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MINI REVIEW

Incretin-based drugs for type 2 diabetes: Focus on East Asian perspectives

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ABSTRACT

Type 2 diabetes in East Asians is characterized primarily by β-cell dysfunction, and with less adiposity and less insulin resistance compared with that in Caucasians. Such pathophysiological differences can determine the appropriate therapeutics for the disease. Incretins, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1, are secreted in response to meal ingestion, and enhance insulin secretion glucose-dependently. Incretin-based drugs, dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists, that ameliorate β-cell dysfunction with limited hypoglycemia risk are now widely used in type 2 diabetes management. Recent meta-analyses of clinical trials on DPP-4i and glucagon-like peptide-1 receptor agonists found that the drugs were more effective in Asians, most likely because of amelioration of β-cell dysfunction. In addition, we found increased glycated hemoglobin-lowering effects of DPP-4i to be associated with intake of fish in type 2 diabetes, which suggests that dietary customs of East Asians might also underlie the greater efficacy of DPP-4i. Despite the limited risk, cases of severe hypoglycemia were reported for DPP-4i/sulfonylureas combinations. Importantly, hypoglycemia was more frequent in patients also receiving glibenclamide or glimepiride, which activate exchange protein directly activated by cyclic adenosine monophosphate 2, a critical mediator of incretin signaling, and was less frequent in patients receiving gliclazide, which does not activate exchange protein directly activated by cyclic adenosine monophosphate 2. Prevention of insulin-associated hypoglycemia by DPP-4i has gained attention with regard to the enhancement of hypoglycemia-induced glucagon secretion by insulinotropic polypeptide, but remains to be investigated in East Asians. Despite the safety issues, which are paramount and must be carefully monitored, the incretin-based drugs could have potential as a first choice therapy in East Asian type 2 diabetes patients.

INTRODUCTION

The rapid increase in type 2 diabetes is one of the most serious global health problems today. The number of patients with diabetes, estimated to be 415 million in 2015, is expected to rise to 642 million by 2040[1], partly as a result of a drastic increase in the number of patients in East Asian countries, which now comprise one-quarter of the global diabetes population. The etiology of type 2 diabetes involves genetic predispositions and lifestyle factors, such as dietary habits and physical activity, as well as aging, all of which influence insulin secretion from the pancreatic β-cells and/or reduce insulin sensitivity of target organs. It is becoming widely recognized that East Asian type 2 diabetes is characterized primarily by β-cell dysfunction, which is evident immediately after glucose ingestion (Figure 1), and by generally lesser obesity and higher insulin sensitivity compared with that in Caucasians[2]. These pathophysiological differences have a crucial impact on the appropriate therapeutic approach. To ameliorate β-cell dysfunction, insulin secretagogues, such as sulfonylureas (SU) and glinides, have been used as preferred drugs in East Asian countries; however, SU and glinides are associated with hypoglycemia and bodyweight gain, and better therapeutics have long been sought. Incretin-based therapies, dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), have been widely used in the management of type 2 diabetes. These drugs

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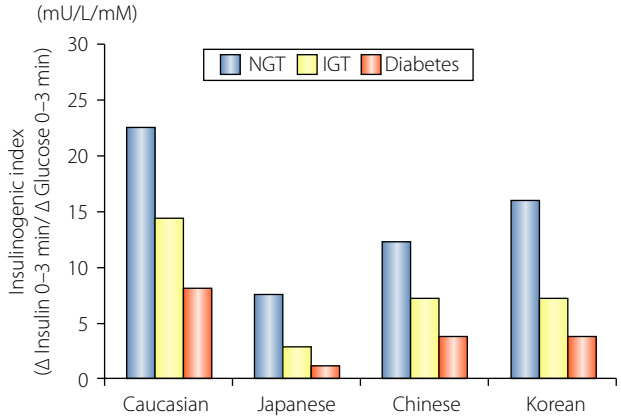

Figure 1 | Reduced early-phase insulin secretion in East Asian individuals compared with Caucasian individuals. Insulinogenic index (ΔInsulin 0–30 min/ΔGlucose 0–30 min) was indirectly compared between East Asians and Caucasians with or without type 2 diabetes. Blue bars, participants with normal glucose tolerance (NGT). Orange bars, participants with isolated impaired glucose tolerance (IGT). Red bars, participants with type 2 diabetes (Diabetes). Reproduced from Yabe *et al.*[50] with permission.

ameliorate β-cell dysfunction with limited risk of hypoglycemia and bodyweight gain, and are widely used in East Asia. More than 70% of patients treated with antidiabetic drugs receive DPP-4i or GLP-1RA today; approximately 60% of these are drug-naïve, indicating that DPP-4i is rapidly becoming a first-line antidiabetic drug in Japan (Figure 2). In the present article, we discuss recent findings regarding the efficacy and safety of DPP-4i and GLP-1RAs from an East Asian perspective. We also discuss the novel interaction of medical nutrition therapy with the glucose-lowering effects of DPP-4i.

β-CELL DYSFUNCTION AND EAST ASIAN TYPE 2 DIABETES

As early as the 1970s, our group and others found that the insulin response to glucose ingestion in Japanese people, those having both normal glucose tolerance and type 2 diabetes, is much lower than it is in Caucasian people[3]. Cross-sectional studies in Japanese people with normal glucose tolerance, impaired glucose tolerance and type 2 diabetes confirmed reduced β-cell function and higher insulin sensitivity in comparison with Caucasian people[3]. These findings are supported by recent important studies: (i) a systematic review and meta-analysis of β-cell function and insulin sensitivity in i.v. glucose tolerance test found reduced β-cell function and higher insulin sensitivity of East Asian people compared with Caucasian people[4]; (ii) studies of Caucasian and Japanese matched individuals in oral glucose tolerance test and i.v. glucose tolerance test showed reduced β-cell function and higher insulin sensitivity in Japanese people[5,6]; and (iii) long-term cohort studies investigating the trajectory of normal glucose tolerance in Korea and the UK showed that decreased β-cell function and impaired β-cell compensation for progressive decline in insulin sensitivity are central in deteriorating glucose intolerance in Koreans, whereas decreased insulin sensitivity is a prerequisite for type 2 diabetes development in Caucasian people[7,8]. Considering such differences in β-cell function and insulin sensitivity, it seems reasonable that East Asians might have reduced β-cell reserve capacity that makes them readily susceptible to a minor decline of insulin sensitivity. Although this model needs to be tested in sufficiently powered multi-ethnic group studies, accumulating evidence implicates β-cell dysfunction as the primary defect of type 2 diabetes in non-obese East Asians, and shows the need for antidiabetic drugs that target β-cell dysfunction for management of the disease. Indeed, insulin secretagogues, such as SU and glinides, have been used as preferred drugs in East Asian countries; more recently, incretin-based drugs, DPP-4i and GLP-1RA that ameliorate β-cell dysfunction with limited risk of hypoglycemia and bodyweight gain have been added. Importantly, recent systematic review and meta-analyses of clinical trials on DPP-4i and GLP-1RA found the drugs to be more effective in Asians people[9,10].

INCRETINS AND INCRETIN-BASED DRUGS

The incretin concept, which opened up the possibility of incretin-based drugs as novel antidiabetic therapeutics, was reported more than 100 years ago[11–13]. Inspired by Bayliss and Starling's discovery of secretin, Moore *et al.* hypothesized in 1906 that gut extracts contain a hormone that regulates the endocrine pancreas, and showed that gut extracts reduce urinary glucose excretion in patients with diabetes, possibly by stimulating the endocrine pancreas. La Barre purified the glucose-lowering element from gut extracts in 1929, and named it incretin (INtestine seCRETtion INsulin). The classical studies by Elrick *et al.* and McIntyre *et al.* showed the pivotal role of incretin in the enhancement of insulin secretion after oral glucose loading in men[14,15]. Later studies confirmed that incretin comprises a pair of intestinal hormones, gastric inhibitory polypeptide (GIP) and GLP-1[11–13], secreted by the K cells and the L cells of the duodenum, respectively.

GIP is a 42-amino-acid hormone secreted from K cells of the upper small intestine (Figure 2)[11]. GIP, originally isolated from porcine intestine by Brown *et al.* on the basis of its ability to inhibit gastric acid secretion, stimulates insulin secretion in a glucose-dependent manner in non-diabetic individuals, and acts directly on pancreatic islets to stimulate insulin secretion glucose-dependently[11]. By studying the insulin response in gastrectomized patients, our group showed that endogenous GIP also stimulates insulin secretion glucose-dependently[16]. These lines of evidence revealed GIP as the first of the incretins, which was then renamed glucose-dependent insulinotropic polypeptide. Because immunological depletion of GIP did not abolish all insulin-stimulating activity in gut extracts, the existence of another incretin was inferred; GLP-1, a 31-amino-acid hormone produced from proglucagon and secreted from L cells of the lower intestine and colon, was later shown to be the second

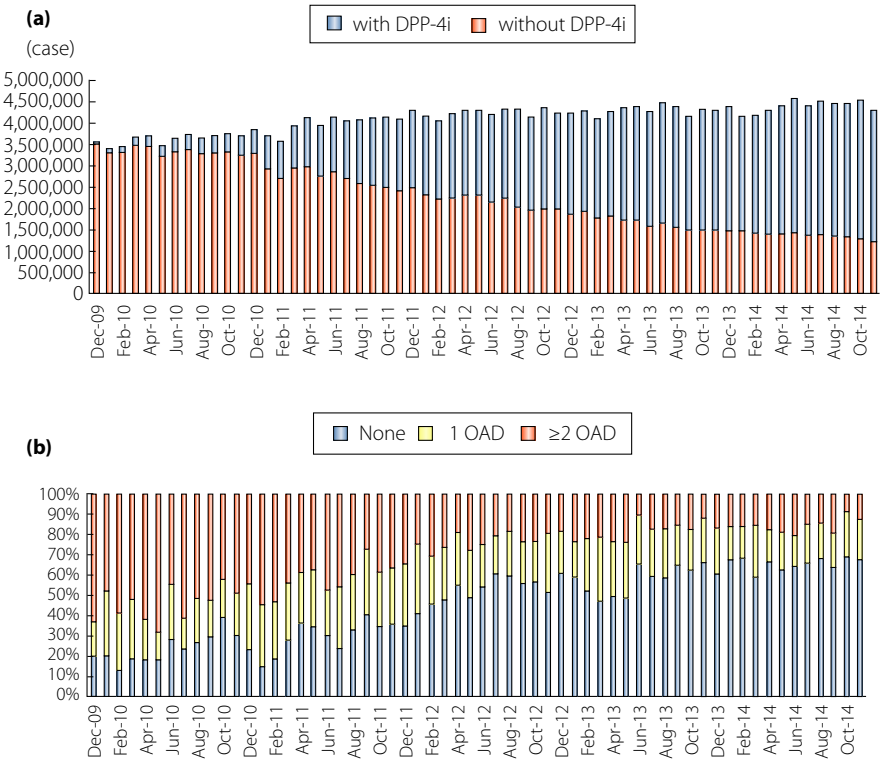

Figure 2 | Wide use of dipeptidyl peptidase-4 inhibitors (DPP-4i) as a first choice therapy in Japan. (a) The number of individuals receiving DPP-4i among those treated with oral antidiabetic drugs (OAD). Those treated with insulin and/or glucagon-like peptide-1 are not included. Note that more than 70% of individuals with OAD receive DPP-4i in Japan today. (b) Profiles of antidiabetic drug use before initiating DPP-4i. Note that approximately 60% of individuals receive DPP-4i as a first choice therapy in Japan. Data were derived from the Japan Medical Data Centre Claims Database (Japan Medical Data Centre Co., Ltd, Tokyo, Japan), which contains the following information on individuals aged <75 years in employment-based health insurance programs: age and sex of patient; diagnosis of disease using International Classification of Diseases-10 code; and prescribed drugs. Reproduced from Yabe *et al.*[29] with permission.

incretin[12,13]. It has been also shown that both GIP and GLP-1 exert their insulinotropic effects through their specific receptors, the GIP receptor (GIPR) and the GLP-1 receptor (GLP-1R); genetic ablation of GIPR and GLP-1R separately or simultaneously in mice shows their critical roles in the potentiation of glucose-induced insulin secretion[11,12]. These lines of evidence confirmed the critical role of GIP and GLP-1 as incretins.

To develop incretin-based drugs, several issues had to be resolved. First, secreted incretins undergo rapid degradation catalyzed by DPP-4, which diminishes the insulinotropic effects of GIP and GLP-1[11,13]. Second, it was initially reported that the insulinotropic effects of GIP are attenuated in individuals with type 2 diabetes[17], identifying GLP-1 as a major target for drug development. The demonstration that GLP-1 secretion is reduced in individuals with type 2 diabetes[18] also suggested amelioration of β-cell dysfunction through activation of GLP-1R signaling by increasing the levels of biologically intact GLP-1 through DPP-4 inhibition or supplementation of DPP-4-resistant GLP-1RA. Although a recent systematic review and meta-analysis showed little reduction of GLP-1 secretion in type 2 diabetes[19,20], long-term i.v. infusion of GLP-1 has been shown to improve glycemic control[21], establishing GLP-1 and GLP-1R signaling as therapeutic targets for type 2 diabetes. However, recent studies showed that the insulin response to GIP is restored in individuals with near-normalized glycemia[22]. This observation is especially important in the treatment of type 2 diabetes with DPP-4i, because its effect is influenced by both GIP and GLP-1. Indeed, a recent report studying the effects of endogenous incretins showed that GLP-1R antagonist did not completely attenuate the glucose-lowering effects of DPP-4i in individuals with near-normalized glycemia[23]. Furthermore, the meal-induced GLP-1 response is attenuated, whereas the GIP response is somewhat increased with long-term treatment of DPP-4i (DY and YS, unpubl. obs.). Taken together with similar observations on the GLP-1 response in DPP-4i-treated patients[24], these results emphasize the importance of GIP in DPP-4i treatment.

GLUCOSE-LOWERING EFFECTS OF DPP-4I IN EAST ASIANS

It has been found that DPP-4i and GLP-1RA have greater glucose-lowering effects in Asian people[9,10,25], which is consistent

with β-cell dysfunction as the primary defect of East Asian type 2 diabetes and incretin-based drugs to target this defect. Although no head-to-head clinical trials comparing long-term glucose-lowering effects of incretin-based drugs exist, accumulating clinical data from East Asian countries suggest that DPP-4i shows sustained glucose-lowering effects in the management of East Asian type 2 diabetes[26–28]. In addition, our analysis on duration before prescription changes after initiating oral antidiabetic drugs using a large Japanese medical claims database showed that DPP-4i exerted longer durability as monotherapy or add-on therapy when compared with oral antidiabetic drugs[29], suggesting efficacy and safety of DPP-4i that is superior to other oral antidiabetic drugs in Japanese people. Interestingly, we also found that GLP-1 secretion, but not GIP secretion, after ingestion of glucose or meals in Japanese people is lower than that of Caucasian people when measured by the same immunoassay[30,31]. Although proof of ethnic differences in the secretion of GLP-1 and GIP requires sufficiently powered multiethnic group studies, GLP-1 deficiency in addition to β-cell dysfunction might well be partly responsible for the superior efficacy of incretin-based drugs in East Asian type 2 diabetes.

Because GLP-1 and GIP are secreted in response to meals, dietary habits might well influence the efficacy of DPP-4i. Indeed, the glycated hemoglobin (HbA1c)-lowering effects of DPP-4i in the relatively short-term are enhanced by fish intake, as estimated by food records and serum levels of eicosapentaenoic acids and docosahexaenoic acids, in individuals with type 2 diabetes (Figure 3)[32,33]. Milk products and meat show weaker associations with the HbA1c-lowering effects of DPP-4i in a relatively short observation period. These findings suggest that nutrients in fish, meat and milk products promote GLP-1 and GIP secretion, and thereby enhance the HbA1c-lowering effects of DPP-4i. Previous studies showed that intake of whey protein, glutamine or olive oils before carbohydrates enhanced GLP-1 secretion and ameliorated postprandial glucose excursions in individuals both with and without type 2 diabetes[34], showing that preload of a small amount of protein or fats before meals might be effective in postprandial glucose excursion through GLP-1. We recently showed that eating fish before rice enhances GLP-1 secretion and ameliorates postprandial glucose excursion in comparison with eating fish after rice[35]. Eating meat before rice has similar results, except that it robustly enhances GIP secretion, possibly because of the saturated and mono-unsaturated fats in meat, which are strong enhancers of GIP secretion. As GIP, in collaboration with these fats, facilitates fat accumulation[36], eating meat before rice chronically might be linked to bodyweight gain and subsequent insulin resistance, negating any HbA1c-lowering effects of DPP-4i. Indeed, a small but significant bodyweight gain is associated with deterioration of the HbA1c-lowering effects of DPP-4i in Japanese individuals with type 2 diabetes[37,38]. Together, these results suggest that the greater efficacy of DPP-4i in East Asians might be partly due to dietary habits along with lesser adiposity and insulin resistance.

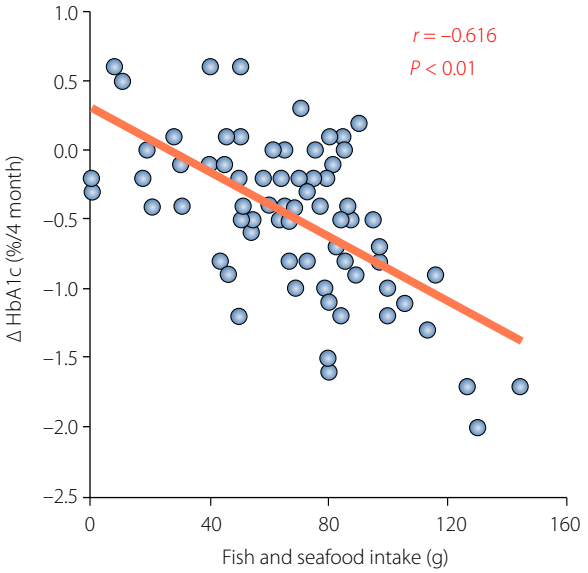

Figure 3 | Association of glycated hemoglobin (HbA1c) reduction by dipeptidyl peptidase-4 inhibitors and estimated intake of fish. Correlation between estimated intake of fish and seafood (fish intake) with HbA1c reduction (ΔHbA1c). Among fish and seafood (i.e., shellfish, squid and octopus, and crustaceans), only estimated intake of fish showed a significant association with HbA1c reduction by single regression analysis ($r = -0.62$, $P < 0.01$). Reproduced from Iwasaki *et al.*[32] with permission.

HYPOGLYCEMIA AND DPP-4I IN EAST ASIANS

Although DPP-4i by itself is considered to have a very limited risk of hypoglycemia, cases of severe hypoglycemia were reported among individuals receiving DPP-4i as add-on to SU when the first DPP-4i sitagliptin emerged in Japanese clinical practice (Figure 4). The estimated incidence of hypoglycemic coma was 16.3 per million patients who received sitagliptin during the first 6 months after its launch in Japan, and was approximately 6.4-fold higher than that of the USA in the corresponding period[39]. The cases in Japan were mostly elderly, and were found to have renal insufficiency and high HbA1c even with use of high-dose SU. Based on the characteristics of the cases with severe hypoglycemia by DPP-4 inhibitor treatment, a committee of experts in the field (Chair, Y Seino of Kansai Electric Power Hospital; T Kadowaki of University of Tokyo; N Inagaki of Kyoto University; T Iwakura of Kobe City Hospital; Y Iwamoto of Tokyo Women's Medical University; S Seino of Kobe University) urged physicians to reduce the doses of preprescribed SU drugs, especially in the elderly and/or individuals with renal insufficiency, before co-administration of DPP-4i.

Two key investigations of incretin signaling in β-cells provided clues to understand the mechanism of severe hypoglycemia on initiation of DPP-4i in SU-treated type 2 diabetes patients. The first study showed that GLP-1R activation ameliorates glucose metabolism in β-cells of non-obese diabetic model

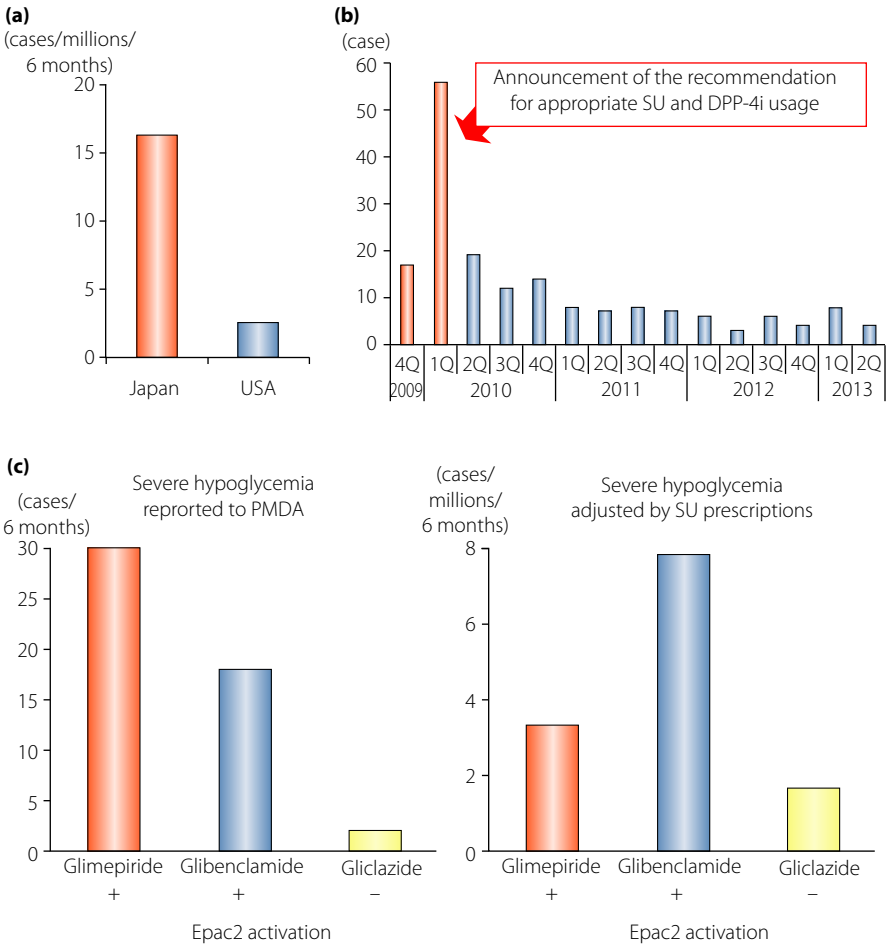

Figure 4 | Severe hypoglycemia in individuals receiving dipeptidyl peptidase-4 inhibitors (DPP-4i) as add-on to sulfonylureas (SUs). (a) Comparison of the incidence rate of severe hypoglycemia in individuals receiving the DPP-4i, sitagliptin, in Japan and the USA. The incidence of hypoglycemic coma with sitagliptin was 16.3 per million patients who received sitagliptin during the first 6 months after its launch in Japan, and was approximately 6.4-fold higher than that of USA in the corresponding period. (b) Transition in cases of severe hypoglycemia in individuals treated with sitagliptin in each quarter. The number was drastically reduced on announcement of the recommendation from the committee for appropriate use of incretin-related drugs (glucagon-like peptide-1 receptor agonists and DPP-4 inhibitors). (c) Comparison of the numbers of severe hypoglycemia cases in individuals receiving sitagliptin as add-on to indicated SUs. Left, the numbers of cases reported to the Japanese Pharmaceuticals and Medical Devices Agency. Right, estimated incidence rates calculated by dividing the numbers of cases reported to the Japanese Pharmaceuticals and Medical Devices Agency by the numbers of individual prescriptions of indicated SUs combination with sitagliptin in the same period. EPAC2, exchange protein directly activated by cyclic adenosine monophosphate 2. Reproduced from Yabe and Seino[39] with permission.

Goto-Kakizaki rats, thereby improving glucose-induced insulin secretion[40]. Chronic hyperglycemia is known to enhance reactive oxygen species production, which then impairs glucose metabolism and reduces production of adenosine triphosphate (ATP) in β-cells. As SU-induced closure of K_{ATP} channels is known to be affected significantly by intracellular ATP levels, chronic hyperglycemia could make β-cells less sensitive to SU, partly explaining "SU secondary failure." The Goto-Kakizaki rat study clearly showed that activation of GLP-1R signaling reduces reactive oxygen species production and increases ATP, an exchange protein directly activated by cyclic adenosine monophosphate 2A (EPAC2A)-dependently[40]. Thus, initiation of DPP-4i in patients with "SU secondary failure" could result in hypoglycemia as a result of improved sensitivity of the pancreatic β-cells to SU. Another clue came from a study revealing novel cross-talk between SU and incretin signaling through EPAC2A[41]. It is known that activation of GIPR and GLP-1R leads to an increase in intracellular cyclic adenosine monophosphate levels, which binds to and activates EPAC2A, thereby enhancing insulin secretion. In addition, SU such as glibenclamide and glimepiride but not gliclazide, bind to and activate EPAC2A, thereby enhancing insulin secretion. These results are

suggestive of the cases in which SU is responsible for severe hypoglycemia. The estimated incidence rates of severe hypoglycemia in patients receiving sitagliptin with glimepiride (3.35 per 10,000) or glibenclamide (7.86 per 10,000) were more than twofold higher than in those receiving sitagliptin with gliclazide (1.66 per 10,000; Figure 4)[39]. Although numerous factors including reduced glucose counter-regulation might affect the incidence rates of severe hypoglycemia by the combinations of sitagliptin and each SU, these data complement the original observations in clinical settings and provide insight on the suitability of the various SU to be used in combination with DPP-4i. Taken together, these important findings explain why activation of incretin signaling by DPP-4i enhances SU-induced insulin secretion even in individuals with "SU secondary failure." Therefore, with careful titration of SU doses and appropriate patient education on hypoglycemia, a combination of DPP-4 inhibitors and SU drugs can be effective type 2 diabetes therapy.

Regarding hypoglycemia, GIP action on glucagon secretion has been gaining much attention recently, because DPP-4i add-on to insulin reduces hypoglycemia[42,43]. As early as the 1970s, our group showed that GIP enhances glucagon secretion in rats and isolated rat islets[44]. Later, enhancement of glucagon secretion by GIP was confirmed in individuals with type 2 diabetes during insulin-induced hypoglycemia[45]. It is also known that DPP-4i vildagliptin enhances the glucagon response to insulin-induced hypoglycemia[46], suggesting that DPP-4i reduces insulin-induced hypoglycemia through GIP. However, our recent studies showed that DPP-4i linagliptin did not enhance insulin-induced glucagon secretion in Japanese type 2 diabetes patients (DY and YS, unpubl. data). Currently, it remains unknown whether differences in ethnicities and/or the DPP-4i used could explain the differing results. Further studies are required to clarify the mechanisms of lower hypoglycemia risk using DPP4-i.

CONCLUSION

The profound glucose-lowering effects and low hypoglycemia risk of incretin-based drugs have made them widely used in non-obese type 2 diabetes across East Asian countries, especially in Japan. However, safety issues must always be kept in mind. As aforementioned, careful considerations are required to avoid severe hypoglycemia when DPP-4i is co-administrated with SU. It is also important to triage patients with risk of acute pancreatitis before prescribing incretin-based drugs. Although the associations of incretin-based drugs with acute pancreatitis in East Asians have been controversial[47,48], recent meta-analysis of prospective, randomized controlled trials of DPP-4i showed a small but significant increase of acute pancreatitis associated with DPP-4i use[49]. Thus, adverse events, both known and unknown, must be carefully monitored for years. Nevertheless, given the pathophysiology of East Asian type 2 diabetes (insulin deficiency rather than insulin resistance), incretin-based drugs, which primarily correct impaired early phase insulin secretion, might well be the more suitable treatment of disease in these patients, and has the potential to be a first choice therapy, as is presently the case for metformin in Caucasian type 2 diabetes patients.

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