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Incretin physiology and pathophysiology from an Asian perspective

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ABSTRACT

Incretin hormones, such as glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1, are secreted on oral nutrient ingestion and regulate postprandial glucose homeostasis by conveying the signal of intestinal glucose flux. In East Asians, the secretion of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 is not reduced in type 2 diabetes relative to normal glucose tolerance. Although the incretin effect is blunted in European patients with type 2 diabetes, a few East Asian studies showed no difference in the incretin effect between type 2 diabetes and normal glucose tolerance. Interestingly, the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 receptor agonists was reported to be greater in Asians than in non-Asians. The difference in the treatment responses could be ascribed to a different pathophysiology of type 2 diabetes (lower insulin secretory function and less insulin resistance), lower body mass index, different genetic makeups, preserved incretin effect and different food compositions in East Asians compared with other ethnic groups. Based on the currently available data, incretin-based therapies appear to be safe and well tolerated in East Asians. Nevertheless, continuous pharmacovigilance is required. The characteristics of incretin biology and treatment responses to incretin-based therapies should be considered in developing ethnicity-specific treatment guidelines and making patient-centered decisions for patients with type 2 diabetes.

INTRODUCTION

All animals, including humans, absorb nutrients from the environment to generate energy and to make building blocks for the body. Therefore, the gastrointestinal tract is vital to maintain the lives of all animals. Even sponges, one of the lowest creatures on earth, have very primitive intestines, although they do not have a nervous system or pancreatic islets[1]. With evolution, higher animals have acquired nervous systems and endocrine systems to efficiently regulate feeding behavior and metabolic homeostasis. In this regard, it seems natural that the gastrointestinal endocrine system regulates appetite/satiety and fuel homeostasis from the point of entry of nutrients.

Incretin hormones are secreted on absorption of nutrients from the intestinal lumen, which in turn augment glucose-stimulated insulin secretion from pancreatic β-cells. To date, there are two known incretin hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)[2–5]. GIP and GLP-1 are secreted from K cells and L cells, respectively. The secretions of both GIP and GLP-1 are mainly determined by absorption of glucose and fat[4,6]. GIP enhances glucose-dependent insulin secretion from pancreatic β-cells and increases glucagon secretion from pancreatic α-cells[3,4]. GIP does not inhibit gastric emptying and has no effect on appetite/satiety[3,4]. In patients with type 2 diabetes, GIP loses its insulinotropic activity, while it preserves its glucagonotropic activity[3,4]. In contrast, GLP-1 increases glucose-dependent insulin secretion and decreases glucagon secretion in both normal subjects and type 2 diabetes patients[2,4]. GLP-1 decelerates gastric emptying, decreases appetite and increases satiety[2,4]. Because of the preserved insulinotropic effect of GLP-1 in type 2 diabetes, GLP-1 receptor agonists have been developed as a new therapeutic weapon in the armamentarium for type 2 diabetes. To overcome the very short half-life of incretin hormones as a result of rapid enzymatic degradation by dipeptidyl peptidase-4 (DPP-4), several strategies have been adopted in the clinical

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development of incretin-based therapy[2]. First, naturally DPP-4-resistant exendin-4 was discovered, and its analogs have been developed. Second, an acyl group was added to a human GLP-1-based analog to extend the half-life of biologically active GLP-1. Third, the penultimate alanine was substituted by other amino acids to successfully escape recognition by DPP-4. Last, orally absorbable small molecule DPP-4 inhibitors have been developed to prolong the biological action of endogenous GIP and GLP-1. With all of these new treatment options, it seems like the present is the incretin era in the long history of diabetes treatment. In the present narrative review, the literature on the incretin system and incretin-based therapy is summarized from an Asian perspective. The term East Asia or East Asians is used when a study was carried out in Japan, China and/or Korea.

CHARACTERISTICS OF TYPE 2 DIABETES IN EAST ASIANS

Asia is the epicenter of the global epidemic of type 2 diabetes because of rapid changes in lifestyle and increasing rates of obesity[7,8]. Compared with their Caucasian counterparts, East Asian patients with type 2 diabetes are characterized by a lower body mass index (BMI)[8,9]. However, at any given BMI or abdominal circumference, the risk of diabetes is significantly higher in East Asians than in Caucasians[10], which could be ascribed to a higher visceral fat amount in East Asians[11,12]. In addition, East Asian patients with type 2 diabetes show apparent insulin secretory defects relative to insulin resistance[13,14]. Hyperinsulinemia to overcome prevailing insulin resistance in subjects with impaired glucose tolerance (IGT) during an oral glucose tolerance test (OGTT), which is commonly found in Caucasians[15,16], was not seen in East Asians[13,17]. Furthermore, in patients with type 2 diabetes, the insulin secretory defect appears to be more prominent in East Asians than in Caucasians[13,16,17]. However, until recently, there have been no direct comparisons of insulin sensitivity or insulin secretory function in East Asians and Caucasians.

In a very recent cross-sectional study including 120 Japanese and 150 Northern Europeans with normal glucose tolerance (NGT), IGT and type 2 diabetes, insulin secretion and insulin sensitivity were directly compared with a 5-h OGTT[18]. In that study, insulin sensitivity was higher and insulin secretion was lower among the Japanese compared with the Northern Europeans, which was consistent with previous reports. However, the disposition index (an index of insulin secretory response corrected by the degree of insulin resistance that is calculated by the insulin sensitivity index [Matsuda index] multiplied by the insulinogenic index during an OGTT) in NGT, IGT and type 2 diabetes was identical among the Japanese and Northern Europeans[18] (Figure 1), which suggests that both ethnic groups have a similar ability to increase insulin secretion matched to the degree of insulin resistance. However, these results do not necessarily mean that Japanese people are able to compensate for increased insulin resistance to the same degree found in Northern Europeans by further augmenting insulin secretion.

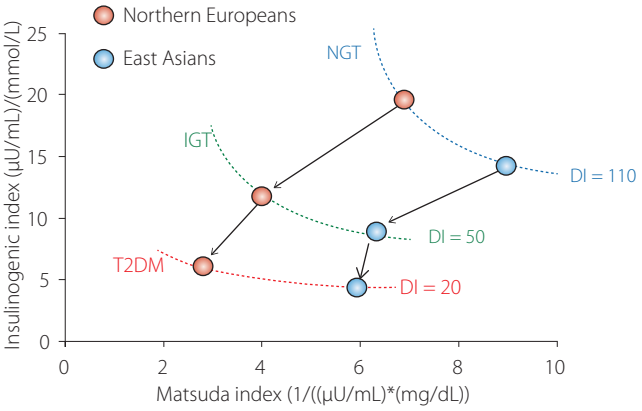

Figure 1 | A comparison of insulin secretion and insulin sensitivity between East Asians and Northern Europeans. The disposition index (DI) was calculated by the product of insulinogenic index (an index of insulin secretion) and the Matsuda index (an index of insulin sensitivity during an oral glucose tolerance test). The dotted lines represent hyperbolic curves of the designated DI of 110 (for normal glucose tolerance [NGT]), 50 (for impaired glucose tolerance [IGT]) and 20 (for type 2 diabetes mellitus [T2DM]). The approximate positions of each circle are drawn based on the data presented by Møller *et al.*[18]

GENETICS OF THE INCRETIN SYSTEM IN EAST ASIANS

During the long history of migration and settlement of human beings, some genes must have been selected by different environmental factors (e.g. climate and food availability)[19]. In this regard, the thrifty genotype hypothesis by Neel[20], which explains the possible acquisition of energy conserving genes to survive inevitable famine during evolution, appears to be very plausible. Because GIP mediates increasing adiposity with a high-fat diet in mice, the *GIP* gene has been postulated to be a thrifty gene[3]. In accordance with this hypothesis, the *GIPR* gene encoding the receptor for GIP was found to be associated with BMI[21]. Interestingly, a recent study showed that a non-synonymous single nucleotide polymorphism (SNP; rs2291725) of the *GIP* gene is enriched in East Asians (the allele frequency is 0.755) compared with other ethnic groups (the allele frequency is 0.483 for Europeans and 0.050 for Africans), presumably by adaptive selection approximately 8,100 years ago[22]. However, the functional significance of this genetic variant in the *GIP* gene is unclear, because it encodes glycine or serine at amino acid position 55, which is normally removed during the post-translational cleavage process of GIP, a 42-amino acid peptide.

There are several genes that were reported to affect the incretin physiology or clinical response to incretin-based therapy (Table 1). If the allele frequencies of these genetic variants are different between East Asians and other ethnic groups, incretin physiology or pathophysiology might show different characteristics. Consistent with the known action of GIP[3,4], *GIPR* was reported to be associated with an index of incretin effect (derived from an OGTT and an intravenous glucose tolerance test), postprandial glucose levels and BMI[21,23]. *GLP1R* encoding the receptor for GLP-1 was also reported to be associated with

Table 1 | Allele frequency of genetic variants associated with incretin biology in Europe and East Asia

Gene	Reported effects in incretin biology	Representative genetic variants	Risk allele frequency in Europeans	Risk allele frequency in East Asians
GIPR	Incretin effect, postprandial glucose and BMI	rs10423928	0.18[23]	0.18[89]
GLP-1R	β-cell response to GLP-1	s6923761	0.36†	0.02†
TCF7L2	GIPR and GLP-1R expression in β-cells, treatment response to linagliptin	rs7903146	0.27[28]	0.03[28]
KCNQ1	Glucose-stimulated GIP and GLP-1 secretion	rs2283228*	0.59[27]	0.92[27]
WFR1	GLP-1 induced insulin secretion	rs6446482*	0.56[90]	0.95[91]
CTRB1/2	Response to GLP-1 and DPP-4 inhibitors	rs7202877	0.89[31]	0.78†

*These particular variants have not been identified to be associated with the reported function of the gene. †Allele frequencies reported in the International HapMap Project site (http://hapmap.ncbi.nlm.nih.gov).

a differential β-cell response (measured by a C-peptide minimal model) to GLP-1 infusion during a hyperglycemic clamp in healthy subjects[24]. *TCF7L2*, a well-known gene conferring susceptibility to type 2 diabetes, was reported to regulate the expression of GIP and GLP-1 receptors in human pancreatic islets[25]. In addition, the diabetes susceptibility allele of the *TCF7L2* gene (rs7903146) was associated with the glucose-lowering efficacy of linagliptin, a DPP-4 inhibitor, in patients with type 2 diabetes[26]. *KCNQ1* is also a diabetogenic gene, which was first discovered in Asians[27,28], and a SNP (rs2283228) in this gene was reported to be associated with glucose-stimulated GIP and GLP-1 secretion[29]. SNP rs10010131, located in the *WFR1* gene, which encodes a transmembrane protein wolframin, is associated with GLP-1-stimulated insulin secretion during a hyperglycemic clamp in humans[30]. In addition, three genetic loci (*TMEM114*, *CHST3* and *CTRB1/2*) were identified being as linked to GLP-1 stimulated insulin secretion under hyperglycemic clamp conditions in non-diabetic Europeans[31]. Among them, rs7202877 nearby *CTRB1/2* encoding chymotrypsinogen, a known diabetogenic locus, was found to be associated with fecal chymotrypsin activity and the glucose-lowering response to DPP-4 inhibitors, including sitagliptin, vildagliptin and others[31]. Interestingly, the risk allele frequency of some SNPs in *GLP1R*, *TCF7L2*, *KCNQ1* and *WFR1* is two- to ninefold different between East Asians and Europeans (Table 1), which could confer different characteristics of incretin biology and different response to incretin-based therapies.

INCRETIN SECRETION IN EAST ASIANS

A study including 55 type 2 diabetes patients and 33 NGT subjects carried out in Europe showed that GLP-1 secretion was reduced in type 2 diabetes patients during a 4-h mixed meal test[32], which was regarded as a potential mechanism of decreased incretin effect in type 2 diabetes. However, in that study[32], postprandial GLP-1 levels were lower only during the late postprandial period (after 1 h) in patients with type 2 diabetes compared with subjects with NGT. The decreased GLP-1 secretion during the late postprandial period is unlikely to affect early insulin secretion, which is important in postprandial glucose metabolism. Furthermore, there has been controversy regarding whether GLP-1 secretion is decreased in type 2 diabetes relative to NGT. In a recent meta-analysis including 275 type 2 diabetes patients and 279 non-diabetic subjects[33], it was shown that GLP-1 secretion during an OGTT and/or mixed meal test did not decrease in type 2 diabetes patients compared with non-diabetic control subjects. However, poor glycemic control was associated with reduced postprandial GLP-1 secretion[33], which could be explained by delayed gastric emptying under a hyperglycemic condition[34].

In general, postprandial GIP secretion is not decreased, and sometimes is even higher in patients with type 2 diabetes compared with non-diabetic healthy control subjects[3]. A meta-analysis including 363 type 2 diabetes patients and 325 non-diabetic subjects showed that GIP secretion in response to oral glucose or mixed meal ingestion is not decreased in type 2 diabetes[35]. In that analysis, a high BMI was associated with increased postprandial GIP secretion[35]. Of note, in this regard, obese animals and high-fat-fed animals showed increased circulating GIP concentrations or increased GIP-secreting K cell densities in the intestines[3].

The studies that compared postprandial incretin secretion between type 2 diabetes patients and non-diabetic control subjects in East Asia are summarized in Table 2. The postprandial increment of total or intact GLP-1 and total or intact GIP during a mixed meal test was not different between NGT and type 2 diabetes patients[36–38]. In addition, the postprandial increment of total or intact GLP-1 and total or intact GIP during a 75-g OGTT was also comparable between NGT and type 2 diabetes patients[37–39]. Therefore, consistent with the results of recent meta-analyses[33,35], postprandial GLP-1 or GIP secretion is not decreased in type 2 diabetic compared with non-diabetic East Asians. In addition, early postprandial GIP secretion was

Table 2 | Comparisons of postprandial circulating glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide concentrations according to glucose tolerance statuses in East Asians

Population and reference	Comparison group	Types of nutrients	GLP-1	GIP	DPP-4
Japanese, Lee *et al.*[37]	T2DM (n = 21), IGT (n = 7), NGT (n = 12)	Mixed meal, 480 kcal (carbohydrate:protein:fat = 2.8:1:1)	No difference in iAUC (intact)	No difference in iAUC (intact*)	No difference in plasma concentrations
		Oral glucose (75 g)	No difference in iAUC (intact)	No difference in iAUC (intact*)	
Japanese, Yabe *et al.*[38]	T2DM (n = 18), non-T2DM (n = 17)	Mixed meal, 480 kcal (carbohydrate:protein:fat = 2.8:1:1)	No difference in iAUC (both total and intact)	No difference in iAUC (both total and intact)	N/A
		Oral glucose (75 g)	No difference in iAUC (both total and intact)	No difference in iAUC (both total and intact)	
Koreans, Han *et al.*[36]	T2DM (n = 20), non-T2DM (n = 20)	Mixed meal, 556 kcal (carbohydrate 87 g protein 15 g, and fat 18 g)	No difference in iAUC (intact)	No difference in iAUC (total)	DPP-4 activity was increased in T2DM.
Koreans, Oh *et al.*[39]	T2DM (n = 16), NGT (n = 14)	Oral glucose (75 g)	No difference in iAUC (total)	No difference in iAUC (total)	N/A

The designation total or intact in parenthesis denotes total or intact hormones. *It was uncertain whether the ELISA kit used in the study measured intact or total glucose-dependent insulinotropic polypeptide (GIP). However, the authors assumed that the values should be intact GIP levels. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; iAUC, incremental area under the curves; IGT, impaired glucose tolerance; N/A, not available; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus.

reported to be positively correlated with BMI in Japanese patients with type 2 diabetes[40]. In a Japanese study, fasting and postprandial GLP-1 levels were negatively correlated with plasma DPP-4 activity in type 2 diabetes patients[41]. Fasting plasma DPP-4 concentrations were not different among NGT, IGT and type 2 diabetes in Japanese[37], whereas a Korean study with a mixed meal test reported that fasting and postprandial plasma DPP-4 activity was higher in type 2 diabetes patients than in non-diabetic subjects[36]. Interestingly, glycemic control in drug-naïve type 2 diabetes patients for 12 weeks using oral antidiabetes drugs except DPP-4 inhibitors or insulin, which lowered the mean glycated hemoglobin (HbA1c) levels from 9.9% to 7.0%, reduced DPP-4 (CD26) expression on peripheral blood T cells[42]. Taken together, postprandial incretin secretion is not decreased in type 2 diabetes patients relative to non-diabetic control subjects in East Asia. The research on the relationship between plasma incretin concentrations and DPP-4 activity has mixed results, and thus requires further studies.

INCRETIN EFFECT IN EAST ASIANS

Oral glucose elicits more insulin secretion than intravenous glucose, even though blood glucose levels are near completely matched[43]. The blood glucose level itself is one of the many factors that regulate insulin secretion from pancreatic β-cells. Therefore, it is not surprising that the amount of insulin secretion by intravenous glucose is smaller than that by oral glucose, as the latter induces insulin secretion through neural, hormonal and other routes in addition to direct stimulation of increased blood glucose levels[44]. The contribution of the gastrointestinal tract in insulin secretion by oral glucose can be experimentally examined by isoglycemic techniques that reproduce blood glucose levels obtained during oral glucose tolerance tests by intravenous glucose infusion with varying glucose infusion rates[43]. In general, the incretin effect is calculated by the difference in the amounts of insulin secretion during OGTTs and the corresponding isoglycemic intravenous glucose infusion (IIGI) relative to the amounts of insulin secretion during OGTTs. In this calculation, the amounts of insulin secretion are usually expressed as the incremental area under the curve (iAUC). The incretin effect can be calculated by plasma insulin levels, plasmas C-peptide levels, or insulin secretion rates obtained by deconvolution methods using plasma C-peptide levels[45]. The formula is as follows[43]:

$$\text{Incretin effect} = 100\% \times (\text{iAUC}_{\text{OGTT}} - \text{iAUC}_{\text{IIGI}})/\text{iAUC}_{\text{OGTT}}$$

Then, why do we need much more insulin to address oral glucose than intravenous glucose, even though the blood glucose levels are virtually the same? Although blood glucose levels are identical, the flux of exogenous glucose is much greater with oral glucose than with isoglycemic intravenous glucose. For example, approximately 30 g of intravenous glucose were required to reproduce the blood glucose levels obtained during 75-g OGTTs in Korean subjects with NGT[39]. Therefore, the excess amount of insulin secretion during OGTTs compared with IIGIs was used to address the extra amount of exogenous glucose (approximately 45 g in this case). Teleologically speaking, the gut sends the signals of the flux of glucose entry from

the gut lumen to increase insulin secretion and decrease hepatic glucose production to prevent a postprandial glucose surge. In fact, the incretin effect is increased with increased amounts of oral glucose or meals both in patients with type 2 diabetes and in normal control subjects[45–47]. Therefore, the gastrointestinal factors or incretin hormones amplify insulin secretion triggered by increased blood glucose levels during the postprandial period. Because the degree of amplification of insulin secretion by incretin hormones is proportional to the flux of glucose entry, there is no need to further increase blood glucose levels to elicit more insulin secretion to cope with the excess amount of glucose absorption from the gut. Both GLP-1 and GIP do not induce insulin secretion in the absence of hyperglycemia[2–5], which provides a fail-safe mechanism to the glucose flux sensing system of the gastrointestinal tract.

Although the incretin effect explains the gastrointestinal contribution of insulin secretion in response to oral glucose, the gastrointestinally-mediated glucose disposal (GIGD) explains the gastrointestinal contribution of glucose disposal on oral glucose ingestion[48]. The GIGD is also calculated using the data from an OGTT and its corresponding IIGI study[48]. The GIGD is the difference of the amount of the glucose load between OGTTs and IIGIs relative to the amount of the glucose load during OGTTs[48]. Therefore, it is calculated by the formula:

$$\mathrm{GIGD} = 100\% \times (\mathrm{glucose}_{\mathrm{OGTT}} - \mathrm{glucose}_{\mathrm{IIGI}})/\mathrm{glucose}_{\mathrm{OGTT}}$$

If 30 g of intravenous glucose were required to match the blood glucose levels during a 75-g OGTT, the GIGD is 60%. Therefore, 60% of orally ingested glucose is disposed by the contribution of the gastrointestinally-mediated mechanisms. Many factors, including incretin hormones, islet hormones, neural signals, the gut–brain–liver axis, the splanchnic utilization of glucose, and hepatic and peripheral insulin sensitivity might contribute to GIGD[48]. The differences of the incretin effect and GIGD are shown in Figure 2. Whereas the incretin effect only reflects the insulin response after an oral glucose load, the GIGD reflects the whole picture of glucose metabolism after an oral glucose load.

In general, both the incretin effect[43,45,49] and the GIGD[39,48] are decreased in patients with type 2 diabetes relative to non-diabetic subjects. Because the secretion of incretin hormones are not decreased in type 2 diabetes patients[33,35], other mechanisms, such as decreased β-cell sensitivity to incretin hormones, generalized β-cell dysfunction and decreased β-cell mass, could explain the decreased incretin effect found in patients with type 2 diabetes[50]. Patients who have diabetic conditions other than type 2 diabetes, such as diabetes associated with chronic pancreatitis[49], maturity-onset diabetes of the young with hepatocyte nuclear factor-1α (HNF1α) mutation[51] and gestational diabetes[52], also have the decreased incretin effect. Therefore, decreased pancreatic β-cell mass and/or decreased β-cell function appear to be closely related to a decreased incretin effect

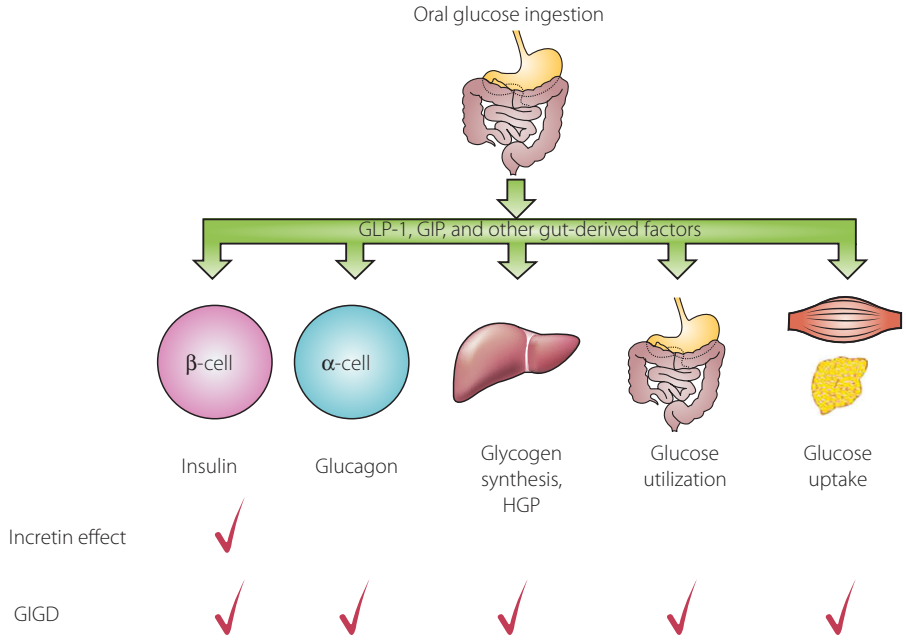

Figure 2 | Components contributing to the incretin effect and the gastrointestinally-mediated glucose disposal (GIGD). Whereas the incretin effect reflects only the insulin secretory function of pancreatic β-cells, the GIGD represents all of the components, including β-cells, α-cells, liver, gut and other visceral organs, skeletal muscle, and fat, in regulating the postprandial glucose metabolism. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HGP, hepatic glucose production.

in patients with type 2 diabetes. Near normalization of the blood glucose levels in poorly controlled type 2 diabetes restored the β-cell response to both GIP and GLP-1[53]. The blunted incretin effect in women with gestational diabetes was restored in accordance with the post-partum normalization of glucose tolerance[52]. In obese type 2 diabetes patients with blunted incretin effects, Roux-en Y gastric bypass restored the incretin effect to that found in among the non-diabetic obese controls 1 month after surgery, which was associated with a marked increase in postprandial plasma GIP and GLP-1 levels[54]. However, islet transplantation, even though it was successful, did not restore normal incretin effect in patients with type 1 diabetes in a small study with just three patients[55], which suggests that the denervated islets might not able to secrete enough insulin in response to gastrointestinal factors on oral glucose ingestion. Therefore, a decreased incretin effect is observed in most diabetes patients regardless of the type of diabetes, and is reversible by the normalization of glucose tolerance except by islet transplantation.

Until recently, all studies regarding the incretin effect have been carried out in Europeans. In summary, the incretin effect calculated by plasma insulin concentrations was 50–70% in non-diabetic subjects[43,45,46,49,50] and 10–40% in type 2 diabetes patients[43,45,49]. Unexpectedly, however, the incretin effect, which was measured by a standard method using OGTTs and IIGIs, was not different between type 2 diabetes and NGT patients in Korea[39]. Because the sample size was rather small (16 patients with type 2 diabetes and 14 subjects with NGT)[39], the incretin effect in East Asian patients with type 2 diabetes needs to be re-examined by future studies including more participants. However, a preliminary Japanese study also reported no difference in the incretin effect, which was measured by OGTTs and IIGIs, between type 2 diabetes and NGT subjects[56]. In addition, a study using a hyperglycemic clamp with a 75-g oral glucose load showed that the relative incretin effect estimated by insulin secretion in response to oral glucose relative to the insulin secretion in response to intravenous glucose was comparable in subjects with NGT, impaired fasting glucose and type 2 diabetes in Koreans[57]. The most remarkable difference between a Korean study[39] and European studies[43,45,49,58] was the plasma insulin levels in response to isoglycemic intravenous glucose in patients with type 2 diabetes. In Europeans, the insulin secretion response to intravenous glucose was not decreased or even slightly increased compared with insulin secretion in response to oral glucose in patients with type 2 diabetes[43,45,49,58]. However, in the Korean study[57], insulin secretion in response to isoglycemic intravenous glucose was significantly lower than in response to oral glucose in patients with type 2 diabetes. A meta-analysis including 3,813 individuals of different ethnicities composed of Africans, Caucasians and East Asians showed that the acute insulin response to glucose during an intravenous glucose tolerance test is lower in East Asians than in Caucasians[59]. Therefore, decreased insulin secretion in response to intravenous glucose could be a trait of East Asians. Because the incretin effect is mainly determined by the difference in insulin secretion between oral and intravenous glucose, the divergent insulin responses to intravenous glucose between Europeans and East Asians could result in different incretin effects in patients with type 2 diabetes. Nevertheless, the contribution of oral glucose relative to intravenous glucose in insulin secretion appears to be relatively preserved in East Asian patients with type 2 diabetes.

The seemingly similar incretin effect between East Asian subjects with type 2 diabetes and NGT[39,56,57] does not necessarily mean that there is no difference in the gastrointestinal contribution for postprandial glucose metabolism. In contrast to the incretin effect, the GIGD was remarkably decreased in type 2 diabetes (~30%) than in NGT (~60%) in Korean subjects[39]. Interestingly, the change in plasma glucagon levels during OGTTs were negatively correlated with GIGD in Koreans[39], which suggests that the suppression of glucagon secretion might be important in regulating GIGD. Taken together and considering the difference in the concepts of the incretin effect and GIGD, as shown in Figure 2, the β-cell response to glucose appears to be a major difference between Caucasians and East Asians in regulating the postprandial glucose metabolism.

CLINICAL RESPONSE TO INCRETIN-BASED THERAPIES AMONG ASIAN PATIENTS

There have been no direct comparisons of the glucose-lowering efficacy of incretin-based therapies between East Asians and other ethnic groups. A meta-analysis including 55 studies (18,328 study participants) investigating the efficacy of DPP-4 inhibitors in patients with type 2 diabetes examined ethnic differences in the HbA1c-lowering efficacy of DPP-4 inhibitors at the study level (not the individual patient level) by dividing published studies into Asian-dominant studies (if Asians ≥50% among the participants) and non-Asian-dominant studies (if Asians <50% among the participants)[60]. The weighted mean difference of the HbA_{1c}-lowering efficacy was greater in Asian-dominant studies than non-Asian-dominant studies by −0.26% (95% confidence interval [CI] −0.36 to −0.17; Table 3)[60]. The rate of achieving the HbA1c goal of <7% was also greater in Asian-dominant studies than in non-Asian-dominant studies (Table 3). Meta-regression analysis showed that the proportion of Asian participants in a study and the baseline BMI were correlated with the HbA1c-lowering efficacy of DPP-4 inhibitors[60]. Of note, in this analysis, the baseline BMI and the proportion of Asian participants were closely correlated ($r = 0.95$, $P < 0.001$)[60], showing that Asians have lower BMIs. In addition, a meta-analysis comparing Japanese ($n = 7$) vs non-Japanese ($n = 55$, mostly non-Asian studies) studies examining the efficacy of the DPP-4 inhibitor in type 2 diabetes also showed a greater HbA1c-lowering efficacy in the Japanese studies[61]. Consistent with the results of the DPP-4 inhibitors, the GLP-1 receptor agonists showed a greater HbA1c-lowering efficacy in Asian-dominant studies than in non-Asian dominant studies by a difference of −0.32% (95% CI −0.64 to −0.01; $P < 0.05$,

Table 3 | Summary of the meta-analyses comparing the efficacy of incretin-based therapy in Asians and non-Asians

Types of therapies and reference/clinical end-points	Asian-dominant studies	Non-Asian-dominant studies	Difference and/or statistical significance
DPP-4 inhibitors[60]			
HbA1c-lowering from baseline (%)	−0.92 (−1.03 to −0.82)	−0.65 (−0.69 to −0.60)	−0.26 (−0.36 to −0.17), $P < 0.001$
RR of achieving HbA1c <7.0%	3.4 (2.6 to 4.7)	1.9 (1.8 to 2.0)	$P < 0.05$
GLP-1 receptor agonists[62]			
HbA1c-lowering from baseline (%)	−1.16 (−1.48 to −0.85)	−0.83 (−0.97 to −0.70)	−0.32 (−0.64 to −0.01), $P < 0.05$
RR of achieving HbA1c <7.0%	5.7 (3.8 to 8.7)	2.8 (2.4 to 3.3)	$P = 0.082$

Numbers in parenthesis denote 95% confidence intervals. If the proportion of Asian participants was ≥50% in a study, it was classified as an Asian-dominant study. Otherwise, it was classified as a non-Asian-dominant study. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; RR, relative risk.

Table 3) in a meta-analysis including 24 studies (5,090 participants) examining the efficacy of GLP-1 receptor agonists[62]. The rate of target HbA1c <7% achievement was also higher in Asian-dominant studies than in non-Asian-dominant studies (Table 3). The HbA1c-lowering efficacy of GLP-1 receptor agonists was greater in studies with a mean baseline BMI < 30 kg/m^2 than in studies with a mean baseline BMI ≥30 kg/m^2[62]. Taken together, these data suggest that the glucose-lowering efficacy of incretin-based therapy including both DPP-4 inhibitors and GLP-1 receptor agonists for the treatment of type 2 diabetes is greater in Asians than other ethnic groups.

POSSIBLE MECHANISMS OF THE DIFFERENTIAL GLUCOSE-LOWERING EFFICACY OF INCRETIN-BASED THERAPIES ACROSS ETHNIC GROUPS

Potential mechanisms for the difference of the glucose-lowering efficacy of incretin-based therapies in Asians and non-Asians are suggested below. However, further studies are absolutely required to uncover the factors that are causally related to the response to incretin-based therapy and the factors that are predictors of good responses.

Different β-Cell Dysfunction and Insulin Sensitivity

Incretin-based therapies improve β-cell dysfunction[2,6,63,64], which has been known to be the most fundamental pathophysiological defect in East Asian patients with type 2 diabetes[7,8]. However, a recent study directly comparing East Asians and Northern Europeans showed that the disposition index was comparable between the two ethnic groups[18]. As shown in Figure 1, which is drawn based on data from Møller *et al.*[18], both East Asians and Northern Europeans are on the same lines of disposition indexes regardless of their glucose tolerance statuses. Although the β-cell function expressed as insulinogenic indexes of East Asians is lower than that of Northern Europeans, the β-cells compensate the prevailing insulin sensitivity in both ethnic groups to the same degree. It is of note that the decrease in β-cell function from IGT to type 2 diabetes is more abrupt in East Asians than in Northern Europeans. In addition, based on the Matsuda index indicating the degree of insulin sensitivity during OGTTs, East Asians are more insulin sensitive than Northern Europeans. The different position in the same curve of the disposition index might contribute to different treatment responses. If the same amount of insulin secretion occurs in type 2 diabetes patients from both groups, what would be the net glycemic lowering effect? Theoretical insulin action would be the product of insulin secretion (insulinogenic index) and insulin sensitivity (Matsuda index)[65], which are expressed as the areas of the rectangles shown in Figure 3. Therefore, the theoretical effect of the identical increment of insulin secretion would be greater in East Asians, who are more insulin sensitive, than in Northern Europeans, who are less insulin sensitive. Taken together, the different nature of insulin secretory function and insulin sensitivity could be ascribed to the differential efficacy of incretin-based therapies in these ethnic groups.

The BMI Threshold Hypothesis

Both DPP-4 inhibitors[60] and GLP-1 receptor agonists[62] showed a greater HbA1c reduction in type 2 diabetes patients with a lower baseline BMI (<30 kg/m^2). In a 16-week Japanese study including patients with type 2 diabetes whose mean baseline BMI was 24.1 ± 5.0 kg/m^2, the HbA1c-lowering efficacy of sitagliptin was correlated with the baseline BMI ($r = 0.419$, $P = 0.0023$)[66]. In another study among Japanese type 2 diabetes patients, the HbA1c-lowering effect of a 24-week treatment with sitagliptin was greater in those with a lower baseline BMI[67]. In a meta-regression analysis[60], a significant correlation between baseline BMI and HbA1c reduction was found only in studies with a mean baseline BMI < 30 kg/m^2. Thus, it seems that there would be a threshold of BMI sensitively affecting the efficacy of incretin-based therapies somewhere near 30 kg/m^2. Below this threshold, we can expect a greater reduction of HbA1c with a lower baseline BMI, whereas there is little effect of BMI on HbA1c reduction above the threshold. Because East Asian patients with type 2 diabetes are characterized by a lower BMI than other ethnic counterparts[7,8], a greater efficacy of

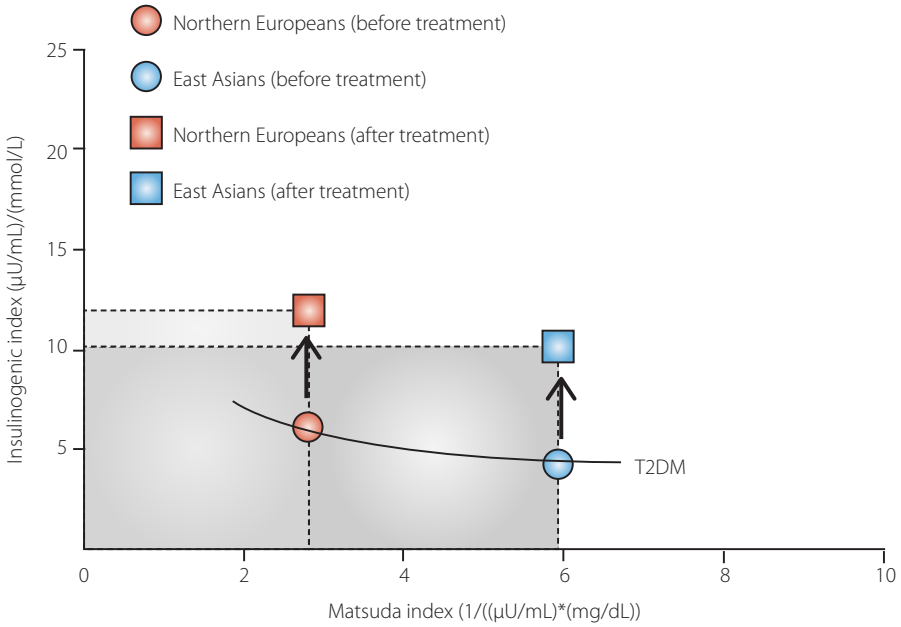

Figure 3 | The theoretical glucose-lowering effects of therapies augmenting insulin secretion according to the different baseline insulin secretion and insulin sensitivity. This figure is drawn with an assumption that the same amount of insulin secretion occurred in East Asians and Northern Europeans with type 2 diabetes shown in Figure 1. The areas of the rectangles (the product of insulin secretion and insulin sensitivity) represent the theoretical glucose-lowering effects in the two ethnic groups with type 2 diabetes (T2DM).

incretin-based therapies, particularly DPP-4 inhibitors, might be mediated by their lower BMI. Considering that BMI is correlated with insulin sensitivity[68], the effect of BMI on the differential efficacy of incretin-based therapies across different ethnic groups might be mediated by different insulin sensitivities. However, it is of note that factors other than BMI could contribute to the greater insulin sensitivity found in Asians, because it was reported that Asian Americans were more insulin sensitive than Caucasians, African Americans and Hispanic Americans, even after correcting the effect of BMI[69]. Although DPP-4 inhibitors are generally weight-neutral, GLP-1 receptor agonists have weight-lowering effects in patients with type 2 diabetes[6,70]. Therefore, the BMI threshold hypothesis might not apply to type 2 diabetes patients who show a considerable weight reduction with GLP-1 receptor agonists. In a retrospective cohort study in the USA[71], the HbA1c-lowering efficacy of liraglutide was comparable across different BMI categories in patients with type 2 diabetes. In that study[71], however, weight reduction was greater in those who had a higher baseline BMI. Therefore, the BMI threshold hypothesis might hold its predictive value in those treated with DPP-4 inhibitors.

Preserved Incretin Effect in East Asians

Interestingly, Korean[39,57] and Japanese[56] patients with type 2 diabetes did not show a decreased incretin effect compared with subjects with NGT. Although there is no study directly comparing the incretin effect in East Asians and other ethnic groups, the preserved incretin effect could mediate the greater glucose-lowering efficacy of incretin-based therapies. Because the incretin effect measured by OGTTs and corresponding IIGI studies does not necessarily represent the β-cell sensitivity to incretin hormones, further studies are necessary to examine the effect of GLP-1 and/or GIP on insulin secretion in East Asians.

Genetic Differences

As described above, some genetic factors might affect insulin secretion in response to incretin hormones (Table 1). In this regard, it is intriguing that rs7903146 in *TCF7L2* confers poor glucose-lowering efficacy of a DPP-4 inhibitor in Europeans[26]. The risk allele frequency of rs7903146 shows a 10-fold difference in East Asians and Europeans (Table 1). Supposing that the risk allele frequency of rs7903146 is 0.3 in Europeans and 0.03 in East Asians, the proportion of individuals carrying homozygotes of the better glucose-lowering allele is 49% and 94% of Europeans and East Asians, respectively, according to the Hardy–Weinberg equilibrium principle[72]. However, it remained to be confirmed whether East Asian patients with type 2 diabetes carrying rs7903146 show different glucose-lowering effects in response to incretin-based therapies.

Differences in Pharmacokinetics

Considering the lower BMI and smaller body size of East Asians relative to non-Asians, it would be conceivable that the different pharmacokinetics or different plasma drug levels could affect the efficacy and safety of a drug. However, there was no difference in the clinical pharmacological characteristics of

some DPP-4 inhibitors across different ethnic groups[47,73]. Furthermore, pharmacokinetics parameters of exenatide[74] and liraglutide[75] were comparable among different ethnic groups, including Asians. Therefore, it is unlikely that the smaller body size of East Asians affects the pharmacokinetics parameters related to incretin-based therapies.

Dietary Factors

Incretin hormone secretion takes place in response to intestinal nutrient absorption. Therefore, it seems possible that different food compositions might affect incretin secretion. In this regard, East Asians consume relatively larger amounts of carbohydrate, because they eat rice as a staple food. However, fat, as well as carbohydrates, is a strong stimulator of GIP and GLP-1 secretion[3,44]. In addition, protein ingestion also contributes to GIP and GLP-1 secretion[3,44]. Although there is a paucity of data on the relationship between food composition and incretin secretion, there are a couple of studies suggesting the possibility that different food compositions could contribute to differential glucose-lowering responses to incretin-based therapies among different ethnic groups. Similarly, it is of note that serum levels of eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA), which reflects the amount of fish consumption, were independent predictors of good glucose-lowering responses of DPP-4 inhibitors in Japanese patients with type 2 diabetes[76,77]. Indeed, the amount of fish consumption measured by self-administered 3-day food records was correlated with changes of HbA1c with DPP-4 inhibitors[76]. In addition, the sequence of food intake might modulate the postprandial incretin secretion and could possibly affect the efficacy of DPP-4 inhibitors. It was reported that 50 g of a whey protein preload decreased the postprandial glucose levels, and increased GLP-1 and insulin secretion in response to a subsequent high-glycemic index breakfast meal, which was provided 30 min after the whey protein preload, in European patients with well-controlled type 2 diabetes[78]. When mackerels rich in EPA and DHA were eaten 15 min before steamed rice, the postprandial glucose levels were lower with higher postprandial GLP-1 levels in Japanese patients with type 2 diabetes[79]. Further studies are required to explore the effect of different food compositions or different meal sequences on the glucose-lowering efficacy of incretin-based drugs.

SAFETY ISSUES RELATED TO INCRETIN-BASED THERAPIES

Hypoglycemia

Hypoglycemia is a rare adverse event when incretin-based therapies are used without sulfonylureas and/or insulin therapy. In two meta-analyses comparing Asians and non-Asians, there was no statistically significant difference in the incidence of hypoglycemia with either DPP-4 inhibitors[60] or GLP-1 receptor agonists[62]. In the analysis with GLP-1 receptor agonists, however, the relative risk for hypoglycemia tended to be greater in Asian-dominant studies than in non-Asian dominant studies (the relative risk was 2.8 [95% CI 2.3–3.5] and 1.5 [95% CI 1.2–1.8], respectively; $P = 0.164$)[62]. This numerical imbalance was likely caused by the difference in background medications in the two groups: a DPP-4 inhibitor was used in addition to sulfonylurea treatment in all Asian-dominant studies used for safety analysis and just a few studies in non-Asian dominant studies used for safety analysis[62]. Nevertheless, the incidence of severe hypoglycemia was similarly very low in the two groups treated with GLP-1 receptor agonists[62]. However, in the real world, outside of the context of clinical trials, severe hypoglycemia was frequently noted when a DPP-4 inhibitor was used in combination with a sulfonylurea in Japan. Therefore, a group of Japanese diabetologists issued a warning related to the risk of severe hypoglycemia and strategies to mitigate the risk by reducing the sulfonylurea dosage[80]. Caution should be exercised for potential hypoglycemia when incretin-based therapies are prescribed with background medications including sulfonylureas and/or insulin.

Gastrointestinal Adverse Effects

Gastrointestinal adverse effects, such as nausea, vomiting and diarrhea, are common with GLP-1 receptor agonists, particularly during the early course of treatment, but are well-tolerated for most patients[70]. Intriguingly, nausea tended to be reported more frequently in association with the use of GLP-1 receptor agonists in Asian-dominant studies than in non-Asian-dominant studies (the relative risk was 13.8 [95% CI 6.2–30.4] and 3.3 [95% CI 2.7–3.9], respectively; $P = 0.100$)[62]. Because nausea is vaguely defined and its frequency is highly variable even with the same GLP-1 receptor agonists[81,82], the statistically marginal imbalance does not seem to have clinical significance.

Pancreatitis

Pancreatic safety issues, such as pancreatitis and pancreatic cancer, have brought about a huge debate since the introduction of incretin-based therapies in clinics. To date, there is no convincing evidence regarding the risk of pancreas-related safety issues. Both the US Food and Drug Administration and the European Medicines Agency announced that there is no sign of increased risk of pancreatitis or pancreatic cancer with incretin-based therapies after a comprehensive review of the currently available data[83]. In addition, studies using health insurance claims databases did not show any increased risk of pancreatitis associated with the use of DPP-4 inhibitors in Japan[84] and Taiwan[85]. Nevertheless, pharmacovigilance is still required for the potential pancreatic side-effects of incretin-based therapies.

Cardiovascular Complications

There is no cardiovascular outcome study with incretin-based therapies carried out solely in Asians. Two large multinational cardiovascular outcome studies with DPP-4 inhibitors have recently been published[86,87]. The risk of death from cardiovascular causes, myocardial infarction or ischemic stroke in

patients treated with saxagliptin was not increased relative to the placebo-treated group, and was not different among white, black, Asian and other ethnic groups[86]. The risk for the primary composite cardiovascular outcome in type 2 diabetes patients treated with alogliptin was also comparable with those treated with the placebo, and was not different between white and non-white subgroups[87]. When the data were analyzed according to geographic regions, there was no increased cardiovascular risk with alogliptin in the Asia–Pacific region, although there was a tendency of a decreasing incidence of primary composite cardiovascular outcome events in Eastern Europe and Africa[87]. To date, there are no published cardiovascular outcome studies with GLP-1 receptor agonists, but the results are expected to be available in the near future[88].

CONCLUSIONS AND FUTURE PERSPECTIVES

The characteristics of type 2 diabetes in East Asians are distinguished from those in other ethnic groups. The physiology and pathophysiology of incretin hormones among Asians and non-Asians are largely alike, but differ in some aspects. The secretion of GLP-1 and GIP is not decreased in Asian patients with type 2 diabetes. However, in contrast to European patients with type 2 diabetes, it is possible that the incretin effect is not blunted in East Asian patients with type 2 diabetes. The glucose-lowering efficacy of DPP-4 inhibitors or GLP-1 receptor agonists is greater in Asians than in non-Asians. The different pathophysiologies of type 2 diabetes, different body compositions, different genetic makeups, preserved incretin effects and different dietary factors might contribute to the seemingly greater glucose-lowering efficacy of incretin-based therapies. Incretin-based therapies appear to be safe and well tolerated in East Asians. The characteristics of incretin biology and clinical responses to incretin-based therapies in East Asians need to be reflected in ethnicity-specific guidelines or the patient-specific approach for the treatment of type 2 diabetes.

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DISCLOSURE

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