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META-ANALYSIS

Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis

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Abstract
Aims/hypothesis The aim of this work was to compare the glucose-lowering efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitors between Asian and non-Asian patients with type 2 diabetes.
Methods We searched MEDLINE, EMBASE, LILACS, CENTRAL, ClinicalTrials.gov and conference proceedings. Studies were eligible if they were randomised controlled trials with a treatment duration of at least 12 weeks, compared a DPP-4 inhibitor with a placebo as either monotherapy or oral combination therapy, had information on ethnicity and HbA_{1c} values and were published or described in English. A systematic review and meta-analysis with a meta-regression analysis was conducted.
Results Among 809 potentially relevant studies, 55 trials were included. A meta-analysis revealed that DPP-4 inhibitors lowered HbA_{1c} to a greater extent in studies with ≥50% Asian participants (weighted mean difference [WMD] −0.92%; 95% CI −1.03, −0.82) than in studies with <50% Asian participants (WMD −0.65%; 95% CI −0.69, −0.60). The between-group difference was −0.26% (95% CI −0.36, −0.17, $p<0.001$). The baseline BMI significantly correlated with the HbA_{1c}-lowering efficacy of DPP-4 inhibitors. The RR of achieving the goal of HbA_{1c} <7.0% (53.0 mmol/mol) was higher in studies with ≥50% Asian participants (3.4 [95% CI 2.6, 4.7] vs 1.9 [95% CI 1.8, 2.0]). The fasting plasma glucose-lowering efficacy was higher with monotherapy in the Asian-dominant studies, but the postprandial glucose-lowering efficacy and changes in body weight were comparable between the two groups.
Conclusions/interpretation DPP-4 inhibitors exhibit a better glucose-lowering efficacy in Asians than in other ethnic groups; this requires further investigation to understand the underlying mechanism, particularly in relation to BMI.

Keywords Asian · BMI · Dipeptidyl peptidase-4 · Meta-analysis · Systematic review · Type 2 diabetes

Abbreviations

DECODA	Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia
DECODE	Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe
DPP-4	Dipeptidyl peptidase-4
FPG	Fasting plasma glucose
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
PPG	Postprandial glucose
WMD	Weighted mean difference

Introduction

The pathophysiology of type 2 diabetes includes both insulin resistance and decreased insulin secretion. The contribution of

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these components is within a spectrum ranging from predominant insulin resistance to a predominant insulin secretory defect [1]. There is a growing body of evidence that the pathophysiology of type 2 diabetes differs by ethnic group [2–4]. Comparing Asian and white patients with type 2 diabetes, Asian patients are characterised by a relatively lower BMI [4], higher amounts of visceral fat with a given BMI or waist circumference [5, 6] and a predominant insulin secretory defect [7–9]. In patients with type 2 diabetes, the insulin secretory defect is more prominent in Asian than in white individuals [7, 10, 11]. The reasons for decreased insulin secretion in Asian patients with type 2 diabetes are yet to be determined but may be explained by lower beta cell mass, impaired beta cell function and genetic differences [2–4].

Incretin hormones are secreted after a meal to increase glucose-dependent insulin secretion [12, 13]. The incretin effect explains approximately 50–70% of insulin secretion after an oral glucose load in healthy individuals but secretion is markedly reduced (approximately 10–30%) in patients with type 2 diabetes [14–16]. To date, two incretin hormones have been identified: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [12, 13]. GLP-1 and GIP are readily degraded into inactive metabolites by dipeptidyl peptidase-4 (DPP-4), resulting in very short half-lives in the circulation [12, 13]. The clinical use of DPP-4 inhibitors, which increase the concentration of the active forms of GLP-1 and GIP, is becoming increasingly popular.

Given the contribution of the insulin secretory defect and insulin resistance to differences in the pathophysiology of type 2 diabetes between Asians and non-Asians, the glucose-lowering efficacy of DPP-4 inhibitors should differ by ethnic group. Thus, we performed a systematic review and meta-analysis on the glucose-lowering efficacy of DPP-4 inhibitors in Asians and non-Asians and conducted meta-regression analyses to identify factors contributing to the difference between the two groups.

Methods

The conduct and results of the study are reported in accordance with the PRISMA statement [17].

Data sources and searches A systematic search was performed to identify potentially relevant studies in the MEDLINE, EMBASE, CENTRAL, LILACS and ClinicalTrials.gov databases up to February 2012. In addition, the electronically searchable abstracts from the scientific conferences of the ADA from 2004 to 2011 and the EASD from 2008 to 2011 were examined. Search terms used in this study are presented in electronic supplementary material (ESM) Methods.

Eligibility criteria and study selection Studies were eligible for inclusion if they met the following criteria: (1) randomised controlled trials comparing a DPP-4 inhibitor with a placebo as either monotherapy or combination therapy with other oral glucose-lowering drugs in patients with type 2 diabetes; (2) a treatment duration of at least 12 weeks; (3) information on the ethnicity of the study participants; (4) information on HbA_{1c} values and (5) studies published or described in English. Eligibility was assessed independently by two authors (Y. G. Kim and T. J. Oh) and any disagreements were resolved by consensus. Studies were excluded if the change in the HbA_{1c} value from the baseline to the end of follow-up in each treatment and control group was unavailable. Duplicate studies and extended studies from original studies were excluded. Studies performed in individuals with renal or hepatic dysfunction were excluded.

Data extraction Data extraction was independently conducted by two authors (Y. G. Kim and T. J. Oh). Any disagreements were resolved by consensus with other authors (S. Hahn and Y. M. Cho). The following data were extracted from the eligible studies: name of the first author, year of publication, country where the study was conducted, treatment regimen, number of participants, duration of diabetes, age, percentage of Asians, percentage of men, baseline HbA_{1c} values and baseline BMI.

For dose-range studies, only data arising from currently approved doses were extracted. In the absence of such data, the data for equivalent amounts of daily doses were used. If no approved dose was used, data for a dose having a maximal HbA_{1c}-lowering efficacy were extracted. If a study had two or three comparisons (one monotherapy arm and one or two combination therapy arms) [18, 19], each comparison was treated separately. When there was a comparison for different administration times in a day (morning vs evening) [20], the data for a morning dose were used. Some data not available in the original papers were extracted supplementarily using information from a full report available at a trial registry, ClinicalTrials.gov [18, 19, 21–61]. With regard to the ethnicity information, we followed the classification of 'Asian' used by the authors of each study. If a study did not disclose ethnic information but was conducted in Asian countries with a relatively homogeneous population (e.g. Korea, China, Japan and Taiwan), we assumed the study participants were Asian.

Study quality and risk of bias assessment We used the Cochrane Collaboration's tool [62] to assess the risk of bias in adequacy of sequence generation, allocation concealment, type of blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other biases. A detailed description is available in ESM Methods.

To assess publication bias, we used a funnel plot and Egger's test.

Data synthesis and analysis The primary outcome of this meta-analysis was the HbA_{1c}-lowering efficacy of DPP-4 inhibitors at the end of the study. Secondary outcomes were the effect of DPP-4 inhibitors on fasting plasma glucose (FPG), 2 h postprandial glucose (PPG) following a 75 g glucose load or a standard meal, body weight and achievement of the HbA_{1c} <7.0% (53.0 mmol/mol) goal in the randomised patients. In each study, for outcomes measured on a continuous scale, a weighted mean difference (WMD) in the mean change of the outcome from the baseline to the end of the study between the treatment and the comparison groups was calculated with a 95% CI. An RR was calculated with a 95% CI for a dichotomised outcome. The pooled effect was estimated using a random-effects model. The I^2 statistic and the χ^2 test were used to evaluate the statistical heterogeneity. We conducted meta-regression analyses to test the subgroup differences between ethnic groups and to investigate the sources of the differences by considering some pre-specified covariates: age, percentage of men, percentage of Asian persons, BMI, duration of treatment, duration of diabetes and baseline HbA_{1c} level. When a correlation coefficient was considered between particular variables, the coefficient was derived from the determinant coefficient obtained from the corresponding meta-regression analysis. According to the treatment regimen, the eligible studies were categorised into a 'monotherapy' or an 'oral combination therapy' group. If the percentage of Asian participants was larger than or equal to 50% in a study, we categorised the study as an Asian-dominant study. Studies were additionally divided into high-BMI groups (BMI ≥30 kg/m^2) and low-BMI groups (BMI <30 kg/m^2). All analyses were performed using the Stata statistical package (version 12; Stata Corp, College Station, TX, USA).

Results

Search results and study characteristics Of the 702 references identified from the four databases, 383 duplicates were eliminated. Of the remaining 319 potentially relevant articles, 259 were excluded after reviewing the titles and abstracts. The full texts of 60 articles were reviewed, and 51 articles were included in the analysis. Of the 107 potentially relevant clinical trials additionally identified from ClinicalTrials.gov (www.clinicaltrials.gov, accessed 8 February 2012), four studies were included in the analysis. Detailed reasons for exclusion are shown in Fig. 1. There were no eligible studies in the ADA or EASD abstracts. We retrieved a total of 55 studies reporting 58 comparison pairs that met the selection criteria for a total of 18,328 study participants (10,270 randomised to treatment group and 8,058 randomised to the comparison group). The doses of DPP-4 inhibitors analysed in this study and a summary of the included studies are shown in Table 1.

Quality of included studies and publication bias assessments Fifty-four of the 55 included studies achieved a double blindness for the participants and the personnel. For the incomplete outcome data, 49 studies were categorised as low risk, one as unclear and five as high risk. The sequence generation was unclear in 30 studies, and allocation concealment was unclear in approximately 80% of the studies. There was no particular indication for selective reporting from any included studies and 88% (51 of 58) were at low risk for other biases (ESM Table 1, ESM Fig. 1). The Egger's test and a funnel plot suggested that there was no asymmetric pattern, and no particular concern regarding a publication bias was given to the analyses in the current study (ESM Fig. 2).

Primary outcome: HbA_{1c}-lowering efficacy A pooling of HbA_{1c} data was performed for 57 pairs from 54 of the 55 studies. One study [37] was excluded because the SD was not available in an adequate form. The WMDs in the changes of HbA_{1c} from the baseline value are depicted in ESM Fig. 3. Overall, the difference between the treatment group and comparison group was −0.72% (95% CI −0.77, −0.67; I^2=67.6%) (Fig. 2a). There was no difference in HbA_{1c}-lowering efficacy among different DPP-4 inhibitors (data not shown). We conducted a subgroup analysis by the percentage of Asian participants. The median (range) duration of diabetes was 6.3 (2.0–13.7) and 4.5 (1.4–9.9) years in the Asian-dominant and non-Asian-dominant studies, respectively. The median (range) baseline HbA_{1c} was 7.9 (7.4–9.7)% (62.8 [57.4–82.5] mmol/mol) and 8.3 (7.7–9.9)% (67.2 [60.7–84.7] mmol/mol) in the Asian-dominant and non-Asian-dominant studies, respectively. In studies with <50% Asian participants (non-Asian-dominant studies, n=41), HbA_{1c} changed by −0.65% (95% CI −0.69, −0.60; I^2=35.4%), while in studies with ≥50% Asian participants (Asian-dominant studies, n=13), HbA_{1c} changed by −0. 92% (95% CI −1.03, −0.82; I^2=74.8%). The difference between the two groups was −0.26% (95% CI −0.36, −0.17), which was statistically significant (p<0.001), suggesting that the HbA_{1c}-lowering efficacy of DPP-4 inhibitors was higher in the Asian-dominant studies than in the non-Asian-dominant studies.

In the monotherapy trials, the overall difference in HbA_{1c} change from baseline between the treatment group and comparison group was −0.74% (95% CI −0.84, −0.64; I^2=73.9%) (Fig. 2a). HbA_{1c} changed by −0.64% (95% CI −0.70, −0.57; I^2=13.8%) in the non-Asian-dominant studies whereas it changed by −1.01% (95% CI −1.14, −0.88; I^2=

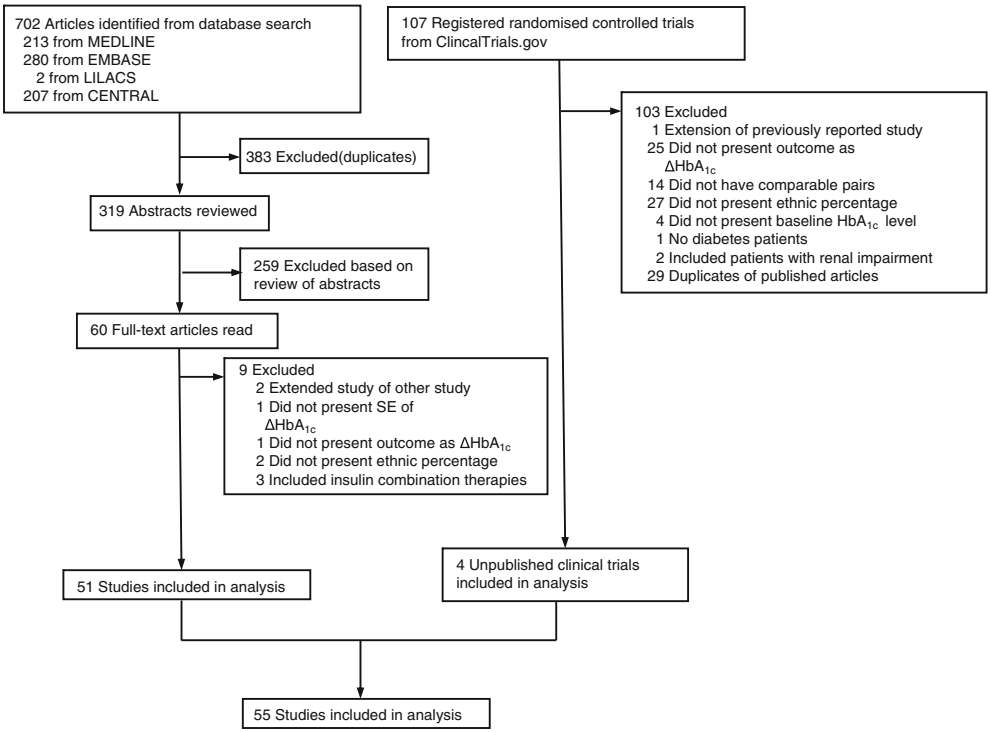

Fig. 1 Selection of studies included in the meta-analysis

58.3%) in the Asian-dominant studies. The difference between the two groups was −0.38% (95% CI −0.52, −0.23), which was statistically significant ($p<0.001$). In trials with oral combination therapy, the overall difference of HbA_{1c} change from the baseline between treatment group and comparison group was −0.70% (95% CI −0.76, −0.65; $I^2=61.2\%$). HbA_{1c} changed by −0.66% (95% CI −0.71, −0.60; $I^2=44.3\%$) in the non-Asian-dominant studies whereas it changed by −0.85% (95% CI −0.97, −0.72; $I^2=72.3\%$) in the Asian-dominant studies. The difference between the two groups was −0.18% (95% CI −0.31, −0.05), which was statistically significant ($p=0.006$). The HbA_{1c}-lowering efficacy exhibited no difference whether a DPP-4 inhibitor was added on top of metformin (WMD −0.68% [95% CI −0.77, −0.60]; $I^2=61.0\%$) or sulfonylurea (WMD −0.68% [95% CI −0.90, −0.47]; $I^2=74.6\%$).

The univariate meta-regression analyses (Fig. 3a, c; ESM Fig. 4) revealed that the percentage of Asian participants ($p<0.001$), BMI ($p<0.001$), age ($p=0.006$), percentage of men ($p=0.027$), duration of disease ($p=0.005$) and duration of treatment ($p=0.013$) were significantly correlated with the change in HbA_{1c} from baseline. Interestingly, the percentage of Asian participants was negatively correlated with average BMI ($r=-0.95$) (Fig. 3b). As the percentage of Asian participants increased or the BMI decreased, the change in HbA_{1c} became larger. The BMI distribution of the Asian-dominant studies ranged from 23.8 to 28.4 kg/m^2 and that of the non-Asian-dominant studies ranged from 28.3 to 33.3 kg/m^2. Therefore, BMI could be a confounding factor in the apparent relationship between the percentage of Asian participants and the HbA_{1c}-lowering efficacy of the DPP-4 inhibitors. The percentage of Asian participants was independently associated with the change in HbA_{1c} from baseline, even in a multiple meta-regression analysis adjusted for treatment duration, percentage of men, duration of diabetes, age and baseline HbA_{1c} level (ESM Table 2). However, the relationship between the percentage of Asians and the change in HbA_{1c} from baseline was no longer significant after adjusting for BMI ($p=0.491$, ESM Table 2), which may be the result of the statistical multicollinearity. The correlation between BMI and HbA_{1c}-lowering efficacy was dependent upon the study populations. In Asian-dominant studies there was a clear correlation between BMI and the HbA_{1c}-lowering effect, but in non-Asian-dominant studies there was no such correlation (ESM Table 2). Similarly, there was no correlation between BMI and the HbA_{1c}-lowering efficacy of the DPP-4 inhibitors in the studies in which the average BMI was ≥30 kg/m^2, but BMI was significantly correlated with the HbA_{1c}-lowering efficacy of the DPP-4 inhibitors in the studies in which the average BMI was <30 kg/m^2 (Fig. 3d).

In addition to the meta-regression analysis, to further resolve the issues associated with heterogeneity and the arbitrary cutoff of the proportion of Asians for Asian-dominance, we classified the included studies into three groups according to the proportion of the Asians participants: low Asian zone (Asian ≤20%), intermediate Asian zone (<20% Asian ≤80%) and high Asian zone

Table 1 Summary of included studies and comparison pairs

Source	No. of participants (treatment/control)[a]	Treatment duration (weeks)/duration of diabetes (years)	Baseline HbA_{1c} level (%)/baseline HbA_{1c} level (mmol/mol)	Mean age (years)	Men (%)	Asian (%)	BMI (kg/m^2)	Treatment group	Control group
Monotherapy									
Non-Asian-dominant studies									
DeFronzo et al [32], 2008	131/65	26/NR	7.9/62.8	53.4	53.2	NR	NR	Alogliptin 25 mg OD	Placebo
NCT00328172	55/67	12/NR	8.3/67.2	57.7	52.5	4.1	31.0	Linagliptin 5 mg OD	Placebo
Del Prato et al [27], 2011	336/167	24/NR	8.0/63.9	55.7	48.3	46.1	29.1	Linagliptin 5 mg OD	Placebo
NCT00819091	161/84	18/NR	8.6/70.5	56.9	52.7	48.6	28.3	Linagliptin 5 mg OD	Placebo
Rosenstock et al [38], 2009_S[b]	106/95	24/2.4	8.0/63.9	53.9	50.2	3.5	31.6	Saxagliptin 5 mg OD	Placebo
Rosenstock et al [74], 2008	47/67	12/1.4	8.0/63.9	54.6	58.8	NR	31.0	Saxagliptin 5 mg OD	Placebo
Hanefeld et al [75], 2007	110/111	12/3.4	7.7/60.7	55.9	59.3	0.5	31.5	Sitagliptin 100 mg OD	Placebo
Scott et al [76], 2007	124/125	12/4.5	7.9/62.8	55.2	57.4	2.4	31.0	Sitagliptin 50 mg BD	Placebo
Raz et al [41], 2006	205/110	18/4.6	8.0/63.9	54.8	56.8	4.1	32.0	Sitagliptin 100 mg OD	Placebo
Goldstein et al [18], 2007_1[c]	179/176	24/4.5	8.8/72.7	53.4	52.4	5.1	31.8	Sitagliptin 100 mg OD	Placebo
Aschner et al [23], 2006	238/253	24/4.5	8.0/63.9	53.9	54.2	13.4	30.6	Sitagliptin 100 mg OD	Placebo
Pratley et al [77], 2006	70/28	12/4.3	8.0/63.9	55.7	42.9	1.0	30.0	Vidagliptin 25 mg BD	Placebo
Pi-Sunyer et al [43], 2007	83/92	24/2.4	8.5/69.4	51.1	55.4	18.3	32.5	Vidagliptin 50 mg BD	Placebo
Ristic et al [78], 2005	63/58	12/2.7	7.7/60.7	55.4	56.2	NR	31.3	Vidagliptin 100 mg OD	Placebo
Dejager et al [42], 2007	152/160	24/1.8	8.5/69.4	52.5	47.3	NR	32.9	Vildagliptin 50 mg BD	Placebo
Asian-dominant studies									
Seino et al [79], 2011_A[d]	80/75	12/6.9	7.9/62.8	59.3	76.8	100	24.6	Alogliptin 25 mg OD	Placebo
Rhee et al [80], 2010	35/34	12/4.4	8.2/66.1	51.9	69.6	100	25.3	Gemigliptin 50 mg OD	Placebo
Nonaka et al [40], 2008	75/76	12/4.1	7.6/59.6	55.3	62.9	100	25.1	Sitagliptin 100 mg OD	Placebo
Mohan et al [24], 2009	352/178	18/2.0	8.7/71.6	50.9	57.7	100	25.0	Sitagliptin 100 mg OD	Placebo
Iwamoto et al [39], 2010	70/73	12/5.9	7.7/60.7	59.3	60.1	100	24.1	Sitagliptin 100 mg OD	Placebo
Kikuchi et al [81], 2009	76/72	12/5.9	7.4/57.4	59.6	65.5	100	24.4	Vidagliptin 50 mg BD	Placebo
Oral combination therapy									
Non-Asian-dominant studies									
Nauck et al [30], 2009	210/104	26/6.0	7.9/62.8	54.7	52.2	8.0	32	Alogliptin 25 mg OD + metformin (≥1,500 mg/day)	Placebo + metformin (≥1,500 mg/day)
Pratley et al [33], 2009_AP[e]	199/97	26/7.5	8.0/64.0	55.3	60.1	11.8	33.1	Alogliptin 25 mg OD + pioglitazone 30 mg or 45 mg ± (metformin or a sulfonylurea)	Placebo + pioglitazone 30 mg or 45 mg ± (metformin or a sulfonylurea)
Pratley et al [44], 2009_AG[f]	198/99	26/7.6	8.1/65.0	56.7	50.5	12.5	30.0	Alogliptin 25 mg OD + glibenclamide (known as glyburide in the USA and Canada)	Placebo + glibenclamide

Table 1 (continued)

Source	No. of participants (treatment/control)[a]	Treatment duration (weeks)/duration of diabetes (years)	Baseline HbA_{1c} level (%)/baseline HbA_{1c} level (mmol/mol)	Mean age (years)	Men (%)	Asian (%)	BMI (kg/m^2)	Treatment group	Control group
Rosenstock et al [45], 2010	164/163	26/3.0	8.8/72.7	53.0	48.9	NR	31.0	Alogliptin 25 mg OD + pioglitazone 30 mg OD	Pioglitazone 30 mg OD
Terra et al [47], 2011	73/76	12/6.9	8.4/68.3	56.6	67.8	0.0	32.0	Gosogliptin 20 mg OD + metformin	Placebo + metformin
Forst et al [26], 2010	66/71	12/6.7	8.4/68.3	59.9	59.1	0.7	32.0	Linagliptin 5 mg OD + metformin	Placebo + metformin
Taskinen et al [25], 2011	523/177	24/NR	8.1/65.0	56.5	54.1	20.9	29.9	Linagliptin 5 mg OD + metformin (≥ 1,500 mg/day)	Placebo + metformin (≥ 1,500 mg/day)
Gomis et al [28], 2011	259/130	24/NR	8.6/70.5	57.5	60.9	24.9	29.0	Linagliptin 5 mg OD + pioglitazone 30 mg OD	Placebo + pioglitazone 30 mg OD
DeFronzo et al [31], 2009	191/179	24/6.5	8.1/65.0	54.7	53.8	1.9	31.4	Saxagliptin 5 mg OD + metformin (≥1,500 mg/day)	Placebo + metformin (≥1,500 mg/day)
Jadzinsky et al [34], 2009	320/328	24/1.8	9.4/79.2	51.9	50.6	15.9	30.1	Saxagliptin 5 mg OD + metformin	Placebo + metformin
Hollander et al [48], 2009	186/184	24/5.2	8.3/67.2	53.6	47.0	34.9	30.0	Saxagliptin 5 mg OD + thiazolidinedione[g]	Placebo + thiazolidinedione[g]
Reasner et al [52], 2011	625/621	18/3.4	9.9/84.7	49.7	56.9	3.3	33.3	Sitagliptin 50 mg BD + metformin >1,000 mg/day	Metformin >1,000 mg/day
Rosenstock et al [51], 2006	175/178	24/6.1	8.0/63.9	56.3	55.5	4.2	31.5	Sitagliptin 100 mg OD + pioglitazone 30 or 45 mg OD	Placebo + pioglitazone 30 or 45 mg OD
Goldstein et al [18], 2007_3[h]	182/182	24/4.4	8.7/71.6	53.3	43.7	5.8	32.3	(Sitagliptin 50 mg + metformin 1,000 mg) BD	Metformin 1,000 mg BD
Goldstein et al [18], 2007_2[i]	190/182	24/4.5	8.8/72.7	53.8	52.2	6.2	32.1	(Sitagliptin 50 mg + metformin 500 mg) BD	Metformin 500 mg BD
Hermansen et al [19], 2007_1[c]	106/106	24/7.6	8.4/68.3	54.8	53.8	8.5	30.9	Sitagliptin 100 mg OD + glimepiride (≥4 mg/day)	Placebo + glimepiride (≥4 mg/day)
Charbonnel et al [22], 2006	464/237	24/6.2	8.0/63.9	54.5	57.1	10.7	31.1	Sitagliptin 100 mg OD+metformin (≥1,500 mg/day)	Placebo+metformin (≥1,500 mg/day)
Hermansen et al [19], 2007_2[i]	116/113	24/9.9	8.3/67.2	57.1	52.4	12.7	31.0	Sitagliptin 100 mg OD + glimepiride (≥4 mg/day) + metformin(≥1,500 mg/day)	Placebo + glimepiride (≥4 mg/day) + metformin (≥1,500 mg/day)
NCT00350779	170/92	18/NR	8.8/72.7	54.5	57.6	31.3	NR	Sitagliptin 100 mg OD+rosiglitazone 4 to 8 mg/day + metformin ≥1,500 mg/day	Placebo + rosiglitazone 4 to 8 mg/day + metformin ≥1,500 mg/day
Yoon et al [50], 2011	261/259	24/2.4	9.5/80.3	50.9	54.2	32.3	29.7	Sitagliptin 100 mg OD + pioglitazone 30 mg OD	Pioglitazone 30 mg OD
Scott et al [49], 2008	94/92	18/5.1	7.8/61.7	55.2	57.0	38.7	30.2	Sitagliptin 100 mg OD + metformin (≥1,500 mg/day)	Placebo + metformin (≥1,500 mg/day)
Raz et al [21], 2008	96/94	18/7.9	9.2/77.0	54.8	46.3	NR	30.2	Sitagliptin 100 mg OD + metformin (≥1,500 mg/day)	Placebo +metformin (≥1,500 mg/day)
Goodman et al [20], 2009	125/122	24/NR	8.6/70.5	54.6	59.9	0.4	31.7	Vildagliptin 100 mg OD + metformin (≥1,500 mg/day)	Placebo + metformin (≥1,500 mg/day)
Ahren et al [82], 2004	56/51	12/5.6	7.7/60.7	56.9	68.2	0.9	29.8	Vildagliptin 50 mg OD + metformin (1,500–3,000 mg/day)	Placebo + metformin (1,500–3,000 mg/day)

Table 1 (continued)

Source	No. of participants (treatment/control)[a]	Treatment duration (weeks)/duration of diabetes (years)	Baseline HbA_{1c} level (%)/baseline HbA_{1c} level (mmol/mol)	Mean age (years)	Men (%)	Asian (%)	BMI (kg/m^2)	Treatment group	Control group
Bosi et al [58], 2009	295/294	24/2.0	8.7/71.6	52.6	58.1	10.2	31.3	Vildagliptin 50 mg BD + metformin 1,000 mg BD	Metformin 1,000 mg BD
Rosenstock et al [55], 2007	148/161	24/2.1	8.7/71.6	51.7	61.2	43.7	29.2	Vildagliptin 100 mg OD + pioglitazone 30 mg OD	Pioglitazone 30 mg OD
Bosi et al [54], 2007	185/182	24/6.0	8.4/68.3	54.2	57.5	NR	33.0	Vildagliptin 100 mg OD + metformin (≥1,500 mg/day)	Placebo + metformin (≥1,500 mg/day)
Garber et al [56], 2007	158/158	24/4.7	8.7/71.6	54.4	47.8	NR	32.3	Vildagliptin 100 mg OD + pioglitazone 45 mg OD	Placebo + pioglitazone 45 mg OD
Garber et al [59], 2008	132/144	24/7.4	8.5/69.4	58.2	58.7	NR	31.6	Vildagliptin 50 mg OD + glimepiride 4 mg OD	Placebo + glimepiride 4 mg OD
Asian-dominant studies									
Kaku et al [83], 2011	113/115	12/6.7	7.9/62.8	59.7	64.0	100	26.2	Alogliptin 25 mg OD + pioglitazone (15 or 30 mg/day)	Placebo + pioglitazone (15 or 30 mg/day)
Seino et al [46], 2011_AV[j]	79/75	12/8.0	8.0/63.9	62.6	63.6	100	23.8	Alogliptin 25 mg OD + voglibose 0.2 mg TD	Placebo + voglibose 0.2 mg TD
Owens et al [36], 2011	792/263	24/NR	8.1/65.0	58.1	47.2	51.7	28.4	Linagliptin 5 mg OD + metformin + sulfonylurea	Placebo + metformin + sulfonylurea
Yang et al [37], 2011	283/287	24/5.1	7.9/62.8	54.1	48.2	100	26.2	Saxagliptin 5 mg OD + metformin (≥1,500 mg/day)	Placebo + metformin (≥1,500 mg/day)
Kashiwagi et al [53], 2011	66/68	12/7.9	7.6/59.6	58.4	64.9	100	26.4	Sitagliptin 50 mg OD + pioglitazone	Placebo + pioglitazone
NCT00813995	197/198	24/NR	8.5/69.4	54.6	50.6	100	NR	Sitagliptin 100 mg OD + metformin	Placebo + metformin
Chien et al [84], 2011	49/48	24/13.7	9.7/82.5	73.0	42.2	100	26.1	Sitagliptin 100 mg OD + others (sulfonylurea, metformin, and α-glucosidase)	Others (sulfonylurea, metformin, and α-glucosidase)
Kikuchi et al [57], 2010	102/100	12/9.2	7.9/62.8	59.7	71.3	100	24.5	Vildagliptin 50 mg BD + glimepiride	Placebo + glimepiride

[a] All numbers are of randomised patients

[b] S, saxagliptin

[c] 1 represents the first pair of the article

[d] A, alogliptin

[e] AP, alogliptin and pioglitazone

[f] AG, alogliptin and glibenclamide

[g] Pioglitazone 30 or 45 mg once a day or rosiglitazone 4 or 8 mg OD or in two divided doses of 4 mg BD

[h] 3 represents the third pair of the article

[i] 2 represents the second pair of the article

[j] AV, alogliptin and voglibose

NR, not recorded; OD, once daily; BD, twice daily; TD, three times a day

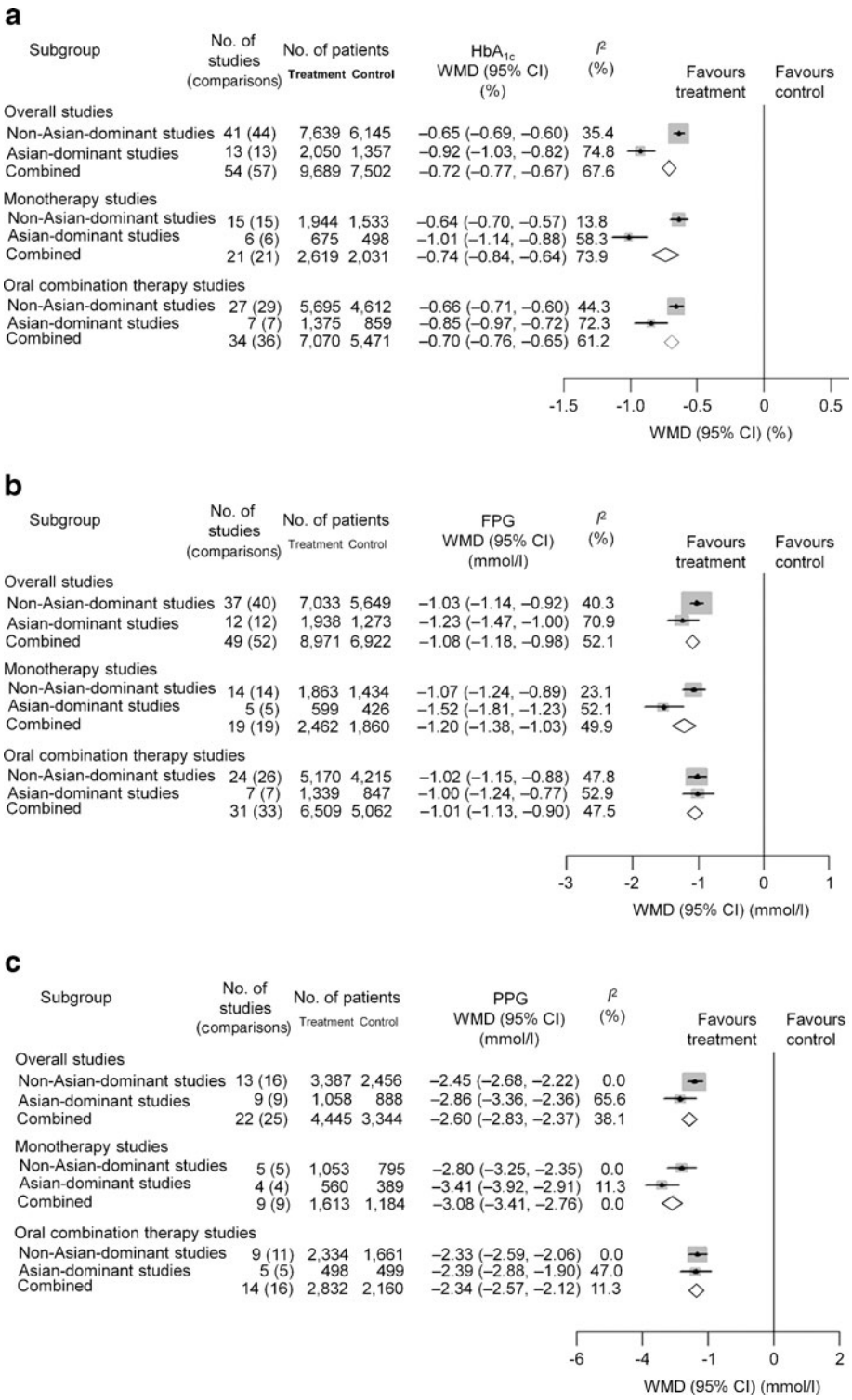

Fig. 2 Differences between Asian-dominant and non-Asian-dominant studies in HbA_{1c}-lowering efficacy (**a**), FPG-lowering efficacy (**b**) and 2 h PPG-lowering efficacy (**c**)

(Asian >80%) (ESM Table 3). Consequently, we could reduce the heterogeneity of three zones compared with that of the binary classification (Asian-dominant vs non-Asian-dominant). The difference in HbA_{1c}-lowering efficacy between the high Asian zone and the low Asian zone was −0.29% (95% CI −0.39, −0.19), which was statistically significant ($p<0.001$).

Secondary outcome: FPG The changes in FPG from baseline are shown in Fig. 2b. We analysed 52 pairs from 49 studies involving FPG. Overall, FPG changed from baseline by −1.08 mmol/l (95% CI −1.18, −0.98; $I^2=52.1\%$). The change in FPG from baseline was −1.03 mmol/l (95% CI −1.14, −0.92; $I^2=40.3\%$) in the non-Asian-dominant studies and −1.23 mmol/l (95% CI −1.47, −1.00; $I^2=$

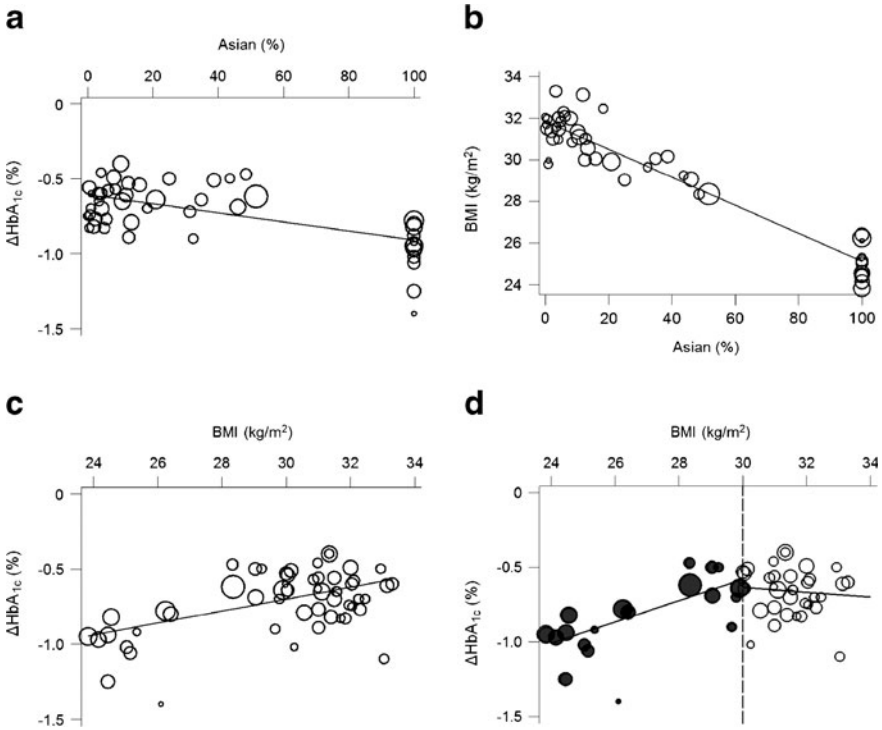

Fig. 3 Correlations between HbA_{1c}-lowering efficacy and percentage of Asian participants or BMI. (**a**) Correlation between HbA_{1c}-lowering efficacy and percentage of Asian participants ($p<0.001$). (**b**) Correlation between BMI and percentage of Asian participants ($r=0.95$, $p<0.001$). (**c**) Correlation between HbA_{1c}-lowering efficacy and BMI ($p<0.001$). (**d**) HbA_{1c}-lowering efficacy in lower- and higher-BMI groups. The equation for the trend line on the left is $Y=0.072\times X-2.7$ ($p<0.001$) and the equation for the trend line on the right is $Y=-0.016\times X-0.2$ ($p=0.623$), where 'p' represents p values of regression coefficients and 'r' represents correlation coefficient calculated from a meta-regression analysis

70.9%) in the Asian-dominant studies. In the monotherapy trials, the overall decrease in FPG was significantly larger in the Asian-dominant studies than in non-Asian-dominant studies; the difference between the two groups was −0.45 mmol/l (95% CI −0.79, −0.10). However, in oral combination therapy trials, there was no difference in the change in FPG from baseline between the two groups.

Secondary outcome: 2 h PPG The changes in 2 h PPG from baseline are shown in Fig. 2c. We analysed 25 pairs from 22 studies involving PPG. Overall 2 h PPG change from baseline was −2.60 mmol/l (95% CI −2.83, −2.37; $I^2=38.1\%$). The change was −2.86 mmol/l (95% CI −3.36, −2.36; $I^2=65.6\%$) in the Asian-dominant studies and −2.45 mmol/l (95% CI −2.68, −2.22; $I^2=0.0\%$) in the non-Asian-dominant studies. Although the mean value of the decrease in 2 h PPG was numerically larger in the Asian-dominant studies, the difference was not statistically significant. A similar trend was observed in both the monotherapy and oral combination therapy trials.

Secondary outcome: RR for achieving HbA_{1c} <7.0% (53.0 mmol/mol) Thirty-one pairs from 28 studies were used to estimate the RR for achieving HbA_{1c} <7.0% (53.0 mmol/mol). The RR was significantly larger in the Asian-dominant studies than in the non-Asian-dominant studies (3.4 [95% CI 2.6, 4.7] vs 1.9 [95% CI 1.8, 2.0]) (ESM Fig. 5).

Secondary outcome: body weight Thirty pairs from 29 studies were used for the analysis on body weight. Overall body weight change from baseline was 0.52 kg (95% CI 0.37, 0.67; $I^2=47.4\%$). There was no significant difference in body weight change between the Asian-dominant studies and the non-Asian-dominant studies (ESM Fig. 6).

Discussion

In this systematic review and meta-analysis, the HbA_{1c}-lowering efficacy of DPP-4 inhibitors in type 2 diabetes was higher in Asians than in other ethnic groups. Differences in BMI across ethnic groups may mediate the HbA_{1c}-lowering efficacy of DPP-4 inhibitors. In the current meta-analysis, there was no correlation between the BMI and the HbA_{1c}-lowering efficacy of DPP-4 inhibitors in the studies in which the average BMI was ≥30 kg/m^2, but BMI was significantly correlated with the HbA_{1c}-lowering efficacy of DPP-4 inhibitors in the studies in which the average BMI was <30 kg/m^2. There was no difference in body weight change from baseline between the Asian- and the non-Asian-dominant studies, which suggests that the baseline BMI might influence the glucose-lowering effect of DPP-4 inhibitors. In fact, a Japanese study revealed a significant correlation ($r=0.419$, $p=0.0023$) between baseline BMI and HbA_{1c} levels after 16 weeks of sitagliptin treatment in patients with type 2 diabetes and a BMI of 24.1±5.0 kg/m^2 [63], which suggests that a lower BMI is a predictor of a good response to a DPP-4 inhibitor. Collectively, the different BMIs among ethnic groups may contribute to the differences in the glucose-lowering response to DPP-4 inhibitors.

Because BMI is highly correlated with insulin sensitivity [64], the apparent effect of BMI on the HbA_{1c}-lowering efficacy observed in our study may be mediated by differences in insulin sensitivity among different ethnic groups. However, factors other than BMI may influence the insulin sensitivity of different ethnic groups. In a study examining 531 first-degree relatives of individuals with type 2 diabetes in the USA [65], Asian–Americans with a normal glucose tolerance or impaired glucose regulation were more insulin-sensitive than all other ethnic groups, including African–Americans, Hispanic–Americans and persons of European descent. These findings remained significant even after adjusting for the effect of BMI. Although clinical variables reflecting insulin sensitivity, such as direct or indirect indices for insulin sensitivity or amount of visceral fat, were not available in this analysis, those variables could provide a missing link between ethnicity and treatment response to DPP-4 inhibitors.

If the pharmacokinetic properties of DPP-4 inhibitors differ between Asians and non-Asians largely because of differences in body size, the glucose-lowering efficacy of DPP-4 inhibitors may differ by ethnic group. However, the clinical pharmacological characteristics of several DPP-4 inhibitors are similar in different ethnic groups [66, 67]. The pharmacokinetic variables of sitagliptin are reported not to be different among whites, blacks, Hispanics and Asians [66]. In a study involving 60 healthy Chinese participants, vildagliptin had pharmacokinetic variables that were similar to non-Asians [67]. Therefore, we cannot explain the better glucose-lowering efficacy of DPP-4 inhibitors in Asians by different pharmacokinetic properties.

According to the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) [68] and the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) [69] studies, the prevalence of post-challenge hyperglycaemia is higher in Asian than in white persons. In the DECODA study, more than half the patients with diabetes had isolated postprandial hyperglycaemia [70], which is additionally a powerful predictor of cardiovascular disease and premature death [71]. DPP-4 inhibitors are known to reduce both FPG and PPG [72]. In particular, DPP-4 inhibitors effectively lower PPG by increasing active GLP-1 and decreasing glucagon levels [73]. We examined whether the efficacy of DPP-4 inhibitors in lowering FPG or PPG differs between Asian- and non-Asian-dominant studies. The FPG-lowering efficacy with DPP-4 inhibitor monotherapy was higher in the Asian-dominant studies than in the non-Asian-dominant studies, while the PPG-lowering efficacy was not significantly different between two groups. Because the number of studies reporting FPG or PPG from baseline was relatively smaller and the PPG values were measured with either a 75 g glucose load or a standardised meal, further studies are needed to examine the difference in FPG- or PPG-lowering efficacy of DPP-4 inhibitors among different ethnic groups.

There was no effect of baseline HbA_{1c} on the efficacy of DPP-4 inhibitors in our analysis. However, Deacon suggested that a higher baseline HbA_{1c} would be a predictor of a greater HbA_{1c} reduction with a DPP-4 inhibitor [72]. Approximately 70% of the studies reviewed in Deacon's paper were also included in our study. However, the analytical methods were different. The values presented by Deacon were delta HbA_{1c} simply in the DPP-4 inhibitor group rather than the change in the delta HbA_{1c} between the placebo and the DPP-4 inhibitor group. If we plot our data in the same way as Deacon, the graph looks similar (data not shown). Therefore, at least in our analysis, the contribution of BMI or Asian proportion outweighs the effect of baseline HbA_{1c} in determining the placebo-subtracted HbA_{1c}-lowering effect.

There are some limitations to this study. First, we did not separate the studies including South Asians (e.g. Indians) from the studies mainly comprised of East Asians. Asian populations are ethnically heterogeneous and have different demographic, cultural and socioeconomic characteristics. Insulin resistance may be the major contributor to the pathogenesis of type 2 diabetes in South Asian populations [3] but not East Asian populations. Second, because the analysis was based only on aggregated information at the study level and was exploratory in nature, additional studies are needed to explain the mechanisms for the different effect by ethnicity. Although DPP-4 inhibitors showed an overall significant treatment effect in a meta-analysis of the current literature, there was substantial heterogeneity in terms of the size of the effect among the studies, whose clinical characteristics additionally differ. To confirm our observation, a patient-level data analysis or a prospective randomised study including different ethnic groups should be performed.

In conclusion, the glucose-lowering efficacy of DPP-4 inhibitors is higher in Asians than other ethnic groups. Different BMIs may contribute to this difference in treatment response to DPP-4 inhibitors. Considering that Asia is the epicentre of the current worldwide epidemic of diabetes [2], this study suggests the need for ethnic-specific guidelines for the pharmacological treatment of diabetes.

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Contribution statement YGK, SH and YMC developed the protocol and were responsible for the study design, main concept and statistical analysis. YGK and TJO were responsible for the study selection and data extraction. SH and YMC additionally contributed to data extraction. YGK, SH, SHK, KSP and YMC were contributors to the result interpretation. All authors wrote the initial draft and revised the paper for important intellectual content. All authors were contributors to the final manuscript and have approved the final version.

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