WHY ARE INCRETIN-BASED THERAPIES MORE EFFICIENT IN EAST ASIANS? PERSPECTIVES FROM THE PATHOPHYSIOLOGY OF TYPE 2 DIABETES AND EAST ASIAN DIETARY HABITS

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ABSTRACT

Type 2 diabetes mellitus (T2D) is one of the most serious global health problems. This is partly a result of its drastic increase in East Asia, which now comprises more than a quarter of the global diabetes population. Ethnicity and lifestyle factors are two determinants in the aetiology of T2D, and changes such as increased animal fat intake and decreased physical activity link readily to T2D in East Asians, which is characterised primarily by β-cell dysfunction that is evident immediately after ingestion of glucose or a meal, and less adiposity compared with T2D in Caucasians. These pathophysiological differences have an important impact on therapeutic approaches. Incretin-based therapies, such as dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), have become widely available for the management of T2D. Incretins, glucose-dependent insulinotropic polypeptide, and glucagon-like peptide-1 are secreted from the gut in response to the ingestion of various nutrients, including carbohydrates, proteins, and fats, and enhance insulin secretion via a glucose-dependent pathway to exert their glucose-lowering effects. Recent meta-analyses of clinical trials of DPP-4i and GLP-1RA found the drugs to be more effective in East Asians, most likely due to amelioration of the primary β-cell dysfunction by increased stimulation through incretin activity. In addition, our finding that the glycosylated haemoglobin-lowering effects of DPP-4i are enhanced by fish intake, and possibly worsened by animal fat intake, suggests that dietary habits such as eating more fish and less meat can affect the secretion of incretins, and supports the greater efficacy of incretin-based therapies in East Asians.

Keywords: Type 2 diabetes mellitus (T2D), East Asian, incretin, dipeptidyl peptidase 4 (DPP-4) inhibitor, glucagon-like peptide-1 receptor agonist (GLP-1RA).

INTRODUCTION

Rapidly increasing Type 2 diabetes mellitus (T2D) is one of the most serious health problems today. The number of patients with diabetes, estimated to be 387 million in 2014, is expected to grow to 592 million by 2035,[1] partly due to the drastic increase in East Asian patients, who now comprise approximately one-quarter of the global diabetes population. T2D in East Asian countries is characterised primarily by β-cell dysfunction, which is evident immediately after ingestion of glucose or mixed meal; there is less obesity compared with Caucasians.[2-4] Insulin resistance, as indicated by the homeostatic model assessment of insulin resistance (HOMA-IR), is generally higher in Caucasian T2D, while β-cell response, as measured by the homeostatic model assessment of β-cell function (HOMA-β) and insulinogenic index (IGI), is lower in East Asian T2D. These pathophysiological differences in the manifestation of the disease have a crucial impact on the appropriate preventive and therapeutic approaches. Due to reduced β-cell function, insulin secretagogues such as sulfonylureas (SU) and glinides have been used as preferred drugs for the management of T2D in the Japanese population and other East Asian populations. In contrast to their superior effects on T2D in Japanese and East Asian populations, SU and glinides are associated with hypoglycaemia and body weight gain. Recently, incretin-based therapies, such as dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), have become widely available for T2D management and are used frequently in East Asia. In this article, we revisit the pathophysiology of East Asian T2D with reference to β-cell dysfunction and insulin resistance, together with incretin secretion and action. We also discuss the efficacy of the incretin-based therapies DPP-4i and GLP-1RA in East Asians, and a novel interaction of medical nutritional therapies with the glycosylated haemoglobin (HbA1c)-lowering effect of DPP-4i.

PATHOPHYSIOLOGY OF T2D IN EAST ASIANS

Historically, the prevalence of T2D among East Asians was low compared with the populations in Western countries, including the USA. Nevertheless, a higher prevalence of diabetes in Japanese Americans compared with the general American population suggested that Japanese people are not protected from diabetes. Indeed, in the early 1960s, the incidence of diabetes in Hawaii was found to be 20.1 per 1,000 person-years for the Japanese and 7.3 for Caucasians,[5] suggesting that the Japanese might be at special risk of developing diabetes upon exposure to lifestyles in the USA. This notion was further supported by research demonstrating higher rates of glucose intolerance among Japanese Americans living in Hawaii and Los Angeles than among those who lived in Japan.[6] It is now widely accepted that obesity, through its association with insulin resistance, increases the risk of T2D.[7] However, Japanese Americans, who generally have a lower body mass index compared with other ethnic groups, develop diabetes at a rate that is associated with obesity in Caucasians.[8] This has been shown recently in East Asians in general.[9]

In the late 1970s, Fujimoto et al.[10] initiated the study of Japanese Americans in Seattle to understand why Japanese Americans so readily developed diabetes. Reported daily calorie intake, although less than that of Caucasians, was comparable between Japanese Americans and the native Japanese, although Japanese Americans consumed fats in amounts similar to those consumed by Caucasians, which were much higher than those in native Japanese people. Thus, Japanese Americans who adopted Western dietary habits including the higher consumption of animal fat showed higher rates of diabetes. This is consistent with the fact that diabetes is rapidly increasing in Japan and across East Asian countries today, together with reduced intake of carbohydrates and increased intake of animal fats (Table 1).[11-15] The apparent high sensitivity of East Asians to Western dietary habits in terms of diabetes development requires further investigation.

T2D is characterised by insulin resistance and impaired insulin secretion. Based mainly on studies of Caucasian subjects, it is proposed that T2D is triggered by insulin resistance that is compensated for initially by increased β-cell response, but which eventually leads to T2D due to exhaustion of pancreatic β-cells.[16,17] As reported by our group and others, Japanese prediabetes and early stage diabetes are characterised by reduced insulin secretion along with lower insulin resistance when compared with Caucasians.[18,19] Insulin secretory capacity has been well characterised by HOMA-β and IGI during the oral glucose tolerance test (OGTT) and, to a lesser degree, by acute insulin response during the intravenous glucose tolerance

test (IVGTT). Our previous studies, from as early as the 1970s, indicated that the insulin response to ingestion of glucose in the Japanese, both in normal glucose tolerance (NGT) and T2D, was much lower than that in Caucasians.[20,21] Later, cross-sectional studies in Japanese subjects with NGT, impaired glucose tolerance (IGT), and T2D confirmed reduced insulin secretion in the Japanese compared with Caucasians.[18,21] These studies suggest that the Japanese may be characterised by impaired early phase insulin secretion, as the IGI of Japanese people is lower throughout NGT via IGT to T2D, while the IGI is higher in Caucasians than in the Japanese throughout all stages of glucose tolerance.[18,22]

Reduced IGI has been reported not only in Japanese people but also in other East Asians, such as Koreans[23] and Chinese[24] (Figure 1). Our previous investigations also suggested that the acute insulin response observed during IVGTT was substantially lower in the Japanese compared with Caucasians.[25,26] These findings are supported by important recent studies: 1) systematic review and meta-analysis of insulin response to glucose in IVGTT revealing reduced insulin secretory capacity of East Asians compared with Caucasians and Africans;[27] and 2) OGTT and IVGTT studies in matched cohorts of Caucasian and Japanese individuals revealing reduced β-cell function in the Japanese.[28,29] Thus, a reduced insulin secretory capacity, especially during the early phase, is typical of East Asians, and may render them sensitive to the development of diabetes in conditions of over-nutrition.

Table 1: Changes in dietary patterns in East Asian countries and the USA.

Japan	Year of survey	1950	1960	1970	1980	1990	2000	2005	2010
	Total energy intake (kcal)	2,098	2,096	2,210	2,219	2,026	1,948	1,904	1,849
	Protein (%)	13.0	13.3	14.0	14.2	15.5	16.0	16.2	14.6
	Fat (%)	7.7	10.4	18.9	22.6	25.3	26.5	25.1	26.1
	Carbohydrate (%)	79.7	76.1	66.6	55.7	56.7	54.6	56.1	55.7
China	Year of survey	1952	1962	1970	1982	1992	2000	2004	2009
	Total energy intake (kcal)	2,056	1,697	1,978	2,518	2,328	M2,146/F1,941	M2,064/F1,807	M1,943/F1,969
	Protein (%)	9.3	9.7	9.6	10.6	11.7	M24.0/F23.7	M24.6/F24.4	M25.5/F24.4
	Fat (%)	7.6	5.5	7.4	17.5	22.5	M26.3/F26.4	M26.9/F26.4	M27.8/F29.2
	Carbohydrate (%)	83.0	84.8	82.9	71.8	65.8	M58.9/F58.7	M57.8/F58.3	M56.2/F54.9
Korea	Year of survey			1969	1979	1989	2000	2005	2010
	Total energy intake (kcal)			2,105	2,098	1,871	1,863	1,826	1,691
	Protein (%)			12.5	13.3	16.1	16.4	16.6	14.7
	Fat (%)			7.2	11.2	13.4	19.7	21.3	20.0
	Carbohydrate (%)			80.4	75.3	69.1	63.9	62.1	65.1
USA	Year of survey	1950	1960	1970	1980	1990	2000	2005	2010
	Total energy intake (kcal)	3,200	3,100	3,300	3,500	3,800	4,200	4,100	4,000
	Protein (%)	11.8	11.9	11.9	12.7	12.4	11.8	12.0	12.0
	Fat (%)	39.1	40.1	40.1	41.7	39.6	40.9	42.6	42.8
	Carbohydrate (%)	52.0	50.1	48.6	46.6	49.3	48.1	47.6	47.4

Data source: The National Health and Nutrition Survey, Japan and The National Nutrition Survey, Japan; China;[11,12] Korea;[13,14] U.S. Department of Agriculture, Center for Nutrition Policy and Promotion, Nutrient Content of the U.S. Food Supply, USA.
M: male; F: female.
Reproduced from Yabe et al.[15]

Insulin resistance is best characterised by HOMA-IR, to a lesser extent by Matsuda index or insulin sensitivity index composite calculated by OGTT data, and less still by sensitivity index (SI), which is an index of insulin sensitivity derived from IVGTT data calculated by minimal model analysis. Cross-sectional studies in Japanese subjects with NGT, IGT, and T2D demonstrated that HOMA-IR is low in the Japanese throughout NGT, IGT, and T2D compared with that of Caucasians.[18,22] In addition, Tripathy et al.[22] reported that HOMA-IR increased approximately 2-fold as glucose tolerance deteriorated from NGT to IGT, and 3.6-fold from NGT to T2D, but the change in HOMA-IR in the Japanese from NGT via IGT to T2D is not so drastic.[18] Our previous investigation, using minimal model analysis during IVGTT, also revealed greater preservation of insulin sensitivity in Japanese T2D patients when compared indirectly with Caucasian T2D patients.[25,26] These findings are supported by recent studies: 1) systematic review and meta-analysis of SI in IVGTT finding less insulin resistance in East Asians compared with Caucasians and Africans;[27] and 2) studies in matched cohorts of Caucasian and Japanese individuals revealing lower HOMA-IR and Matsuda index, but not higher insulin sensitivity, in the Japanese throughout the different stages of glucose tolerance.[28,29]

Counterbalance between insulin secretion and insulin resistance is critical for T2D pathogenesis. Being less obese with less insulin resistance, the Japanese have a greater amount of visceral fat in comparison with Caucasians after adjusting for age, gender, and subcutaneous fat,[30] suggesting that Japanese people readily accumulate visceral fat. Recent investigations confirm that East Asians have a higher visceral versus subcutaneous fat ratio despite being less obese with less insulin resistance.[31] Thus, a subtle increase in insulin resistance due to visceral fat accumulation may disturb the fine balance with the reduced insulin secretory capacity often seen in East Asians, and could easily trigger the onset of T2D. This model might well explain why there is a higher proportion of isolated IGT in isolated impaired fasting glucose (IFG), IFG/IGT, and isolated IGT in Asia than is found in Europe.[32,33] While conversion rates from NGT to T2D via isolated IGT, IFG/IGT, and isolated IGT need to be compared between Asians and Europeans prospectively in the future, the model may also underlie the appearance of diabetes in East Asians who are not nearly as obese as Caucasians,[9,34] as well as the increased T2D incidence among East Asians, such as Japanese Americans in the USA who consume similar daily energy but significantly more fats than their counterparts in Japan.[10] This is consistent with the fact that diabetes is rapidly increasing in Japan and across East Asian countries today, along with a reduced intake of carbohydrates and increased intake of animal fats.

INCRETIN FOR AMELIORATION OF β-CELL DYSFUNCTION IN EAST ASIANS

Incretin is an important area of research in relation to β-cell function: it has been demonstrated that incretins are responsible for 50–70% of post-challenge insulin secretion in Caucasians.[35,36] The incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted from the gut in response to ingestion of various nutrients including carbohydrates, proteins, and fats, and enhance insulin secretion via a glucose-dependent pathway.[35-37] Studies in mice deficient in both GIP and GLP-1 receptors indicate that insulin secretion immediately after oral glucose load is largely dependent on the actions of incretins,[36] suggesting enhancement of incretin activity to ameliorate impaired early phase insulin secretion. While earlier studies reported reduced GLP-1 secretion and enhanced GIP secretion in Caucasian T2D,[35,36] later studies failed to confirm this,[38-40] which suggests that incretin secretion may not be involved in the pathogenesis of T2D in Caucasians.

Recently, our group and others have characterised secretions of GLP-1 and GIP among NGT and T2D and found that there are no differences among the two groups in the Japanese[41-43] or Koreans,[44] indicating that incretin secretion per se is not involved in the pathogenesis of T2D in East Asians, similar to the case in Caucasians. However, it is noteworthy that meal-induced secretion of GLP-1 is negligible in the Japanese,[41,45] and that GLP-1 secretion in response to 75-g OGTT is lower in the Japanese compared with that in Caucasians when measured by the same assay system.[41,46] In addition, very low levels of biologically intact GLP-1 in the Japanese[41-43] might suggest increased dipeptidyl peptidase 4 (DPP-4) activity, although this is partly because recent incorporation of an extraction step improves specificity but reduces the observed measurements of intact GLP-1 within the circulation.[45,47] While it has been demonstrated

that DPP-4 activity is enhanced in T2D,[48] little is known about ethnic differences in DPP-4 activity. Although it remains to be determined whether differences in secretion and/or degradation of GLP-1 contribute to the difference in β-cell function between East Asians and Caucasians, these observations suggest that endogenous and exogenous GLP-1 supplementation by incretin-based therapies, such as DPP-4i and GLP-1RA, might exert greater efficacy in the management of T2D in East Asians. While recent studies suggest that DPP-4i treatment increases the levels of a putative insulin-sensitising adipocytokine and adiponectin,[49,50] which might contribute to the greater HbA1c-lowering effects of DPP-4i in Asians and especially in South Asians who often have severe hypoadiponectin,[51] it remains to be investigated in East Asians.

Another difference that may contribute to ethnic variance in insulin secretory capacity could be impaired incretin action, which is a major pathophysiological characteristic of T2D, at least in Caucasians.[52-54] Attenuated GIP-induced but not GLP-1-induced insulin secretion is thought to play a role.[55] Genetic variants of the GIP receptor have been identified as T2D-susceptible genes by genome-wide gene-association studies, confirming the importance of incretins in T2D progression.[56] However, the incretin effect is not impaired in Japanese and Korean T2D patients.[44,57] Furthermore, a novel model of the glucose-dependent insulinotropic action of incretins shows impairment in obese model rats but not in non-obese diabetic model rats.[58] These lines of evidence may reflect the effectiveness of incretin-based therapies among East Asian T2D patients.

EFFICACY OF INCRETIN-BASED THERAPIES IN EAST ASIANS IS DUE TO PATHOPHYSIOLOGY AND DIETARY HABITS

Incretin-based therapies most likely exert their glucose-lowering effects by ameliorating primary β-cell dysfunction through increased incretin activity.[59,60] Incretin-based therapies might therefore show a greater glucose-lowering effect in East Asian T2D, which is characterised by β-cell dysfunction that is evident immediately after ingestion of glucose or mixed meal together with less obesity compared with Caucasians.

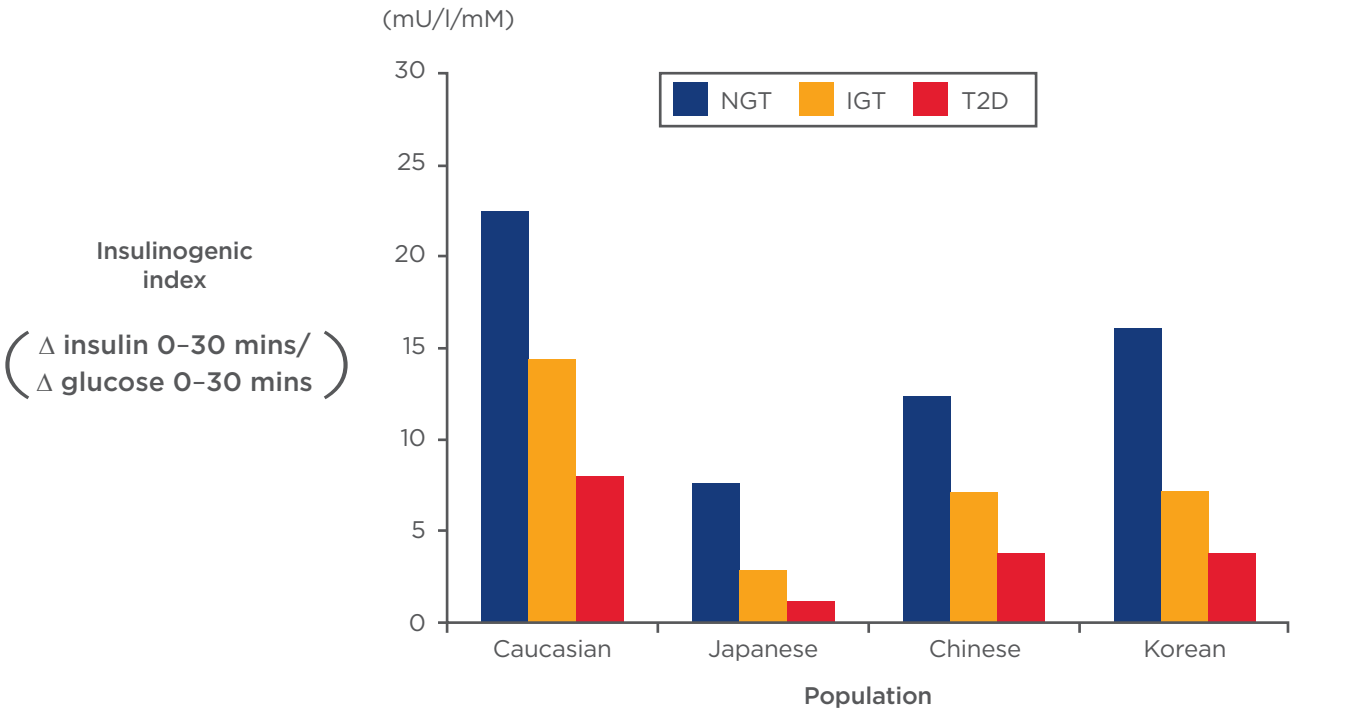

Figure 1: Reduced early phase insulin secretion in East Asians compared with Caucasians.
Insulinogenic index (Δ insulin 0–30 mins/Δ glucose 0–30 mins) was indirectly compared between East Asians and Caucasians with or without Type 2 diabetes. Blue bars represent subjects with normal glucose tolerance (NGT). Orange bars represent subjects with impaired glucose tolerance (IGT). Red bars represent subjects with Type 2 diabetes (T2D). Images were drawn based on previous publications.[2,18,19]

	β	P
Sex	0.065	0.621
Age (years)	0.103	0.583
Duration of diabetes (years)	0.119	0.402
Baseline HbA1c (%)	-0.451	0.005
BMI	0.100	0.474
Cereals	0.132	0.328
Potatoes and starchy flours	0.077	0.592
Sugar and sweeteners	0.109	0.414
Beans	0.262	0.075
Nuts and seeds	-0.067	0.694
Vegetables	0.160	0.391
Fruits	0.014	0.940
Mushrooms	0.109	0.476
Seaweeds	-0.031	0.842
Fish and seafood	-0.475	<0.01
Meats	-0.297	0.077
Eggs	0.057	0.720
Milk products	-0.343	<0.05
Lipids	-0.002	0.990
Snacks	0.230	0.104
Beverages	-0.120	0.393

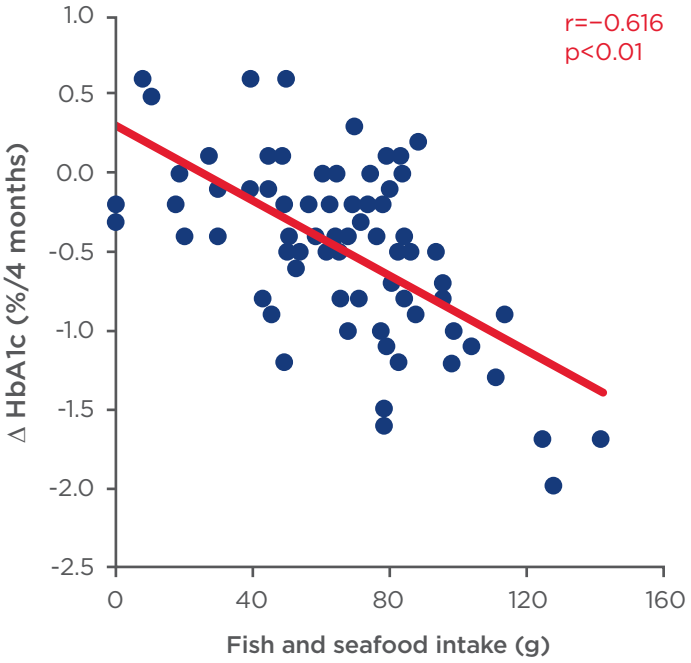

Figure 2: Association of HbA1c reduction by dipeptidyl peptidase-4 inhibitors and estimated intake of various food categories.

Left: Multiple regression analysis regarding changes in HbA1c levels (Δ HbA1c) by taking into account sex, age, duration of diabetes, body mass index (BMI), baseline HbA1c, and estimated intake of various food categories in 3-day food records of 72 patients with Type 2 diabetes. β denotes standardised regression coefficients. For analysis of changes in HbA1c levels, the correlation coefficient squared was 0.550 and the F value with 15 degrees of freedom was 3.499 for a p value of 0.003.

Right: Correlation between estimated intake of fish and seafood with HbA1c reduction. Among fish and seafood (i.e. seashell, squid and octopus, and crustacean), only the estimated intake of fish showed significant association with HbA1c reduction by single regression analysis (r=−0.62, p<0.01).

HbA1c: glycosylated haemoglobin.

Adapted from Iwasaki et al.[49]

Initially, superior HbA1c-lowering effects were noted in East Asian T2D when outcomes from several clinical trials using various DPP-4i and GLP-1RA were compared between East Asians and Caucasians.[36,61] While some retrospective studies could not associate a better response in East Asians,[62] the findings were confirmed by Kim et al.[63,64] and Park et al.[65] in their systematic review and meta-analysis of clinical trials on DPP-4i and GLP-1RA, which showed that the drugs are more effective in East Asians. The greater HbA1c-lowering effects of incretin-based therapies in East Asians may affirm that β-cell dysfunction has a greater responsibility for hyperglycaemia in East Asians compared with Caucasians.

Our recent studies have found a possible link between dietary habits and the efficacy of DPP-4i. The HbA1c-lowering effects of DPP-4i are enhanced by fish intake, as estimated by food records and serum levels of eicosapentaenoic acids and docosahexaenoic acids in Japanese T2D patients (Figure 2),[50,51] presumably because nutrients in fish promote GLP-1 secretion. We demonstrated, in a hospital setting, that eating fish before rice enhanced GLP-1 secretion and ameliorated postprandial glucose excursion by

improving glucose-induced insulin secretion and delaying gastric emptying in comparison with those eating fish after rice (manuscript in preparation). Similar reversal of rice and meat, which is rich in saturated and mono-unsaturated fats that enhance not only GLP-1 secretion but also that of GIP, failed to ameliorate glucose excursions and therefore might facilitate fat accumulation. Indeed, a small but significant body weight gain, presumably due to enhanced GIP secretion from consumption of saturated and mono-unsaturated fatty acids and increased fat deposition by GIP, and subsequent increase of insulin resistance is associated with deterioration of the HbA1c-lowering effects of DPP-4i in Japanese T2D patients.[65,66] The greater efficacy of DPP-4i in East Asians may be partly due to dietary habits along with lesser insulin resistance and adiposity, and the recent increase in animal fat intake among East Asians may overwhelm the superior HbA1c-lowering of DPP-4i in future.

CONCLUSION

The profound glucose-lowering effects and low hypoglycaemia risk of incretin-based therapies have made them widely used in non-obese T2D across East Asian countries, especially in Japan. However, safety issues are always in mind. Although incretin-based therapies ameliorate β-cell dysfunction with little hypoglycaemia risk, cases of severe hypoglycaemia were reported when DPP-4i were first introduced in Japan.[67] The estimated incidence of hypoglycaemic coma with the DPP-4i sitagliptin was 16.3 per 1 million patients during the first 6 months after its launch, approximately 6.4-fold higher in Japan than in the USA during the corresponding period. This was partly due to the local use of DPP-4i with SU, which had been widely recommended to improve β-cell dysfunction in Japan.[67] Recent studies have detailed the mechanisms underlying severe hypoglycaemia with DPP-4i and SU combinations;[67,68] careful consideration to dose titration and patient education when initiating this combination can avoid this negative outcome. Prospective, randomised controlled trials of incretin-based therapies are in progress to assess potential adverse events, some of which have shown no increased risk of acute pancreatitis or pancreatic cancer.[69,70] However, because evidence among East Asians is limited,[71,72] careful observation of patients using incretin-based drugs is highly recommended. In conclusion, incretin-based therapies presently show greater glucose-lowering capacity in East Asian T2D, which is characterised primarily by β-cell dysfunction and less obesity compared with Caucasians. Dietary habits such as eating more fish and less meat can affect the secretion of incretins and enhance the efficacy of incretin-based therapies in East Asians.

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