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Increasing Age Associated with Higher Dipeptidyl Peptidase-4 Inhibition Rate Is a Predictive Factor for Efficacy of Dipeptidyl Peptidase-4 Inhibitors

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Background: It is not known which type 2 diabetes mellitus (T2DM) patients would most benefit from dipeptidyl peptidase-4 (DPP-4) inhibitor treatment. We aimed to investigate the predictors of response to DPP-4 inhibitors considering degree of DPP-4 inhibition.
Methods: This study is a *post hoc* analysis of a 24-week, randomized, double-blind, phase III trial that compared the efficacy and safety of a DPP-4 inhibitor (gemigliptin vs. sitagliptin) in patients with T2DM. Subjects were classified into tertiles of T1 <65.26%, T2=65.26%–76.35%, and T3 ≥76.35% by DPP-4 inhibition. We analyzed the change from baseline in glycosylated hemoglobin (HbA1c) according to DPP-4 inhibition with multiple linear regression adjusting for age, ethnicity, body mass index, baseline HbA1c, and DPP-4 activity at baseline.
Results: The mean age was greater in the high tertile group compared with the low tertile group (T1: 49.8±8.3 vs. T2: 53.1±10.5 vs. T3: 55.3±9.5, $P<0.001$) of DPP-4 inhibition. Although HbA1c at baseline was not different among tertiles of DPP-4 inhibition ($P=0.398$), HbA1c after 24-week treatment was lower in the higher tertile compares to the lower tertile (T1: 7.30%±0.88% vs. T2: 7.12%±0.78% vs. T3: 7.00%±0.78%, $P=0.021$). In multiple regression analysis, DPP-4 enzyme inhibition rate was not a significant determent for HbA1c reduction due to age. In subgroup analysis by tertile of DPP-4 inhibition, age was the only significant predictor and only in the highest tertile ($R^2=0.281$, B=–0.014, $P=0.024$).
Conclusion: This study showed that HbA1c reduction by DPP-4 inhibitor was associated with increasing age, and this association was linked with higher DPP-4 inhibition.

Keywords: Aged; Diabetes mellitus; Dipeptidyl-peptidase IV inhibitors; Glycated hemoglobin A

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been widely used as a therapeutic option for patient with type 2 diabetes mellitus (T2DM) [1]. They improve glycemic control in patients with T2DM by increasing circulating levels of incretins, endogenous gut-derived peptide hormones that enhance insulin secretion and suppress glucagon release in a dose-dependent manner [2]. Despite the widespread use of DPP-4 inhibitors; however, it has not yet been established which patients would benefit most from the treatment. Although previous studies have suggested predictors of better clinical response to DPP-4 inhibitors [3-6], the results were somewhat inconsistent.

It has been demonstrated that currently available DPP-4 inhibitors might differ in potency of DPP-4 inhibition [7]. For example, once-daily treatment with sitagliptin provided signif-

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icantly greater DPP-4 inhibition than saxagliptin or vildagliptin administered once daily and was similar to that of vildagliptin administered twice daily [8]. Furthermore, a meta-analysis of alogliptin, saxagliptin, sitagliptin, and vildagliptin efficacy results demonstrated that weighted average inhibition of DPP-4, a summary of the time course of DPP-4 inhibition over the dosing interval, was a useful biomarker related to glycosylated hemoglobin (HbA1c) response after chronic therapy with DPP-4 inhibitor [9]. However, few studies have suggested the predictors of better clinical response to DPP-4 inhibitors based on degree of DPP-4 inhibition.

Gemigliptin (LC15-0444) is a potent, highly selective, and long acting DPP-4 inhibitor. Various studies have demonstrated the efficacy and safety of gemigliptin for treatment of T2DM [10,11]. In addition, gemigliptin and sitagliptin were more effective than glimepiride in reducing glycemic variability as measured by continuous glucose monitoring as an initial combination with metformin in patients with T2DM [12]. In this study, we aimed to investigate the predictors of better clinical response to DPP-4 inhibitors according to degree of DPP-4 inhibition.

METHODS

Study population

This study is a post-hoc analysis of a multinational, randomized, active-controlled, parallel group, double-blind, phase 3 clinical trial in which the efficacy and safety of a DPP-4 inhibitor, gemigliptin versus sitagliptin added to metformin, were investigated in patients with T2DM (https://clinicaltrials.gov/ct2/show/NCT01602003). The detailed protocol of the study has been previously described [13]. Briefly, after screening (n=604), patients with T2DM (18 to 75 years of age) who were being treated with metformin monotherapy for at least 12 weeks with at least 4 weeks of 1,000 mg/day or higher dose of metformin before screening were randomized to one of the three treatment groups (sitagliptin 100 mg daily [n=142], gemigliptin 25 mg twice a day [n=141], or gemigliptin 50 mg daily [n=142]) at a 1:1:1 ratio. Each group was treated with the assigned treatment regimen for 24 weeks. We analyzed 323 patients who completed the treatment regimen and underwent measurement of DPP-4 activity at baseline and after 24 weeks. Approval was obtained from the Institutional Review Board of Kangbuk Samsung Hospital for the study protocol (KBSMC 2021-02-036). Informed consent was waived by the board.

Endpoint assessment

The primary endpoint of this post-hoc analysis was the change in HbA1c from baseline according to the degree of DPP-4 inhibition after treatment with DPP-4 inhibitors for 24 weeks.

Laboratory measurements

All blood samples for efficacy assessment were analyzed at the Seoul Clinical Laboratory, except for HbA1c and glucose collected during the first visit in Indian sites, which were analyzed at Super Religare Laboratories Ltd., Mumbai, India. Measurement techniques included the hexokinase method for glucose and enzymatic colorimetric assays (7600 Clinical Analyzer, Hitachi, Tokyo, Japan) for total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. Immunoradiometric assays were used for insulin (INS-IRMA, BiosourceKit, Biosource, Nivelles, Belgium) and C-peptide (IRMA, Immunotech Kit, Immunotech, Prague, Czech Republic) measurements. HbA1c was measured using turbidimetric inhibition immunoassays (TINIA, A1C-2 [tina-quant hemoglobin A1c Gen2], Roche Diagnostics, Mannheim, Germany). Homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) at baseline were calculated as previously described [14]. Fasting plasma samples were stored at –80°C for measurement of DPP-4 activity using a continuous fluorometric assay with the substrate Gly-Pro-AMC (Bachem, Bubendorf, Switzerland) [15]. The degree of DPP-4 inhibition was calculated as 100×(1–W24/W0), where W0 was the enzyme activity measured before administration, and W24 was the activity measured after administration at week 24.

Statistical analysis

This *post hoc* analysis was based on the full analysis set population consisting of all patients at our institute who received the investigational drug at least once and showed signs of efficacy after randomization. Continuous variables were expressed as mean±standard deviation, whereas categorical variables were expressed as proportion (%). The tertile groups according to degree of DPP-4 inhibition were as follows: T1 <65.26%, T2=65.26%–76.35%, and T3 ≥76.35%. Demographic and biochemical characteristics of the study population according to degree of DPP-4 inhibition were compared using two-sample t-test or Wilcoxon's rank sum test for continuous variables and the chi-square test for categorical variables. The difference in change of HbA1c from baseline to week 24 according to degree

of DPP-4 inhibition was compared using Kruskal-Wallis test, while the change of HbA1c from baseline to week 24 within each tertile group by degree of DPP-4 inhibition was analyzed using Wilcoxon signed rank test. The association between degree of DPP-4 inhibition and HbA1c reduction was investigated by multiple linear regression, with HbA1c reduction as the dependent variable. This analysis was adjusted for age, ethnicity (Korean vs. Indian), body mass index, HbA1c at baseline, and DPP-4 activity at baseline. All statistical analyses were carried out with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographics and baseline characteristics according to degree of DPP-4 inhibition

As previously described [13], 425 (296 from Korea and 129 from India) of 604 screened patients with T2DM were enrolled in the double-blind treatment period: 142 received sitagliptin 100 mg daily, 141 received gemigliptin 25 mg twice a day, and 142 received gemigliptin 50 mg daily. Among the 425 eligible patients, 323 had data for HbA1c level and DPP-4 activity at baseline and 24 weeks. Table 1 shows the baseline clinical and biochemical characteristics according to degree of DPP-4 inhibition. The average age of the study subjects was 52.9±9.7 years, and the average body mass index was 25.8±3.5 kg/m^2. The mean HbA1c at baseline was 8.01%±0.8%, and mean fasting plasma glucose (FPG) value was 144.7±30.6 mg/dL. Sex (P=0.161), ethnicity (P=0.170), body mass index (P=0.676), waist circumference (P=0.618), HbA1c (P=0.398), FPG (P=0.152), lipid profile (total cholesterol [P=0.996], HDL-C [P=0.067], LDL-C [P=0.572], and triglyceride [P=0.375]), HOMA-IR (P=0.558), and HOMA-β (P=0.880) at baseline were similar across degrees of DPP-4 inhibition. However, the higher was the tertile by degree of DPP-4 inhibition, the higher was mean age (T1: 49.8±8.3 vs. T2: 53.1±10.5 vs. T3: 55.3±9.5, P<0.001). And the higher tertile by degree of DPP-4 inhibition showed higher baseline DPP-4 activity (T1: 21.70±5.58 vs. T2: 21.99±4.37 vs. T3: 23.47±4.32, P=0.013)

Table 1. Baseline clinical and biochemical characteristics according to degree of DPP-4 inhibition

Characteristic	DPP-4 enzyme inhibition rate				
	Total	T1 (<65.26%)	T2 (65.26%–76.35%)	T3 (≥76.35%)	*P* value
No. of patients	323	96	112	115	
Age, yr	52.9±9.7	49.8±8.3	53.1±10.5	55.3±9.5	<0.0001
Male sex, %	53.9	58.3	57.1	44.0	0.1611
Ethnicity (Indian/Korean), %	29.7/70.3	32.3/67.7	23.2/76.8	33.9/66.1	0.1702
The proportion of each DPP-4 inhibitor (sitagliptin/gemigliptin), %	31.6/68.4	57.3/42.7	25.0/75.0	16.5/83.5	<0.0001
Body mass index, kg/m^2	25.8±3.5	25.9±3.2	26.0±3.6	25.6±3.6	0.6759
Waist circumference, cm	89.45±9.1	90.2±9.0	89.2±8.6	89.1±9.7	0.6176
HbA1c at baseline, %	8.01±0.8	8.1±0.8	8.0±0.8	8.0±0.8	0.3978
FPG at baseline, mg/dL	144.7±30.6	145.8±29.7	148.2±35.0	140.4±26.2	0.1515
Total cholesterol at baseline, mg/dL	166.9±38.8	168.2±43.9	166.0±36.5	166.6±36.6	0.9962
HDL-C at baseline, mg/dL	43.9±12.0	41.7±12.1	45.0±12.5	44.6±11.4	0.0681
LDL-C at baseline, mg/dL	91.9±31.4	93.4±31.2	92.3±31.3	90.3±31.9	0.5721
TG at baseline, mg/dL	161.6±122.2	173.0±143.6	155.2±135.4	158.1±83.7	0.3746
HOMA-IR at baseline	3.73±4.2	3.7±2.1	4.1±6.7	3.4±1.7	0.5581
HOMA-β at baseline	49.9±33.7	51.0±36.9	50.4±38.2	48.3±25.5	0.8798
Baseline DPP-4 activity	22.43±4.71	21.70±5.58	21.99±4.37	23.47±4.32	0.0130

Values are presented as mean±standard deviation.
DPP-4, dipeptidyl peptidase-4; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function.

Table 2. Change of HbA1c from baseline to week 24 according to degree of DPP-4 inhibition

Variable	DPP-4 enzyme inhibition rate				*P* value
	Total	T1 (<65.26%)	T2 (65.26%–76.35%)	T3 (≥76.35%)	
HbA1c at baseline, %	8.01±0.80	8.10±0.84	7.97±0.79	7.98±0.77	0.3978
HbA1c at week 24	7.13±0.82	7.30±0.88	7.12±0.78	7.00±0.78	0.0212
P value	<0.001	<0.001	<0.001	<0.001	
HbA1c change from baseline to week 24, %	–10.74±8.67	–9.60±9.34	–10.29±8.50	–12.12±8.11	0.0620 (0.037[a])

Values are presented as mean±standard deviation.
HbA1c, glycosylated hemoglobin; DPP-4, dipeptidyl peptidase-4.
[a]*P* value by *t*-test between T1 and T3.

HbA1c reduction according to degree of DPP-4 inhibition

Table 2 shows HbA1c at baseline and at week 24 after DPP-4 inhibitor treatment. The mean HbA1c at baseline was not different among the tertile groups by degree of DPP-4 inhibition (P=0.398) (Table 2). Overall, there was significant HbA1c reduction of –0.88%±0.76% after 24-week treatment (P<0.001) and in each tertile group by degree of DPP-4 inhibition (all P<0.001). The HbA1c at week 24 was significantly lower with increasing degree of DPP-4 inhibition (T1: 7.30%±0.88% vs. T2: 7.12%±0.78% vs. T3: 7.00%±0.78%, P=0.021). And the decrease of HbA1c from baseline to week 24 was higher with increasing degree of DPP-4 inhibition (T1: –9.60%±9.34% vs. T2: –10.29%±8.50% vs. T3: –12.12%±8.11%, P=0.062; P=0.037, between T1 and T3).

Independent association of degree of DPP-4 inhibition with HbA1c reduction

Table 3 shows the association of degree of DPP-4 inhibition with HbA1c reduction by multiple linear regression, with HbA1c reduction serving as the dependent variable.

In model 3 (R^2=0.240) in which age, ethnicity, body mass index, HbA1c at baseline, DPP-4 activity at baseline, and degree of DPP-4 inhibition were adjusted, age (B=–0.013, P=0.001), ethnicity (Korean vs. Indian, B=0.169, P=0.047), and HbA1c at baseline (B=–0.470, P<0.001) were significant determinants for HbA1c reduction. In model 6 in which age was not adjusted, degree of DPP-4 inhibition (R^2=0.240, B=–0.005, P<0.031) was a significant determinant for HbA1c reduction and ethnicity (Korean vs. Indian, B=0.213, P=0.013), as was HbA1c at baseline (B=–0.463, P<0.001).

Predictors of better clinical response to DPP-4 inhibitors by degree of DPP-4 inhibition

We conducted subgroup analysis by tertile group according to degree of DPP-4 inhibition (T1 <65.26%, T2=65.26%–76.35%, and T3 ≥76.35%), with HbA1c reduction serving as the dependent variable (Table 4). In subgroup analysis, baseline HbA1c was a significant predictor of better clinical response to DPP-4 inhibitors in all subgroups, and age was a significant predictor of better clinical response to DPP-4 inhibitors in the highest tertile (B=–0.014, P=0.024), marginal in the middle tertile (B=–0.012, P=0.057), and not significant in the lowest tertile (B=–0.014, P=0.161) (Table 4).

DISCUSSION

This present study investigates the predictors of better clinical response (HbA1c reduction) to DPP-4 inhibitors with consideration of pharmacokinetic response (degree of DPP-4 inhibition). The predictors of clinical response to DPP-4 inhibitors were age, ethnicity, and HbA1c at baseline in this study. In the consideration of pharmacokinetic response, the highest degree of DPP-4 inhibition was associated with higher age and with greater HbA1c reduction, but it was dependent on patient age.

Some studies have investigated the HbA1c response to DPP-4 inhibitors in patients with T2DM, but the results were heterogeneous. A meta-analysis by Kim et al. [16] reported that DPP-4 inhibitors exhibit better glucose-lowering efficacy in Asians than in other ethnic groups, and body mass index was significantly correlated with HbA1c reduction in response to DPP-4 inhibitors in patients with T2DM, especially in an Asian population. The Predicting Response to Incretin Based Agents in Type 2 Diabetes (PRIBA) study comprised mostly of Caucasians showed that markers of higher insulin resistance were associated with reduction in response to DPP-4 inhibitors [5]. This suggests that Asian populations have a higher risk of developing diabetes due to genetic defects affecting insulin secretory function and β-cell mass compared to the Caucasian pop-

Table 3. The relationship between degree of DPP-4 inhibition and degree of HbA1c reduction from baseline to week 24

Variable	R^2	B	SE	*P* value
Model 1				
Age	0.0245	−0.0100	0.0045	0.0279
Enthinicity (Indian/Korean), %		0.0509	0.0953	0.5937
Body mass index		0.0004	0.0125	0.9751
Degree of DPP-4 inhibition		−0.0024	0.0024	0.3210
Model 2				
Age	0.2615	−0.0125	0.0040	0.0019
Enthinicity (Indian/Korean), %		0.1827	0.0840	0.0304
Body mass index		0.0011	0.0109	0.9173
HbA1c at baseline		−0.4758	0.0472	<0.0001
Degree of DPP-4 inhibition		−0.0039	0.0021	0.0678
Model 3				
Age	0.2403	−0.0129	0.0040	0.0013
Enthinicity (Indian/Korean), %		0.1688	0.0848	0.0474
Body mass index		0.0015	0.0848	0.8902
HbA1c at baseline		−0.4701	0.0109	<0.0001
DPP-4 activity at baseline		−0.0094	0.0474	0.2324
Degree of DPP-4 inhibition		−0.0033	0.0021	0.1195
Model 4	0.0096			
Enthinicity (Indian/Korean), %		0.0842	0.0946	0.3742
Body mass index		0.0047	0.0124	0.7035
Degree of DPP-4 inhibition		−0.0033	0.0024	0.1650
Model 5	0.2386			
Enthinicity (Indian/Korean), %		0.2214	0.0842	0.0090
Body mass index		0.0065	0.0109	0.5528
HbA1c at baseline		−0.4669	0.0477	<0.0001
Degree of DPP-4 inhibition		−0.0050	0.0021	0.0186
Model 6	0.2403			
Enthinicity (Indian/Korean), %		0.2128	0.0850	0.0128
Body mass index		0.0069	0.0109	0.5281
HbA1c at baseline		−0.4626	0.0480	<0.0001
DPP-4 activity at baseline		−0.0066	0.0080	0.4041
Degree of DPP-4 inhibition		−0.0047	0.0021	0.0305

Model 1: age, ethnicity, body mass index; Model 2: age, ethnicity, body mass index, HbA1c at baseline; Model 3: age, ethnicity, body mass index, HbA1c at baseline, DPP-4 activity at baseline; Model 4: ethnicity, body mass index; Model 5: ethnicity, body mass index, HbA1c at baseline; Model 6: ethnicity, body mass index, HbA1c at baseline, DPP-4 activity at baseline.
DPP-4, dipeptidyl peptidase-4; HbA1c, glycosylated hemoglobin; SE, standard error.

ulation developing diabetes due to insulin resistance [17]. Like the above study, Korean of this study showed lower insulin resistance (HOMA-IR: 3.15±1.59 vs. 5.33±6.66, $P<0.001$) and lower β-cell function (HOMA-β: 42.54%±22.28% vs. 67.85%±45.15%, $P<0.001$) (Supplementary Table 1) comparing with Indian of this study. And ethnicity (Korean vs. Indian) was statistically significantly associated with HbA1c reduction but not degree of DPP-4 inhibition in our study. These showed that

Table 4. The association between age and clinical response to DPP-4 inhibitors by tertile of DPP-4 enzyme inhibition rate

DPP-4 enzyme inhibition rate	Model 1			Model 2			Model 3		
	B	SE	*P* value	B	SE	*P* value	B	SE	*P* value
<65.26%									
Age	–0.0167	0.0108	0.1269	–0.0137	0.0097	0.1623	–0.0138	0.0097	0.1612
HbA1c at baseline	-	-	-	–0.4400	0.0884	<0.0001	–0.4422	0.0891	<0.0001
65.26%–76.35%									
Age	–0.0039	0.0070	0.5786	–0.0098	0.0062	0.1169	–0.0123	0.0064	0.0568
HbA1c at baseline	-	-	-	–0.4959	0.0814	<0.0001	–0.4903	0.0811	<0.0001
≥76.35%									
Age	–0.0117	0.0072	0.1065	–0.0137	0.0063	0.0321	–0.0144	0.0063	0.0244
HbA1c at baseline	-	-	-	–0.4754	0.0808	<0.0001	–0.4628	0.0811	<0.0001

Model 1: age, ethnicity, body mass index; Model 2: age, ethnicity, body mass index, HbA1c at baseline; Model 3: age, ethnicity, body mass index, HbA1c at baseline, DPP-4 activity at baseline.
DPP-4, dipeptidyl peptidase-4; SE, ; HbA1c, glycosylated hemoglobin.

there was significantly different in HbA1c reduction in response to DPP-4 inhibitors between ethnicity, but this difference was not relying on the degree of DPP-4 inhibition. Body mass index was not statistically significantly associated with HbA1c reduction or degree of DPP-4 inhibition in our study despite the Asian population. In other meta-analysis with 98 randomized clinical trials (RCTs) with 100 arms, Esposito et al. [6] observed that baseline HbA1c level explained most of the variance in HbA1c reduction in response to DPP-4 inhibitors (34% of the variance between studies), but mean baseline age, duration of treatment, and previous diabetes drugs did not provide predictive power (less than 1%) to the DPP-4 inhibitor treatment response. However, in another meta-analysis with 63 RCTs, Monami et al. [3] reported the results of meta-analysis with 63 RCTs that DPP-4 inhibitors are more effective in older patients with mild to moderate fasting hyperglycemia, compatible with our study. Compared to previous study, the strengths of our study include inclusion of degree of DPP-4 inhibition in the analysis as a predictor of clinical response to DPP-4 inhibitors. Age is an independent predictor of clinical response to DPP-4 inhibitor based on degree of DPP-4 inhibition.

Age is one of the most important risk factors for T2DM, and there is evidence of differences in pathophysiology of T2DM in older compared with younger patients. It has been hypothesized that impaired insulin secretion, rather than insulin resistance, is responsible for most diabetes in elderly populations compared with younger populations. It has been repeatedly reported that the capacity of pancreatic β-cells to provide adequate insulin for metabolic demand is decreased with increasing age [18-21]. This age-related loss of β-cell secretory capability has been attributed to several factors, including attenuation of the enteroinsular axis, incretin potentiate insulin secretion. Faerch et al. [22] have suggested that a reduction in GLP-1 response to oral glucose could predispose one to T2DM. Other longitudinal study showed that a low tertile of GLP-1 response to the oral glucose tolerance test was associated with a steeper increase in fasting glucose level than higher tertiles during 7 years of follow-up [23]. A recent longitudinal study showed that fasting GIP and GLP-1 and glucose-stimulated GLP-1 decreased significantly over a mean period of 5.9 years and suggested that reduction in incretin hormone responses with aging may predispose one to the glucose intolerance and T2DM [24]. A major mechanism of action of DPP-4 inhibitors is potentiation of β-cell insulin secretion and inhibition of glucagon secretion by elevating endogenous GLP-1 in a glucose-dependent mode of action [25]. In our study, we divided study population into younger (<53 years old) and older (≥53 years old) group with median age (Supplementary Table 2), there were significant different in HOMA-IR between younger group (4.328±15.354) and older group (3.281± 15.354, $P<0.001$) but HOMA-β (%) at baseline were not different between younger group (53.13±42.47) and older group (46.94±23.15, $P=0.10$). Although there was significant difference in HbA1c difference from baseline between younger and older groups (–0.76±0.79 vs. –1.00±0.72, $P<0.001$), there was no proof that the insulin secretory function was more improved by DPP-4 inhibitors

therapy in the older group compared to younger group. HOMA-β (%) change from baseline to week 24 were not different between younger and older groups (18.06±53.48 vs. 30.53±123.35, $P=0.25$). And these were also similar in highest tertile of DPP-4 inhibition rate group (21.28±40.02 vs. 41.87±123.35, $P=0.45$) (Supplementary Table 3). Therefore, there was possibility for other mechanism for HbA1c reduction by DPP-4 inhibitors in older patients with high DPP-4 inhibition rate, further study needed.

There are some limitations to this study. First, due to the nature of *post hoc* analysis, the sample size could be inadequate to find other less significant predictors of clinical response to DPP-4 inhibitors. Second, the relatively short-term follow-up of the study (24 weeks) could hinder evaluation of predictors of clinical response to DPP-4 inhibitors. However, previous randomized studies showed great HbA1c reduction within the first 8 to 12 weeks of such treatment [26,27]. Third, we described as the elder patients were more beneficial in the treatment with DPP-4 inhibitors. However, the average age of T3 was 55.3 years old and not very advanced age and we did not suggest a cut off of any age which was more beneficial in the treatment with DPP-4 inhibitors. Therefore 'elder' patients should not restrict to 'elderly' patients.

In conclusion, our study showed that age, ethnicity, and HbA1c at baseline were predictors of clinical response to DPP-4 inhibitors. In elder but not younger patients with diabetes, DPP-4 enzyme inhibition rate was associated with HbA1c reduction. Therefore, a DPP-4 inhibitor might be adequate treatment in elder patient with diabetes.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2020.0253.

CONFLICTS OF INTEREST

Sangmo Hong, Chang Hee Jung, and Cheol-Young Park had no potential conflict of interest relevant to this article. Song Han was hired by LG Chem Ltd., Seoul.

AUTHOR CONTRIBUTIONS

Conception or design: S.H., C.H.L., C.Y.P.
Acquisition, analysis, or interpretation of data: S.H, C.H.L., S.H., C.Y.P.
Drafting the work or revising: S.H., C.H.L.
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Supplementary Table 1. Baseline clinical and biochemical characteristics according to ethnicity

Characteristic	Korean	Indian	*P* value
Number of patients	227	96	
Age, yr	54.1±9.7	50.0±9.2	0.0001
Male sex, %	53.7	54.2	0.9445
Body mass index, kg/m^2	25.390±3.200	26.868±3.905	0.0009
Waist circumference, cm	87.59±8.39	93.85±9.25	<0.0001
Duration of T2DM, yr	6.899±4.901	4.355±4.119	<0.0001
The proportion of each DPP-4 inhibitor (sitagliptin/gemigliptin), %	32.6/67.4	29.2/70.8	0.5442
HbA1c at baseline, %	7.924±0.793	8.226±0.765	0.0002
FPG at baseline, mg/dL	145.066±30.532	143.906±30.919	0.9537
Total cholesterol at baseline, mg/dL	166.361±34.409	168.083±47.754	0.9076
HDL-C at baseline, mg/dL	47.996±11.063	34.052±7.869	<0.0001
LDL-C at baseline, mg/dL	93.476±30.131	88.281±34.121	0.2412
TG at baseline, mg/dL	145.841±104.366	198.698±150.781	<0.0001
HOMA-IR at baseline	3.090±1.550	5.252±7.214	<0.0001
HOMA-β at baseline	41.699±22.005	69.130±46.605	<0.0001

Values are presented as mean±standard deviation.
T2DM, type 2 diabetes mellitus; DPP-4, dipeptidyl peptidase-4; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function.

Supplementary Table 2. Baseline clinical and biochemical characteristics according to age group

Age group	<53 Years	≥53 Years	*P* value
Number	152	171	
Age, yr	44.6±6.5	60.2±5.3	<0.0001
Male sex, %	52.6	55.0	0.6738
Nationality (Indian/Korean), %	40.1/59.9	20.5/79.5	0.0001
Body mass index, kg/m^2	26.391±3.613	25.329±3.298	0.0013
Waist circumference, cm	90.48±9.47	88.55±8.69	0.0573
Duration of T2DM, yr	4.245±3.382	7.830±5.266	<0.0001
DPP-4 inhibitor (sitagliptin/gemigliptin), %	30.3/69.7	32.7/67.3	0.6315
HbA1c at baseline, %	8.136±0.797	7.905±0.782	0.0023
FPG at baseline, mg/dL	151.809±35.226	138.421±24.228	0.0002
Total cholesterol at baseline, mg/dL	170.020±41.886	164.076±35.700	0.2277
HDL-C at baseline, mg/dL	40.888±11.459	46.485±11.958	<0.0001
LDL-C at baseline, mg/dL	92.553±32.744	91.380±30.253	0.4992
TG at baseline, mg/dL	186.072±143.187	139.754±95.223	<0.0001
HOMA-IR at baseline	4.322±5.863	3.208±1.736	<0.0001
HOMA-β at baseline	53.129±42.467	46.939±23.154	0.8974
Baseline DPP-4 activity	22.334±5.197	22.529±4.470	0.7169
HbA1c difference from baseline to week 24, %	−0.757±0.787	−0.998±0.724	0.0011
DPP-4 inhibition rate at week 24, %	64.03±18.64	70.85±16.47	<0.0001

Values are presented as mean±standard deviation.
T2DM, type 2 diabetes mellitus; DPP-4, dipeptidyl peptidase-4; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function.

Supplementary Table 3. Change of HOMA-β from baseline to week 24 according to degree of DPP-4 inhibition and age groups

Variable	Total	DPP-4 enzyme inhibition rate			*P* value
		T1 (<65.26%)	T2 (65.26%–76.35%)	T3 (≥76.35%)	
Age <53 yr					
Number	152	63	47	42	
HOMA-β at baseline	53.129±42.467	49.857±28.292	58.283±63.343	52.271±29.702	0.5310
HOMA-β at week 24	71.187±55.684	65.929±38.048	76.115±79.031	73.560±46.334	0.3672
HOMA-β change from baseline to week 24, %	18.058±53.477	16.072±32.004	17.833±81.022	21.288±40.022	0.8273
Age ≥53 yr					
Number	171	32	65	74	
HOMA-β at baseline	46.939±23.154	45.718±25.392	47.477±21.388	46.994±23.931	0.6636
HOMA-β at week 24	77.469±130.734	65.490±38.200	70.392±78.218	88.866±183.246	0.2214
HOMA-β change from baseline to week 24, %	30.531±123.348	19.772±32.795	22.915±72.108	41.873±173.733	0.2035
P value for HOMA-β change between age group	0.6853	0.4810	0.1486	0.9108	

Values are presented as mean±standard deviation.
HOMA-β, homeostasis model assessment of β-cell function; DPP-4, dipeptidyl peptidase-4.