

Treatment response between Asian and non-Asian patients with type 2 diabetes: is there any similarity or difference?

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Introduction

According to the latest edition of Diabetes Atlas, the prevalence of diabetes is increasing globally, but the situation is particularly alarming in Asia and in China.^[1-3] It was estimated that, for the same body mass index (BMI), Asian population had a higher prevalence of diabetes than the non-Asian counterparts,^[4] because of the lower BMIs reported in Asian diabetes population. Based on the physiologic and pathologic background, it was believed that compared to non-Asian patients with type 2 diabetes, Asian patients might have a different pattern as more defect in β -cell function than decreased insulin sensitivity.^[5-7] Moreover, given the different genetic and pharmacogenetics ethnic background,^[8,9] it was deduced that the treatment response in terms of glucose control and body weight control between the two ethnicities might be different. Is there any similarity or difference in the treatment response between Asian and non-Asian patients with type 2 diabetes? Asian diabetes, do it really exist? There is a need to better understand this question.

Treatment response to oral anti-diabetes drugs

In the treatment of alpha glucosidase inhibitors (AGIs), based on a recently published meta-analysis with 67 trials included, comparisons between Asian and Caucasian patients with type 2 diabetes indicated that no significant difference was observed in hemoglobin A1c (HbA1c) change (difference between ethnicities=0.097%, 95% confidence interval [CI]: -0.42% to 0.62%, $P=0.709$), or in body weight change (difference between ethnicities=0.45 kg, 95% CI: -1.28 to 2.18 kg, $P=0.599$).^[10] The difference between Asian and non-Asian patients in fasting plasma glucose (FPG) change (difference between ethnicities=0.39 mmol/L, 95% CI: -0.40 to 1.19 mmol/L, $P=0.318$), post-prandial plasma glucose (PPG) change

(difference between ethnicities=-0.29 mmol/L, 95% CI: -1.80 to 1.22 mmol/L, $P=0.692$) or incidence of hypoglycemia (odds ratio [OR]=1.25, 95% CI: 0.82-1.91 in Asian; OR=1.75, 95% CI: 1.19-2.55 in non-Asian) also did not show any significance. Previously published meta-analysis also demonstrated this no significant difference between Asian and Caucasian patients with type 2 diabetes.^[11]

In terms of dipeptidyl peptidase-4 (DPP-4) inhibitor treatment, published systematic reviews, and meta-analysis^[12] comparing the efficacy between Asians and non-Asians revealed that the between-group difference of HbA1c reduction was -0.26% with significance (95% CI: -0.36% to -0.17%, $P<0.001$), while body weight changes corrected by placebo were comparable between Asians and Caucasians (weighted mean difference corrected by placebo: 0.37 and 0.45 kg, respectively).^[13] Another study by using univariate meta-regression analysis also applied that the percentage of Asian subjects was associated with the glucose-lowering efficacy in DPP-4 inhibitor treatment.^[14] However, according to individual patient data, a study with a small sample size of patients included, evaluated DPP-4 inhibitor as a third-line add-on therapy in patients inadequately controlled by metformin and sulfonylurea, which concluded that the glycemic improvement in HbA1c was similar between Asian and non-Asian patients.^[15]

In the treatment of sodium-glucose cotransporter 2 inhibitors, a meta-analysis including 17 trials with Asian patients and 39 trials with non-Asian patients^[16] suggested that there was a non-significant difference of HbA1c decreases between groups (difference 0.05%, $P>0.05$) and a non-significant difference of weight reductions as well (difference 0.08 kg, $P>0.05$). The changes in systolic blood pressure and diastolic blood pressure were neither with significant difference between these two ethnicities. However, compared with non-Asians, reduction in

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triglyceride (difference -0.14 mmol/L, $P < 0.05$) and elevation in high-density lipoprotein cholesterol (difference 0.09 mmol/L, $P < 0.05$) were significantly more in Asians.

So far, no direct or indirect comparison between Asian and non-Asian patients with diabetes in the treatment of metformin, sulfonylureas, or thiazolidinediones was found. However, data from some clinical trials may provide some evidence. In a prospective, multicenter, open-label study in China,^[17] mean HbA1c decreases at week 16 were -1.84% , -1.78% , and -1.78% in normal-weight, overweight, and obese patients ($P = 0.664$), which was comparable with the decrease in a diabetes outcome progression trial (ADOPT) with metformin therapy in newly diagnosed Caucasian patients with diabetes.^[18] In a controlled, double blind, multicentre non-inferiority trial, Chinese patients with Xiaoke Pill treatment, a compound of Chinese herbs combined with glibenclamide, or with glibenclamide treatment, both showed significant absolute HbA1c changes from baseline (-0.70% , 95% CI: -1.06% to -0.34% in Xiaoke Pill group; -0.66% , 95% CI: -1.05% to -0.28% in glibenclamide group) at 48 weeks,^[19] which was also comparable with the decrease in ADOPT with glibenclamide therapy in patients with diabetes with mainly Caucasians.^[18] In Japanese patients with type 2 diabetes, mean HbA1c was reduced by 0.67% in patients receiving pioglitazone plus metformin during a 12-week observation period.^[20] In another randomized, open-labeled, active-controlled trial in China, HbA1c change from baseline at week 48 was $-1.49\% \pm 0.05\%$ in avandamet treatment.^[21] Results from a meta-analysis indicated that thiazolidinediones led to a decrease of 0.80% (95% CI: -1.00% to -0.66% , $P < 0.05$) in Caucasian patients.^[22]

Treatment response to glucagon-like peptide-1 receptor agonist

In terms of glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment, a meta-analysis with 15 trials included comparing the HbA1c-lowering efficacy of GLP-1RA between Asians and non-Asians with type 2 diabetes^[23] illustrated that GLP-1RA lowered HbA1c more in Asian-dominant studies than in non-Asian-dominant studies (between-group difference, -0.32% , 95% CI: -0.64 to -0.01 ; $P = 0.04$). Body weight changes were similar between the two groups. However, the risk of hypoglycemia tended to be higher in Asian-dominant studies (risk ratio [RR] = 2.8 , 95% CI: 2.3 – 3.5) than that in non-Asian-dominant studies (RR = 1.5 , 95% CI: 1.2 – 1.8).

Treatment response to insulin

A post-hoc analysis^[24] with more than 2000 patients with type 2 diabetes enrolled to explore the impact of race/ethnicity on efficacy and safety of twice-daily insulin lispro mix 75/25 (LM75/25) and once daily insulin glargine (GL), outlined that Asian patients had less HbA1c reduction from baseline vs Caucasian patients (LM75/25: -1.46% vs. -1.84% , $P < 0.01$; GL: -1.25% vs. -1.78% , $P < 0.01$), with a higher PPG post-lunch (GL: 40 ± 3 mg/dL vs. 30 ± 2 mg/dL, $P < 0.01$), a lower weight gain (LM75/25:

2.6 ± 0.3 kg vs. 3.6 ± 0.2 kg; $P < 0.05$), a higher insulin dose (GL: 0.47 ± 0.02 U/kg vs. 0.39 ± 0.01 U/kg, $P < 0.01$; LM75/25: 0.63 ± 0.02 U/kg vs. 0.44 ± 0.01 U/kg, $P < 0.01$), and a lower hypoglycemia rate (15 ± 2 vs. 23 ± 1 events/patient per year). Another post-hoc analysis using insulin-naïve patients data with the aim to explore the efficacy of insulin lispro mix 25 (LM25) or insulin glargine plus insulin lispro (G+L) among different racial/ethnic groups,^[25] stated that East Asians (LM25, -2.03% ; G+L, -1.76%) and non-Asians (LM25, -2.07% ; G+L, -2.05%) achieved similar HbA1c reduction in the LM25 arm, but East Asians got a lower rate of hypoglycemia (LM25: 69.8% vs. 94.1% ; G+L: 77.3% vs. 91.8%). The total daily insulin dose for non-Asians was 0.67 U/kg (LM25) and 0.61 U/kg (G+L), for East Asians was 0.53 U/kg (LM25) and 0.59 U/kg (G+L). The mean change in body weight (kg) for each subgroup was comparable between East Asians (LM25: 2.95 ± 2.97 kg vs. 3.00 ± 4.09 kg; G+L: 2.81 ± 3.39 kg vs. 3.43 ± 4.72 kg).

A recently published analysis using 235 Asian patients' data and 3351 non-Asian patients data from 16 trials with the aim to compare outcomes between Asian and non-Asian patients with type 2 diabetes initiating insulin glargine 100 U/mL (Gla-100),^[26] found that Gla-100 resulted in less reduction in HbA1c from baseline in Asian patients (-1.3% vs. -1.6% , respectively; $P = 0.0001$) and less absolute weight gain ($+1.3$ kg vs. $+1.9$ kg, $P = 0.013$) compared with non-Asian patients. But reduction in FPG and incidence of hypoglycemia were similar between Asian and non-Asian patients. In addition, Asian patients required a lower insulin dose than non-Asian patients (0.36 U/kg vs. 0.41 U/kg, $P = 0.045$).

Of course, there are limitations to the published studies. These studies, whether post-hoc analysis based on patient level data, or meta-analyses based on randomized control trials, none of which, were specifically designed to assess the impact of race/ethnicity on treatment or pre-specified the ethnicity as subgroup analysis. In addition, multiple factors of culture between Asian population and non-Asian population were not possible to be adequately controlled, such as style of diet and exercise, access to medical care, socioeconomic factors, patient adherence to medical treatment, etc. Despite these limitations, understanding the similarities and differences between these two ethnicities may be important in designing treatment plans for Asian patients with type 2 diabetes.

Conclusion

Although Asian individuals with type 2 diabetes had a lower BMI and a younger age than non-Asian individuals, with a genetic susceptibility for developing type 2 diabetes, and was characterized by early decline in b-cell function, which may influence their response to anti-diabetes treatment, results from systematic reviews and meta-analyses, as well as post-hoc analyses, illustrated that for some hypoglycemic treatments, the response between Asian and non-Asian patients tended to be similar, while for some other hypoglycemic treatments, the difference of treatment response between these two ethnicities was somehow with significance.

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Conflicts of interest

The authors report no conflicts of interest.

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