, and $AUC_{C\text{-}peptide}$ were lower, while HOMA-IR and $AUC_{glucose}$ were higher in patients in the highest quartile of ΔHbA1c compared with their counterpart in the lowest quartile of ΔHbA1c.

Table 1. Changes in anthropometric and biochemical parameters for 52-week treatment of sitagliptin and metformin combination in drug-naïve patients with type 2 diabetes

	Baseline	24 weeks	52 weeks
Body mass index (kg/m^2)	25·3 ± 3·4	25·2 ± 3·4	25·1 ± 3·2
Waist circumference (cm)	89·1 ± 8·5	89·4 ± 8·1	89·0 ± 10·1
Systolic blood pressure (mmHg)	126·0 ± 15·8	130·8 ± 16·4	128·5 ± 12·4
Diastolic blood pressure (mmHg)	78·3 ± 11·5	79·3 ± 11·1	78·9 ± 9·8
Fasting plasma glucose (mM)	9·2 ± 3·0	7·5 ± 2·0*	7·2 ± 1·8*
Postload 30-m glucose (mM)	15·2 ± 3·9	12·1 ± 3·4*	12·3 ± 2·0*
Postload 2-h glucose (mM)	17·5 ± 5·1	11·9 ± 4·5*	10·9 ± 3·6*
HbA1c (%)	8·7 ± 1·4	7·1 ± 1·2*	7·2 ± 1·3*
Fasting insulin (pM)	81·3 ± 34·0	97·2 ± 43·1*	91·7 ± 37·5*
Postload 30-m insulin (pM)	148·6 ± 12·5	290·3 ± 38·2*	271·5 ± 72·9*
Postload 2-h insulin (pM)	232·7 ± 29·9	423·0 ± 74·3*	341·0 ± 107·6*
Fasting C-peptide (ng/ml)	2·2 ± 1·1	2·0 ± 0·9	1·9 ± 1·0
Postload 30-m C-peptide (ng/ml)	2·9 ± 0·2	3·8 ± 0·3*	3·3 ± 0·6*
Postload 2-h C-peptide (ng/ml)	5·0 ± 0·3	6·7 ± 0·6*	5·6 ± 0·9*
Fasting glucagon (pg/ml)	56·2 ± 17·1	51·1 ± 13·5	49·2 ± 11·8
Total cholesterol (mM)	4·9 ± 1·0	4·6 ± 0·9*	4·7 ± 1·1*
Triglycerides (mM)	1·9 ± 1·3	1·6 ± 1·0*	1·6 ± 0·9*
HDL cholesterol (mM)	1·3 ± 0·3	1·2 ± 0·3	1·2 ± 0·3
LDL cholesterol (mM)	2·9 ± 0·9	2·5 ± 0·8*	2·6 ± 0·7*
AST (IU/l)	23·6 ± 10·2	23·8 ± 12·9	22·9 ± 9·3
ALT (IU/l)	31·2 ± 22·4	29·2 ± 22·9	27·5 ± 18·4
Creatinine (μM)	76·3 ± 15·3	68·6 ± 15·3	68·6 ± 15·3
hsCRP (mg/l)	0·16 ± 0·27	0·15 ± 0·48	0·13 ± 0·31
Urine albumin-to-creatinine (mg/g)	32·8 ± 71·2	15·0 ± 16·7	17·6 ± 12·5
HOMA-B	50·3 ± 33·5	81·5 ± 51·1*	75·1 ± 32·8*
HOMA-IR	4·9 ± 2·6	4·7 ± 2·6	4·5 ± 2·2
Insulinogenic index	11·3 ± 1·3	41·3 ± 7·5*	35·0 ± 6·3*
$AUC_{glucose}$	31·6 ± 7·4	22·8 ± 7·2*	21·3 ± 5·7*
$AUC_{insulin}$	345·2 ± 278·5	627·1 ± 386·1*	544·5 ± 226·4*
$AUC_{C\text{-}peptide}$	7·2 ± 2·9	9·3 ± 3·4*	8·4 ± 2·9*

HOMA-IR and HOMA-B, homoeostasis model assessment for insulin resistance and beta-cell function; AUC, area under the curve; ALT, alanine aminotransferase; AST, aspartate aminotransferase; hsCRP, high-sensitivity CRP. *$P < 0·05$ *vs* baseline.

Predictive parameters for therapeutic efficacy of initial combination therapy with sitagliptin and metformin

Multiple regression analyses were performed for the reduction in HbA1c for the 52-week treatment of sitagliptin and metformin combination (Table 3). Age, sex, BMI, family history of DM, systolic blood pressure, triglycerides, creatinine, hsCRP, glucagon, duration of DM, HOMA-IR, and C-peptide were used as independent variables in model 1. Instead of C-peptide, HOMA-B and IGI were included in model 2 and model 3, respectively. C-peptide, HOMA-B, and IGI were all included in model 4.

In model 1, high baseline HbA1c level was a significant independent predictor for a reduction in HbA1c by initial combination therapy with sitagliptin and metformin, although C-peptide level had a borderline significance. In model 2, high baseline HbA1c, low HOMA-B, and short duration of DM were independent predictors. In model 3, high baseline HbA1c, low IGI, and short duration of DM were found to be independent predictors for a reduction in HbA1c by combined therapy with sitagliptin and metformin. When C-peptide, HOMA-B, and IGI were all included in the multivariate regression model (model 4), the significance of high baseline HbA1c, low IGI, and short duration of DM were maintained as independent predictors.

Safety and tolerability

The incidence of adverse experience was modest (Table S2). All adverse experiences and drug-related adverse experiences were 21·3% and 9·3% in the coadministration of sitagliptin with metformin, respectively. Serious adverse experiences were found in two patients, and one drug-related serious adverse experience was reported (severe abdominal pain). Ten patients (6·7%) discontinued therapy because of adverse experiences. There were no episodes of severe hypoglycaemia in all patients. The proportion of patients reporting gastrointestinal adverse experiences was 10·7% ($n = 16$).

Discussion

In this study, initial combination treatment of sitagliptin and metformin was assessed for therapeutic efficacy in drug-naïve patients with type 2 diabetes. After 52 weeks of follow-up, the mean HbA1c level decreased significantly. Reduction in HbA1c was significantly

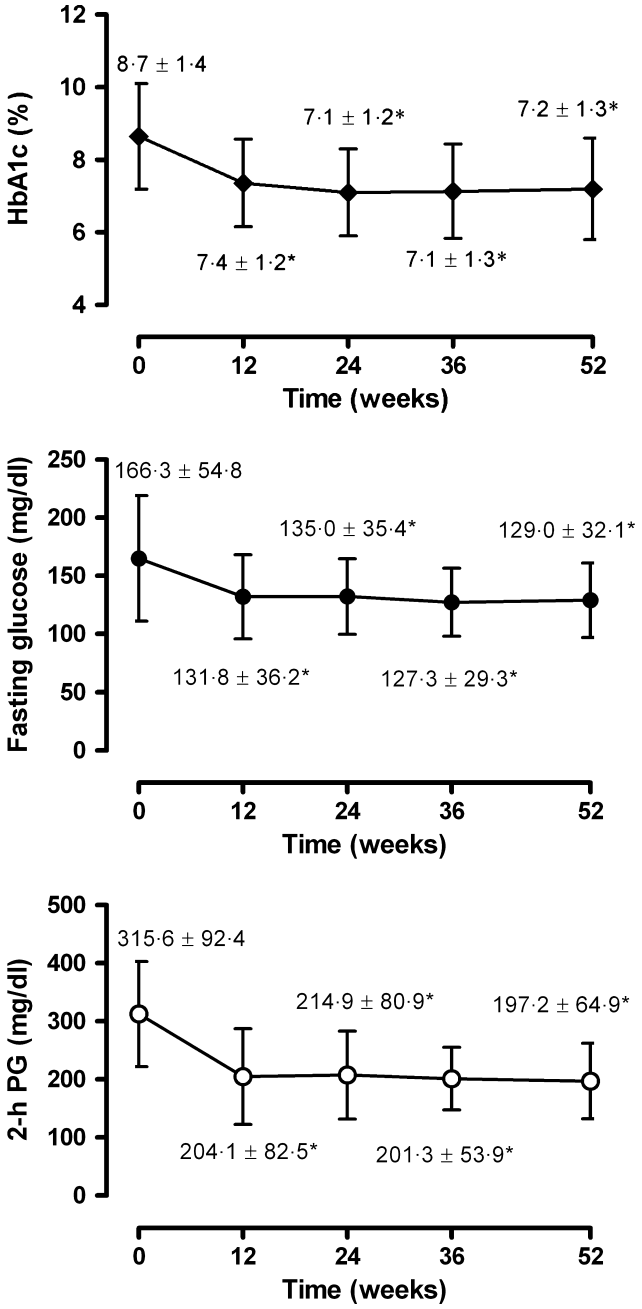

Fig. 1 Changes in HbA1c, fasting plasma and postprandial 2-h glucose (2-h PG) over 52-week treatment of sitagliptin and metformin combination (*$P < 0{\cdot}05$ *vs* baseline).

greater in the lowest quartile of IGI or HOMA-B group than other quartiles ($P < 0{\cdot}01$). In multiple regression analysis, reduction in HbA1c was significantly associated with high baseline HbA1c level, low IGI at baseline, and short duration of DM after adjusting for various parameters including HOMA-IR.

The initial combination of sitagliptin and metformin produced clinically meaningful reductions in HbA1c, FPG, and 2-h PG. After a substantial reduction in HbA1c (1·3%) at 12 weeks, HbA1c level continued to decrease modestly but significantly at 24 and 52 weeks (1·6% and 1·5%, respectively, both $P < 0{\cdot}05$). There were greater reductions in 2-h PG compared with FPG at 24 and 52 weeks, which was indicative of pharmacologic property of DPP-4 inhibitors. Previous randomized controlled studies showed that the initial combination of sitagliptin (100 mg/day) and metformin (1000 mg/day) reduced HbA1c more significantly than metformin or sitagliptin monotherapy during 24–54 weeks of treatment (1·4–1·6% *vs* 0·8% or 1·0%, respectively).[10] Although there was no comparator group in our study, our results of combination treatment efficacy were comparable with these studies.

Among various factors assessed in our study, high baseline HbA1c level was significantly associated with greater reduction in HbA1c with sitagliptin and metformin treatment, which is consistent with previous data suggesting greater glucose-lowering effect of oral antidiabetic medications in patients with higher baseline HbA1c level.[18] Besides baseline HbA1c level, the low IGI was a significant predictor of better treatment response in the multiple regression analyses including baseline HbA1c and various estimates of pancreatic β-cell function or insulin resistance. This result suggests that low IGI remains as an independent predictor for achieving better glycaemic control by initial combination treatment of sitagliptin and metformin regardless of baseline HbA1c levels. Many studies have proven that IGI is temporarily suppressed by high glucose condition[16] and the reduced IGI is reversed by glucose lowering by antidiabetic medications or lifestyle modification.[19,20] In addition, reactive oxygen species (ROS) and endoplasmic reticulum stress are generated during acute hyperglycaemia,[21,22] and these may play a role in suppressing pancreatic β-cell function and subsequent reduction in IGI.[23] This process can also be attenuated by appropriate use of antidiabetic agents.[24] Thus, the low IGI in the early phase of type 2 diabetes may indicate the reversible potential of pancreatic β-cell dysfunction.

Alternatively, reduced IGI and short duration of DM may indicate the status of suppressed incretin receptor expression by high glucose concentration. Under this condition, it is possible that the use of metformin may have reversed the reduced expression of incretin receptor. A recent animal study has demonstrated that metformin enhances the expression of the genes encoding the receptors for both GLP-1 and GIP in mouse islets and also increases the effects of GLP-1 and GIP on insulin secretion from pancreatic β-cells.[25] As incretin receptor recovers, sitagliptin can enhance the incretin effect and induce glucose lowering more effectively.[26] In fact, the HbA1c level was most reduced by 3·6% in those with the lowest quartile group of IGI and shorter duration of DM, defined as <1 year. These findings support the rationale for the combined use of DPP 4 inhibitors and metformin in the early period of type 2 diabetes.

In this study, HOMA index or IGI was used to evaluate the pancreatic β-cell function. The HOMA model has a physiological basis of hepatic and peripheral glucose efflux and uptake and has been validated against a variety of physiological methods.[27–29] The IGI is a more dynamic estimate of the first-phase insulin secretion, which is calculated from the OGTT.[16] IGI has also been validated in many studies ranging from healthy subjects to diverse phenotypes such as impaired glucose homoeostasis, obesity, and chronic renal failure.[30–36] However, HOMA index or IGI can only provide an estimate, and not a precise measurement of pancreatic β-cell function, which requires appropriate use and cautious interpretation.

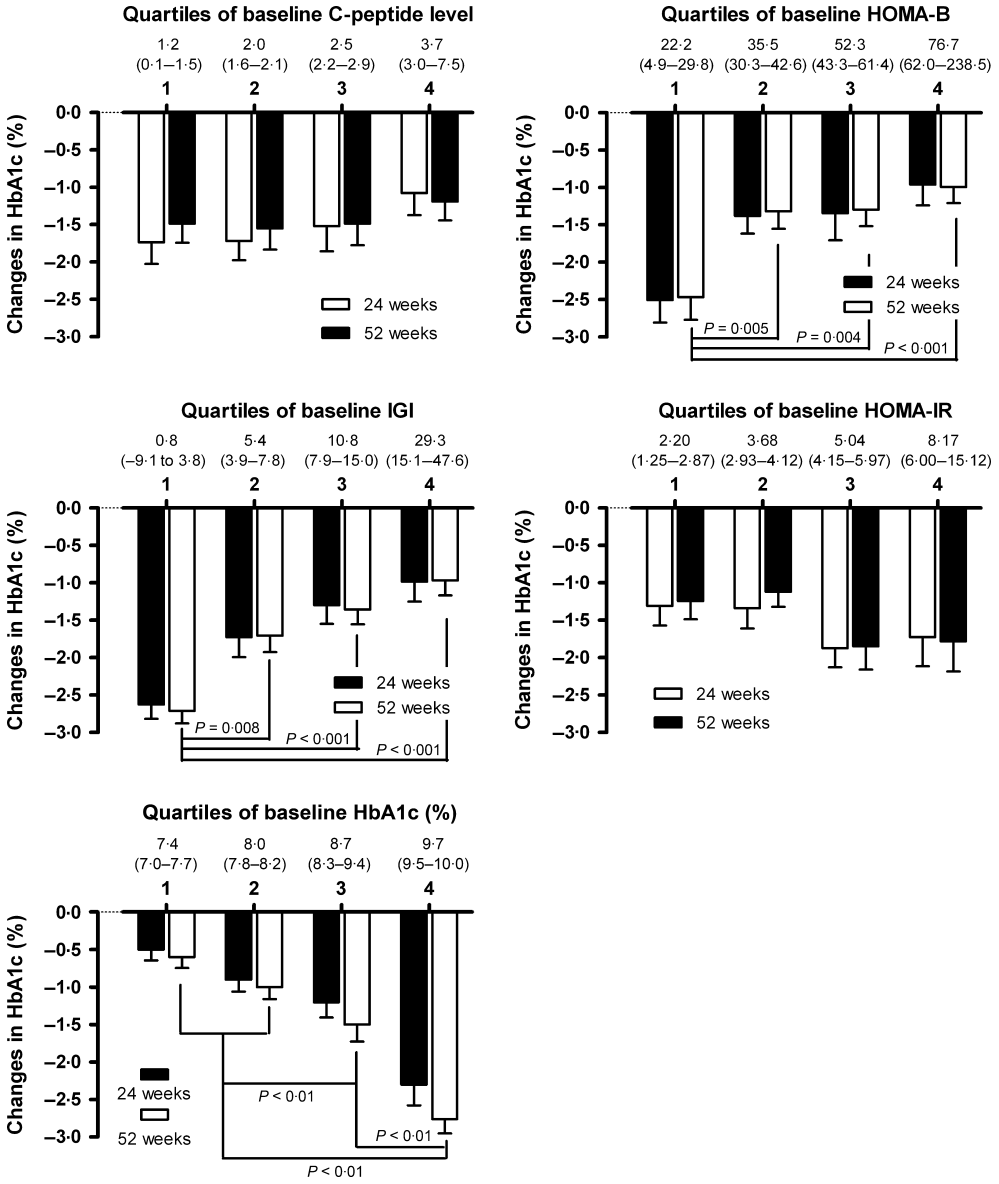

Fig. 2 Changes in HbA1c according to quartiles of baseline C-peptide, insulinogenic index, homoeostasis model assessment β-cell function, and homoeostasis model assessment-insulin resistance over 52-week treatment of sitagliptin and metformin combination.

Interestingly, there has been a debate on the role of metformin in inhibiting DPP-4 activity. DPP-4 activity in the circulation has been reported to be reduced in rodents and humans treated with metformin.[37,38] However, *in vitro* studies have shown that metformin does not directly inhibit DPP-4 activity.[7,8,37] Maida *et al.*[25] also found that metformin at doses exhibiting GLP-1-increasing effects exerted no effects on plasma DPP-4 levels. Accordingly, it is unlikely that the elevated GLP-1 levels after the metformin treatment can be explained by the decreased DPP-4 activity. Taken together, the ability of metformin to increase GLP-1 levels independent of DPP-4 activity suggests that there may be a direct benefit in terms of incretin action when metformin is combined with DPP-4 inhibitors.

In this study, there was a 1·0% reduction in HbA1c in the highest quartile of IGI. Higher IGI implies that patients in this group have less β-cell dysfunction and relatively more insulin resistance, and therefore, improvements in HbA1c in this group can be explained by either the metformin effect or the glucagon-lowering effect of sitagliptin.

In terms of body weight and waist circumference, there were no changes in these parameters during the 52 weeks of combination treatment. This result is consistent with previous findings showing that metformin or sitagliptin treatment has neutral or small reductions in obesity indices.[1,3,39]

The combination treatment was generally well tolerated in this study. There were 9·3% drug-related adverse events such as gastrointestinal adverse experiences, which were most likely due to metformin treatment. Despite marked improvements in glycaemic control, there were no cases of severe hypoglycaemia in this study.

There are several strengths to our study. First, dynamic data such as OGTT were obtained and analysed for pancreatic β-cell

Table 2. Phenotype comparison between patients with greatest and least response to combination treatment with sitagliptin and metformin*

	Lowest quartile of ΔHbA1c [0·3 (0·2–0·7)]†		Highest quartile of ΔHbA1c [3·3 (2·5–5·4)]†		
	Mean	SD	Mean	SD	*P*
Age (years)	56·7	13·8	49·4	10·4	0·019
Body mass index (kg/m^2)	24·9	3·6	25·8	3·9	0·264
Duration of DM (years)	3·4	4·2	1·1	2·3	0·008
Systolic blood pressure (mmHg)	127·9	15·0	128·8	16·6	0·812
Fasting plasma glucose (mM)	8·0	1·7	11·4	3·8	<0·001
Postload 2-h glucose (mM)	14·4	4·4	20·9	5·0	<0·001
HbA1c (%)	8·2	0·8	9·2	1·2	<0·001
Fasting insulin (pM)	81·3	38·2	84·0	41·0	0·792
Fasting C-peptide (ng/ml)	2·3	1·1	2·0	0·9	0·184
Fasting glucagon (pg/ml)	50·1	18·2	52·0	17·0	0·679
Triglycerides (mM)	1·8	1·1	1·9	1·5	0·684
ALT (IU/l)	29·8	24·2	30·4	20·7	0·917
Creatinine (μM)	77·8	13·7	70·2	16·8	0·033
hsCRP (mg/l)	0·05	0·06	0·20	0·38	0·169
Urine albumin-to-creatinine (mg/g)	25·6	28·6	15·6	27·2	0·280
HOMA-B	58·8	35·4	37·5	24·6	0·008
HOMA-IR	4·2	2·4	6·1	3·4	0·011
Insulinogenic index	22·3	10·5	7·8	12·4	0·002
$AUC_{glucose}$	28·2	6·6	33·9	8·3	0·080
$AUC_{insulin}$	341·7	125·0	285·4	195·2	0·925
$AUC_{C\text{-}peptide}$	8·0	3·1	5·9	2·5	0·077

*Lowest and highest quartile of ΔHbA1c was used for low responders and high responders, respectively.
†Median [range].
ALT, alanine aminotransferase; AUC, area under the curve; DM, diabetes mellitus; HOMA-B, homoeostasis model assessment β-cell function; HOMA-IR, homoeostasis model assessment-insulin resistance; hsCRP, high-sensitivity CRP.

Table 3. Multiple regression analysis for changes in HbA1c for 52-week treatment of sitagliptin and metformin combination

	Model 1		Model 2		Model 3		Model 4	
	β	*P*	β	*P*	β	*P*	β	*P*
Age (years)	0·130	0·614	0·036	0·835	0·071	0·672	0·002	0·991
Sex (1 = male, 2 = female)	0·241	0·418	0·014	0·941	0·032	0·858	0·314	0·238
BMI (kg/m^2)	−0·122	0·682	−0·057	0·731	−0·153	0·425	−0·090	0·710
SBP (mmHg)	0·154	0·434	0·159	0·279	0·231	0·109	0·297	0·185
HbA1c (%)	0·684	<0·001	0·651	<0·001	0·515	0·001	0·497	0·002
Triglyceride (mM)	0·332	0·160	0·140	0·357	0·435	0·061	0·451	0·053
Creatinine (μM)	−0·222	0·464	−0·088	0·669	−0·010	0·960	−0·172	0·534
hsCRP (mg/l)	0·154	0·454	0·130	0·333	0·065	0·619	0·186	0·270
Glucagon (pg/ml)	−0·232	0·136	−0·296	0·120	−0·293	0·051	−0·333	0·134
Duration of DM (years)	−0·329	0·170	−0·399	0·024	−0·462	0·018	−0·521	0·010
HOMA-IR	0·366	0·197	0·307	0·145	0·401	0·109	0·340	0·132
C-peptide (ng/ml)	−0·417	0·086	–	–	–	–	−0·039	0·858
HOMA-B	–	–	−0·394	0·006	–	–	−0·204	0·311
Insulinogenic index	–	–	–	–	−0·426	0·004	−0·382	0·008

SBP, systolic blood pressure; DM, diabetes mellitus; HOMA-B, homoeostasis model assessment β-cell function; HOMA-IR, homoeostasis model assessment-insulin resistance; hsCRP, high-sensitivity CRP.

function and insulin resistance. Second, over 90% of study subjects have completed the 52-week treatment regimen. Third, multiple parameters were adjusted in the multivariate regression analysis.

There are also many limitations in this study. First, although the current study aimed to assess the predictive parameters for therapeutic efficacy of initial combination therapy rather than its superior efficacy over other interventions, the absence of a control group

and the lack of randomization and blinding may have introduced bias in selecting subjects and evaluating study results. Second, the gold standard technique that evaluates pancreatic β-cell function and insulin resistance, such as a clamp study, was not used. Third, the 52-week study duration may not be long enough to assess long-term results. Lastly, information on duration of DM was obtained from patients' response and not confirmed by their medical records.

In summary, initial combination therapy with sitagliptin and metformin provided a substantial glycaemic improvement possibly owing to synergistic effects in drug-naïve patients with type 2 diabetes. Low IGI and short duration of DM as well as high baseline HbA1c level were significant predictors for greater treatment response. This result suggests that sitagliptin and metformin coadministration can be most effective in glucose lowering when given to drug-naïve patients with low β-cell function during the early stage of DM.

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Conflict of interest

Nothing to declare. The funding agency had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1 Nauck, M.A., Meininger, G., Sheng, D. *et al.* (2007) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes, Obesity & Metabolism*, **9**, 194–205.

2 Nonaka, K., Kakikawa, T., Sato, A. *et al.* (2008) Efficacy and safety of sitagliptin monotherapy in Japanese patients with type 2 diabetes. *Diabetes Research and Clinical Practice*, **79**, 291–298.

3 Aschner, P., Katzeff, H.L., Guo, H. *et al.* (2010) Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. *Diabetes, Obesity & Metabolism*, **12**, 252–261.

4 Xu, L., Man, C.D., Charbonnel, B. *et al.* (2008) Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on beta-cell function in patients with type 2 diabetes: a model-based approach. *Diabetes, Obesity & Metabolism*, **10**, 1212–1220.

5 Brazg, R., Xu, L., Dalla, M.C. *et al.* (2007) Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and beta-cell function in patients with type 2 diabetes. *Diabetes, Obesity & Metabolism*, **9**, 186–193.

6 Herman, G.A., Bergman, A., Stevens, C. *et al.* (2006) Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism*, **91**, 4612–4619.

7 Hinke, S.A., Kuhn-Wache, K., Hoffmann, T. *et al.* (2002) Metformin effects on dipeptidylpeptidase IV degradation of glucagon-like peptide-1. *Biochemical and Biophysical Research Communications*, **291**, 1302–1308.

8 Yasuda, N., Inoue, T., Nagakura, T. *et al.* (2002) Enhanced secretion of glucagon-like peptide 1 by biguanide compounds. *Biochemical and Biophysical Research Communications*, **298**, 779–784.

9 Mannucci, E., Ognibene, A., Cremasco, F. *et al.* (2001) Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. *Diabetes Care*, **24**, 489–494.

10 Goldstein, B.J., Feinglos, M.N., Lunceford, J.K. *et al.* (2007) Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care*, **30**, 1979–1987.

11 Williams-Herman, D., Johnson, J., Teng, R. *et al.* (2010) Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. *Diabetes, Obesity & Metabolism*, **12**, 442–451.

12 Rosenstock, J., Brazg, R., Andryuk, P.J. *et al.* (2006) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clinical Therapeutics*, **28**, 1556–1568.

13 Kim, S.A., Shim, W.H., Lee, E.H. *et al.* (2011) Predictive clinical parameters for the therapeutic efficacy of sitagliptin in Korean type 2 diabetes mellitus. *Diabetes & Metabolism Journal*, **35**, 159–165.

14 Kim, W.J., Park, C.Y., Jeong, E.H. *et al.* (2011) Retrospective analysis on the efficacy, safety and treatment failure group of sitagliptin for mean 10-month duration. *Diabetes & Metabolism Journal*, **35**, 290–297.

15 Matthews, D.R., Hosker, J.P., Rudenski, A.S. *et al.* (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, **28**, 412–419.

16 Seltzer, H.S., Allen, E.W., Herron Jr, A.L. *et al.* (1967) Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. *Journal of Clinical Investigation*, **46**, 323–335.

17 Ni, M.C., Rodgers, A., Pan, W.H. *et al.* (2004) Body mass index and cardiovascular disease in the Asia-Pacific region: an overview of 33 cohorts involving 310 000 participants. *International Journal of Epidemiology*, **33**, 751–758.

18 Sherifali, D., Nerenberg, K., Pullenayegum, E. *et al.* (2010) The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. *Diabetes Care*, **33**, 1859–1864.

19 Pratley, R.E., Schweizer, A., Rosenstock, J. *et al.* (2008) Robust improvements in fasting and prandial measures of beta-cell function with vildagliptin in drug-naive patients: analysis of pooled vildagliptin monotherapy database. *Diabetes, Obesity & Metabolism*, **10**, 931–938.

20 Michishita, R., Shono, N., Kasahara, T. *et al.* (2008) Effects of low intensity exercise therapy on early phase insulin secretion in overweight subjects with impaired glucose tolerance and type 2 diabetes mellitus. *Diabetes Research and Clinical Practice*, **82**, 291–297.

21 King, G.L., Kunisaki, M., Nishio, Y. *et al.* (1996) Biochemical and molecular mechanisms in the development of diabetic vascular complications. *Diabetes*, **45**(Suppl 3), S105–S108.

22 Giugliano, D., Ceriello, A. & Paolisso, G. (1996) Oxidative stress and diabetic vascular complications. *Diabetes Care*, **19**, 257–267.

23 Miyazaki, Y., Kawano, H., Yoshida, T. *et al.* (2007) Pancreatic B-cell function is altered by oxidative stress induced by acute hyperglycaemia. *Diabetic Medicine*, **24**, 154–160.
24 van Raalte, D.H. & Diamant, M. (2011) Glucolipotoxicity and beta cells in type 2 diabetes mellitus: target for durable therapy? *Diabetes Research and Clinical Practice*, **93**(Suppl 1), S37–S46.
25 Maida, A., Lamont, B.J., Cao, X. *et al.* (2011) Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor-alpha in mice. *Diabetologia*, **54**, 339–349.
26 Cho, Y.M. & Kieffer, T.J. (2010) New aspects of an old drug: metformin as a glucagon-like peptide 1 (GLP-1) enhancer and sensitiser. *Diabetologia*, **54**, 219–222.
27 Hermans, M.P., Levy, J.C., Morris, R.J. *et al.* (1999) Comparison of tests of beta-cell function across a range of glucose tolerance from normal to diabetes. *Diabetes*, **48**, 1779–1786.
28 Emoto, M., Nishizawa, Y., Maekawa, K. *et al.* (1999) Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. *Diabetes Care*, **22**, 818–822.
29 Hosker, J.P., Matthews, D.R., Rudenski, A.S. *et al.* (1985) Continuous infusion of glucose with model assessment: measurement of insulin resistance and beta-cell function in man. *Diabetologia*, **28**, 401–411.
30 Simonis-Bik, A.M., Boomsma, D.I., Dekker, J.M. *et al.* (2011) The heritability of beta cell function parameters in a mixed meal test design. *Diabetologia*, **54**, 1043–1051.
31 Elder, D.A., Woo, J.G. & D'Alessio, D.A. (2010) Impaired beta-cell sensitivity to glucose and maximal insulin secretory capacity in adolescents with type 2 diabetes. *Pediatric Diabetes*, **11**, 314–321.
32 Tanabe, N., Saito, K., Yamada, Y. *et al.* (2009) Risk assessment by post-challenge plasma glucose, insulin response ratio, and other indices of insulin resistance and/or secretion for predicting the development of type 2 diabetes. *Internal Medicine*, **48**, 401–409.
33 Mari, A., Tura, A., Pacini, G. *et al.* (2008) Relationships between insulin secretion after intravenous and oral glucose administration in subjects with glucose tolerance ranging from normal to overt diabetes. *Diabetic Medicine*, **25**, 671–677.
34 Faerch, K., Vaag, A., Holst, J.J. *et al.* (2008) Impaired fasting glycaemia vs impaired glucose tolerance: similar impairment of pancreatic alpha and beta cell function but differential roles of incretin hormones and insulin action. *Diabetologia*, **51**, 853–861.
35 Alssema, M., Schindhelm, R.K., Rijkelijkhuizen, J.M. *et al.* (2009) Meal composition affects insulin secretion in women with type 2 diabetes: a comparison with healthy controls. The Hoorn prandial study. *European Journal of Clinical Nutrition*, **63**, 398–404.
36 Cretti, A., Lehtovirta, M., Bonora, E. *et al.* (2001) Assessment of beta-cell function during the oral glucose tolerance test by a minimal model of insulin secretion. *European Journal of Clinical Investigation*, **31**, 405–416.
37 Lenhard, J.M., Croom, D.K. & Minnick, D.T. (2004) Reduced serum dipeptidyl peptidase-IV after metformin and pioglitazone treatments. *Biochemical and Biophysical Research Communications*, **324**, 92–97.
38 Lindsay, J.R., Duffy, N.A., McKillop, A.M. *et al.* (2005) Inhibition of dipeptidyl peptidase IV activity by oral metformin in type 2 diabetes. *Diabetic Medicine*, **22**, 654–657.
39 Charbonnel, B., Karasik, A., Liu, J. *et al.* (2006) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care*, **29**, 2638–2643.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. A flow chart of enrollment of the study subjects.

Table S1. Correlation between changes in HbA1c for 52 weeks with various parameters at baseline.

Table S2. Clinical adverse events.

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