Glucose-lowering action through targeting islet dysfunction in type 2 diabetes: Focus on dipeptidyl peptidase-4 inhibition

Bo Ahren*1

Department of Clinical Sciences Lund, Lund University, Lund, Sweden

Keywords
Asian subjects, Dipeptidyl peptidase-4 inhibition, Type 2 diabetes

*Correspondence
Bo Ahren
Tel.: +46-46-222-0758
E-mail address: Bo.Ahren@med.lu.se

J Diabetes Investig 2021; 12: 1128–1135
doi: 10.1111/jdi.13564

ABSTRACT
Dipeptidyl peptidase-4 (DPP-4) inhibition is a glucose-lowering medication for type 2 diabetes. It works through stimulation of insulin secretion and inhibition of glucagon secretion in a glucose-dependent manner, resulting in lowered fasting and postprandial glycemia with low risk of hypoglycemia. As impaired insulin secretion and augmented glucagon secretion are key factors underlying hyperglycemia in type 2 diabetes, DPP-4 inhibition represents a therapy that targets the underlying mechanisms of the disease. If insufficient in monotherapy, it can preferably be used in combination with metformin, which targets insulin resistance, and also in combination with sodium–glucose cotransporter 2 inhibition, thiazolidinediones and insulin, which target other mechanisms. In individuals of East Asian origin, islet dysfunction is of particular importance for the development of type 2 diabetes. Consequently, it has been shown in several studies that DPP-4 is efficient in these populations. This mini-review highlights the islet mechanisms of DPP-4 inhibition, islet dysfunction as a key factor for hyperglycemia in type 2 diabetes and that, consequently, DPP-4 is of particular value in populations where islet dysfunction is central, such as in individuals of East Asian origin.

INTRODUCTION
Based on its ability to prevent the inactivation of the incretin hormone glucagon-like peptide-1 (GLP-1), dipeptidyl peptidase-4 (DPP-4) inhibition was explored as a target for glucose-lowering therapy of type 2 diabetes in the 1990s1,2. Mechanistic studies have shown that DPP-4 inhibition also prevents the inactivation of the incretin hormone, glucose-dependent insulinotropic polypeptide, and the combined effects of DPP-4 inhibition result in stimulation of insulin secretion and inhibition of glucagon secretion3.

The first clinical studies showing a glucose-lowering action of DPP-4 inhibition in type 2 diabetes patients was published in 20024. After subsequent development, DPP-4 inhibition was introduced into the clinical market in 2006, and has since been further developed and is now used in many countries5,6. Sitagliptin, linagliptin, vildagliptin, saxagliptin and alogliptin are the most commonly used DPP-4 inhibitors, but also others have been developed, particularly in Japan and South Korea, such as anagliptin, gemigliptin, evogliptin, teneligliptin, teliglaptin, gasagliptin and retagliptin7.

There are several advantages of the use of DPP-4 inhibitors (Table 1). They are orally active and they reduce glycated hemoglobin (HbA1c) efficiently within the range of 0.5–1.0%5,6. They can be used in both monotherapy and in combination therapy with metformin, sodium–glucose cotransporter 2 inhibitors, thiazolidinediones and insulin6,8-10. They are also weight neutral and do not cause weight gain6,11. Furthermore, the risk for hypoglycemia is very low12 and DPP-4 inhibitors can be used also in patients with renal impairment13. DPP-4 inhibitors are also effective in elderly patients14. DPP-4 inhibitors show no drug–drug interaction with other glucose-lowering medications or other commonly used pharmacotherapies in type 2 diabetes patients5. They are also safe and show good tolerability, with only a few adverse events reported – as evidenced by long experience, long-term large outcomes trials6,11,15-19 and experience in the treatment of elderly patients14 – except for an increased risk for hospitalization as a result of heart failure with saxagliptin15. There has been a discussion regarding signals for pancreatitis and pancreatic cancer, but long-term studies have not confirmed a definitive risk in this respect20,21.
Table 1 | Characteristics of dipeptidyl peptidase-4 inhibition

| Characteristic                                      |
|-----------------------------------------------------|
| Orally active                                       |
| Reduce HbA1c                                        |
| Can be used in monotherapy                          |
| Can be used in combination with sulphonylureas, insulin, SGLT2-inhibitors and thiazolidinediones |
| Can be used in renal impairment                     |
| Can be used in elderly patients                     |
| Weight neutral, no weight gain                      |
| Very low risk of hypoglycemia                       |
| No drug-to-drug interaction with medications commonly used in type 2 diabetes |
| Tolerable with low risk of adverse events           |
| Safe in long-term treatment, including cardiovascular safety |

SGLT2, sodium-glucose cotransporter 2.

MECHANISMS OF DPP-4 INHIBITION
The DPP-4 inhibitors differ in chemical structure, pharmacokinetics and metabolism, and they also have different mechanisms when they interact with the catalytic site of the DPP-4 enzyme. Despite these differences, all DPP-4 inhibitors prevent the inactivation of GLP-1 and glucose-dependent insulinotropic polypeptide, thereby prolonging the increase in active forms of the two incretin hormones after meal ingestion. This results in stimulation of insulin secretion, as judged by increased insulin and C-peptide levels relative to glucose after oral glucose or mixed meal ingestion in individuals with type 2 diabetes. This has also been observed in Japanese patients. Furthermore, DPP-4 inhibitors also augment insulin secretion after intravenous glucose administration in humans. What is also important is that the effect is glucose-dependent, which means that insulin secretion is stimulated when glucose levels are elevated, but that DPP-4 inhibition does not stimulate insulin secretion at low glucose levels. This is explained by an increased glucose sensitivity in the β-cells, which has been shown with the DPP-4 inhibitors, vildagliptin and sitagliptin. This is mainly explained by the glucose-dependent mechanism of the insulin secretory effect of GLP-1, which was initially shown in vivo model experiments in mice.

Another important effect of DPP-4 inhibition is inhibition of glucagon secretion. This was first shown in humans for vildagliptin after a mixed meal in individuals with type 2 diabetes, and was later confirmed for other DPP-4 inhibitors in white patients. In Japanese patients, glucagon levels were slightly suppressed by DPP-4 inhibition after meal ingestion in two studies, but not significantly changed in another study, whereas in Chinese patients, a clear reduction in glucagon levels after meal ingestion was observed for DPP-4 inhibition. These results might suggest that the increase in insulin secretion is more important than the reduction in glucagon in some populations, although this needs to be tested in further comparative studies. The glucagon-reducing effect of DPP-4 inhibition is most likely mediated by GLP-1, which already in 1992 was shown to inhibit glucagon secretion in individuals with type 2 diabetes. More detailed studies on islet effects of DPP-4 inhibition exist, and they have been summarized and reviewed in more detail. There are additional beneficial effects of DPP-4 inhibition on lipid metabolism, which was recently reviewed.

It was recently shown that the increase in insulin secretion and the inhibition of glucagon secretion by DPP-4 inhibitors persist throughout the day; that is, it occurs both after breakfast, lunch and dinner. In fact, the reduction in postprandial glycemia, the increase in insulin secretion relative to glucose and the inhibition of glucagon secretion by three different DPP-4 inhibitors (vildagliptin, sitagliptin and saxagliptin) were similar after the three daily meals in individuals with metformin-treated type 2 diabetes.

ISLET DYSFUNCTION IN TYPE 2 DIABETES
As shown in Figure 1, key defects for the development of glucose dysregulation in type 2 diabetes is insufficient release of...
insulin from islet β-cells in association of exaggerated release of glucagon from islet α-cells. This conclusion has been possible to establish from the results of several clinical studies, showing defective insulin secretion50-55 or inappropriately high glucagon secretion in type 2 diabetes56-59. The impaired insulin secretion results in inappropriately low circulating levels of insulin, leading to impaired stimulation of glucose utilization in peripheral tissues, and the inappropriately high glucagon levels result in exaggerated hepatic glucose production and release. These processes together raise circulating glucose. It has also been shown that these combined islet defects are present in individuals with impaired glucose tolerance; that is, before the onset of type 2 diabetes60. Furthermore, a long-term 12 year follow-up study in 49 white people with normal glucose tolerance showed that impaired insulin secretion and elevated glucagon secretion exist several years before the onset of impaired glucose tolerance61. Figure 2 shows these results. Insulin and glucagon secretion were evaluated using the glucose-dependent arginine stimulation test regularly for 12 years in individuals who had normal glucose tolerance at the start. By dividing the results into those who developed impaired glucose tolerance during the 12 year follow-up period and those who maintained normal glucose tolerance, it is evident that those developing impaired glucose tolerance had impaired insulin secretion and elevated glucagon secretion before the onset of diabetes.

When judging insulin secretion, it is important to relate the finding to insulin sensitivity, because insulin secretion is inversely upregulated in reduced insulin sensitivity, which is a relationship that has been described as a hyperbolic relationship62,63. When insulin secretion falls below the curve, it is insufficient for the prevailing insulin sensitivity, which results in glucose dysregulation64. Type 2 diabetes evolves when insulin secretion is high, but still insufficient to a reduced insulin sensitivity, which is illustrated as the blue dot in Figure 3, and which might be seen in individuals with obesity. Conversely, type 2 diabetes also evolves in high insulin sensitivity, if insulin secretion is lower than required, which is illustrated as the red dot. These two examples, therefore, show two different types of type 2 diabetes, which have therapeutic implications. A patient represented by the blue dot with combined insufficient insulin secretion and insulin resistance might be treated with agents that stimulate insulin secretion, such as DPP-4 inhibition or GLP-1 receptor agonists65, in combination with agents that increase insulin sensitivity, such as metformin. In contrast, agents that stimulate insulin secretion might be sufficient in patients illustrated by the red dot. Both types of patients might, however, also be treated with agents that have other mechanisms, such as insulin or sodium–glucose cotransporter 2-inhibitors, as suggested previously66.

**DPP-4 INHIBITION TARGETS ISLET DYSFUNCTION**

The islet focus of the mechanism of action of DPP-4 inhibitors and the critical role of islet dysfunction for the development of type 2 diabetes would make DPP-4 inhibitors appropriate for individuals with the greatest reduction in islet function. Hypothetically this would be particularly so in individuals with high insulin sensitivity; that is, patients illustrated by the red dot in Figure 3. This would imply that DPP-4 inhibition would be particularly powerful in patients with low body mass index (BMI) compared with high BMI, as BMI correlates inversely with insulin sensitivity, and, consequently, that DPP-4 inhibitors would be less efficient in individuals with high insulin sensitivity.
DPP-4 inhibition and islet dysfunction

Figure 3 | Schematic illustration of the inverse hyperbolic relationship between insulin sensitivity and insulin secretion in normal individuals with two patterns of pathophysiology of type 2 diabetes. The blue dot represents a patient with insulin resistance and insufficient increase in insulin secretion, whereas the red dot represents a patient with high insulin sensitivity and with low, and therefore insufficient insulin secretion.

resistance. Such hypotheses are important for the examination of the discussion of precision medicine. This hypothesis was supported by the results of a 6-month study showing that DPP-4 inhibition was less active in reducing HbA1c in individuals with high insulin resistance, as estimated by indirect markers, whereas there was no association with markers of insulin secretion.

However, studies aiming at predicting changes in HbA1c by DPP-4 inhibitors using BMI have in general been inconclusive, as although some studies have reported an association between BMI and less response to DPP-4 inhibition, most studies have reported no such influence. A problem in the interpretation of these studies is, however, that the most powerful predictor is baseline HbA1c, which might mask any independent prediction by BMI. Hence, baseline HbA1c has been shown to predict 34% of change in HbA1c in one meta-analysis consisting of 98 randomized clinical trials with various DPP-4 inhibitors in more than 24,000 patients. Similarly, in five randomized clinical trials with vildagliptin, 36% of change in HbA1c was attributed to baseline HbA1c, and a pooled analysis of three trials with linagliptin showed similarly that BMI did not predict the change in HbA1c. Therefore, whereas insulin resistance might be a factor in reducing the efficacy of DPP-4 inhibitors, this is not translated to clinical markers, such as BMI, and is therefore of less clinical importance.

TARGETING ISLET DYSFUNCTION AND TYPE 2 DIABETES IN EAST ASIA

Several studies have presented results that are consistent with a view that type 2 diabetes in East Asia is relatively more dependent on insufficient insulin secretion relative to insulin resistance or hyperglucagonemia when compared with white individuals. This has been demonstrated by showing a lower insulin response to oral and intravenous glucose in East Asian than in white patients, and that a progressive reduction in insulin secretion relative to insulin resistance is the critical key factor for the development of type 2 diabetes in Korean individuals.

It has also recently been proposed that the dietary intake of macronutrients is of relevance for the glucose-lowering action of DPP-4 inhibition. Thus, it was shown that the HbA1c lowering action of DPP-4 inhibition was higher in individuals who consumed less saturated fat. This might be related to the action of glucose-dependent insulinoactive polypeptide, which after high-fat intake facilitates energy storage in adipocytes. This might contribute to the explanation that DPP-4 inhibition is more efficient in populations with a lower intake of saturated fats as east Asians.

The importance of islet dysfunction for the development of type 2 diabetes in East Asian people suggests that DPP-4 inhibition will be an effective glucose-lowering therapy in this population. This is supported by several studies in East Asian individuals. It has also been shown, which is of particular interest, that the glucose-lowering efficacy of DPP-4 inhibition seems to be greater in East Asian people than in white people, as has been reviewed by meta-analyses. In a meta-analysis of 55 studies, HbA1c was reduced by 1.01% in Asian individuals versus 0.74% in non-Asian individuals, which was a significant difference. Also, the fasting plasma glucose-lowering efficacy was higher with DPP-4 inhibition in the Asian individuals.

In another meta-analysis, a reduction in HbA1c by DPP-4 inhibition was 0.65% in non-Japanese individuals in 55 studies versus by 0.74% in non-Asian individuals, which was a significant difference. It has also been shown, which is of particular interest, that the glucose-lowering efficacy of DPP-4 inhibition seems to be greater in East Asian people than in white people, as has been reviewed by meta-analyses. In a meta-analysis of 55 studies, HbA1c was reduced by 1.01% in Asian individuals versus 0.74% in non-Asian individuals, which was a significant difference. Also, the fasting plasma glucose-lowering efficacy was higher with DPP-4 inhibition in the Asian individuals.

In a meta-analysis of 93 studies showed a reduction in HbA1c by DPP-4 inhibition was 0.65% in non-Japanese individuals in 55 studies versus by 1.67% in Japanese individuals in seven studies. Similarly, a meta-analysis of 93 studies showed a reduction in HbA1c by DPP-4 inhibition was 0.65% in non-Japanese individuals versus 0.86% in Japanese individuals. This was also shown in a meta-analysis of studies using GLP-1 receptor agonists. Hence, although no direct head-to-head study exists comparing the efficacy of DPP-4 inhibition in East Asian versus white individuals, there is a clear and significant trend that the efficacy is greater in East Asian individuals.

CONCLUSION

There is a firm basis that DPP-4 inhibition is an efficient and safe glucose-lowering therapy for type 2 diabetes that is orally effective and associated with a low risk of hypoglycemia, weight gain or other adverse events. There is also a large amount of data, both clinical and experimental, showing that improvement of islet function is a key mechanism behind the glucose-lowering action of DPP-4 inhibition, both related to an increase in insulin secretion and inhibition of glucagon secretion. Furthermore, there are experimental and clinical bases for a conclusion that islet dysfunction is a more important key factor for the development of type 2 diabetes in individuals from East Asia than in white individuals. Therefore, DPP-4 inhibition is an important alternative for glucose-lowering medication in...
East Asia, and clinical experience with efficacy and durability supports this.

ACKNOWLEDGMENTS
The author thanks all researchers who have devoted their time and effort to study incretin therapy, pathophysiology of type 2 diabetes and diabetes in East Asian people. The author also apologizes for not being able to cite all important work that has brought this important field forward.

DISCLOSURE
The author has throughout the years been consulting for and/or lecturing for Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi and Takeda, which all are companies producing DPP-4 inhibitors or GLP-1 receptor agonists.

REFERENCES
1. Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. *Diabetes* 1998; 47: 1663–1770.
2. Ahrén B. Dipeptidyl peptidase-4 inhibitors – clinical data and clinical implications. *Diabetes Care* 2007; 30: 1344–1350.
3. Ahrén B, Foley JE. Improved glucose regulation in type 2 diabetic patients with DPP-4 inhibitors: focus on alpha and beta cell function and lipid metabolism. *Diabetologia* 2016; 59: 907–917.
4. Ahren B, Simonsson E, Larsson H, et al. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4 week study period in type 2 diabetes. *Diabetes Care* 2002; 25: 869–875.
5. Ahrén B. DPP-4 inhibition and the path to clinical proof. *Front Endocrinol* 2019; 10: 376.
6. Gallwitz B. Clinical use of DPP-4 inhibitors. *Front Endocrinol* 2019; 10: 389.
7. Cahn A, Cernea S, Raz I. An update on DPP-4 inhibitors in the management of type 2 diabetes. *Exp Opin Emerg Drugs* 2016; 21: 409–419.
8. Ahrén B, Foley JE, Bosi E. Clinical evidence and mechanistic basis for vildagliptin’s action when added to metformin. *Diabet Obes Metab* 2011; 13: 193–203.
9. Li D, Shi W, Wang T, et al. SGLT2 inhibitor plus DPP-4 inhibitor as combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Diabet Obes Metab* 2018; 20: 1972–1976.
10. Ahrén B. Insulin plus incretin. A glucose-lowering strategy for type 2-diabetes. *World J Diabetes* 2014; 15: 40–51.
11. Sesti G, Avogaro AS, Belcastro S, et al. Ten years of experience with DPP-4 inhibitors for the treatment of type 2 diabetes. *Acta Diabetol* 2019; 56: 605–617.
12. Famgren J, Ahrén B. Incretin-based medications (GLP-1 receptor agonists, DPP-4 inhibitors) as a means to avoid hypoglycaemic episodes. *Metabolism* 2019; 99: 25–31.
13. Walker SR, Komenda P, Khojah S, et al. Dipeptidyl peptidase-4 inhibitors in chronic kidney disease: a systematic review of randomized clinical trials. *Nephron* 2017; 136: 85–94.
14. Schwartz SL. Treatment of elderly patients with type 2 diabetes mellitus: a systematic review of the benefits and risks of dipeptidyl peptidase-4 inhibitors. *Am J Geriatr Pharmacother* 2010; 8: 405–418.
15. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; 369: 1317–1326.
16. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013; 369: 1327–1335.
17. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015; 373: 232–242.
18. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: The CARMELINA Randomized Clinical Trial. *JAMA* 2019; 321: 69–79.
19. Subrahmanyan NA, Koshy RM, Jacob K, et al. Efficacy and cardiovascular safety of DPP-4 inhibitors. *Curr Drug Saf* 2021; 16: 154–164.
20. Meier JJ, Nauck MA. Risk of pancreatitis in patients treated with incretin-based therapies. *Diabetologia* 2014; 57: 1320–1344.
21. Pinto LC, Rados DV, Barkan SS, et al. Dipeptidyl peptidase-4 inhibitors, pancreatic cancer and acute pancreatitis: a meta-analysis with trial sequential analysis. *Sci Rep* 2018; 8: 782.
22. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabet Obes Metab* 2011; 13: 18.
23. Ahrén B, Schweizer A, Dejager S, et al. Mechanisms of action of the dipeptidyl peptidase-4 inhibitor vildagliptin in humans. *Diabet Obes Metab* 2011; 13: 775–783.
24. Ahrén B, Pacini G, Foley JE, et al. Improved meal related β-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. *Diabetes Care* 2005; 28: 1936–1940.
25. He Y-L, Wang Y, Bullock JM, et al. Pharmacodynamics of vildagliptin in patients with type 2 diabetes during OGTT. *J Clin Pharmacol* 2007; 47: 633–641.
26. Wu T, Ma J, Bound MJ, et al. Effects of sitagliptin on glycemia, incretin hormones, and antroploroduodenal motility in response to intraduodenal glucose infusion in healthy lean and obese humans and patients with type 2 diabetes treated with or without metformin. *Diabetes* 2014; 63: 2776–2787.
27. Herman GA, Bergman A, Stevens C, et al. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2006; 91: 4612–4619.
28. Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Curr Med Res Opin 2009; 25: 2401–2411.
29. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care 2009; 32: 1649–1655.
30. Alsalim W, Göransson O, Carr RD, et al. Effect of single dose DPP-4 inhibitor sitagliptin on β-cell function and incretin hormone secretion after meal ingestion in healthy volunteers and drug-naïve, well-controlled type 2 diabetes subjects. Diabet Obes Metab 2018; 20: 1080–1085.
31. Nonaka K, Kakikawa T, Sato A, et al. Efficacy and safety of sitagliptin monotherapy in Japanese patients with type 2 diabetes. Diabet Res Clin Pract 2008; 79: 291–298.
32. Ohkura T, Fujioka Y, Surni K, et al. Sitagliptin improves the impaired acute insulin response during a meal test in Japanese patients with type 2 diabetes mellitus: small-scale real-world study. Diabet Ther 2014; 5: 285–297.
33. Pratley RE, Schweizer A, Rosenstock J, et al. Robust improvements in fasting and prandial measures of β-cell function with vildagliptin in drug-naïve patients: analysis of pooled vildagliptin monotherapy database. Diabet Obes Metab 2008; 10: 931–938.
34. D’Alessio DA, Denney AM, Hermiller LM, et al. Treatment with the dipeptidyl peptidase-4 inhibitor vildagliptin improves fasting islet-cell function in subjects with type 2 diabetes. J Clin Endocrinol Metab 2009; 94: 81–88.
35. Vardarli I, Nauck MA, Köthe LD, et al. Inhibition of DPP-4 with vildagliptin improved insulin secretion in response to oral as well as “isoglycemic” intravenous glucose without numerically changing the incretin effect in patients with type 2 diabetes. J Clin Endocrinol Metab 2011; 96: 945–954.
36. Aaboe K, Knop FK, Vilsbøll T, et al. Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus. Diabet Obes Metab 2010; 12: 323–333.
37. Mari A, Scherbaum WA NPM, et al. Characterization of the influence of vildagliptin on model-assessed β-cell function in patients with type 2 diabetes and mild hyperglycemia. J Clin Endocrinol Metab 2008; 93: 103–109.
38. Muscelli E, Casaloro A, Gastaldelli A, et al. Mechanisms for the antihyperglycemic effect of sitagliptin in patients with type 2 diabetes. J Clin Endocrinol Metab 2012; 97: 2818–2826.
39. Ahrén B. Insulinotrophic action of truncated glucagon-like peptide-1 in mice. Acta Physiol Scand 1995; 153: 205–206.
40. Ahrén BO, Landin-Olsson M, Jansson P-A, et al. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. J Clin Endocrinol Metab 2004; 89: 2078–2084.
41. van Raalte DH, van Genugten RE, Eliasson B, et al. The effect of alogliptin and pioglitazone combination on various aspects of β-cell function in patients with recent-onset type 2 diabetes. Eur J Endocrinol 2014; 170: 565–574.
42. Murali K, Katsuno T, Miyagawa J, et al. Very short-term effects of the dipeptidyl peptidase-4 inhibitor sitagliptin on the secretion of insulin, glucagon and incretin hormones in Japanese patients with type 2 diabetes mellitus: analysis of meal tolerance test data. Drugs R D 2014; 14: 301–308.
43. Nakagawa T, Nagai Y, Yamamoto Y, et al. Effects of alogliptin on plasma glucagon levels and gastric emptying in patients with type 2 diabetes: an exploratory randomized controlled trial versus metformin. Diabet Res Clin Pract 2019; 158: 107892.
44. Yabe D, Eto T, Shiramoto M, et al. Effects of DPP-4 inhibitor linagliptin and GLP-1 receptor agonist liraglutide on physiological response to hypoglycaemia in Japanese subjects with type 2 diabetes: a randomized, open-label, 2-arm parallel comparative, exploratory trial. Diabet Obes Metab 2017; 19: 442–447.
45. Sjöstrand M, Iqbal N, Lu J, et al. Saxagliptin improves glycemic control by modulating postprandial glucagon and C-peptide levels in Chinese patients with type 2 diabetes. Diabet Res Clin Pract 2014; 105: 185–191.
46. Gutniak M, Ørskov C, Holst JJ, et al. Antidiabetic effect of glucagon-like peptide-1 (7–36) amide in normal subjects and patients with diabetes mellitus. N Engl J Med 1992; 326: 1316–1322.
47. Ahrén B. DPP-4 inhibition and islet function. J Diabet Invest 2012; 3: 3–10.
48. Omar B, Ahrén B. Pleiotropic mechanisms for the glucose-lowering action of DPP-4 inhibitors. Diabetes 2014; 63: 2196–2202.
49. Aalseth W, Göransson O, Ahrén B, et al. Persistent whole-day meal effects of three dipeptidyl peptidase-4 inhibitors on glycemia and hormonal responses in metformin-treated type 2 diabetes. Diabet Obes Metab 2020; 22: 590–598.
50. Cerami E, Luft R. The plasma insulin response to glucose infusion in healthy subjects and in diabetes mellitus. Acta Endocrinol 1967; 55: 278–304.
51. Efendic S, Luft R, Wajngot A. Aspects of the pathogenesis of type 2 diabetes. Endocr Rev 1984; 5: 395–410.
52. Porte D Jr. Banting lecture 1990. Banting lecture 1990. Diabetes 1991; 40: 166–180.
53. Polonsky KS. Evolution of beta-cell dysfunction in impaired glucose tolerance and diabetes. Exp Clin Endocrinol Diabetes 1999; 107: 5124–5127.
54. Ahrén B. Type 2 diabetes, insulin secretion and beta-cell mass. Curr Mol Med 2005; 5: 275–286.
55. Kahn SE, Cooper ME, del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet 2014; 383: 1068–1083.
56. Unger RH. The banting memorial lecture 1975. Diabetes and the alpha cell. Diabetes 1976; 25: 136–151.
57. Dunning BE, Gerich J. The role of alpha-cell dysregulation in fasting and postprandial hyperglycemia in type 2 diabetes and therapeutic implications. Endocr Rev 2007; 28: 253–283.

58. Ahren B. Glucagon-Early breakthroughs and recent discoveries. Peptides 2015; 67: 74–81.

59. Gilon P. The role of alpha-cells in islet function and glucose homeostasis in health and type 2 diabetes. J Mol Biol 2020; 432: 1367–1394.

60. Larsson H, Ahren B. Islet dysfunction in obese women with impaired glucose tolerance. Metabolism 1996; 45: 502–509.

61. Ahren B. Beta- and alpha-cell dysfunction in subjects developing impaired glucose tolerance: outcome of a 12-year prospective study in postmenopausal Caucasian women. Diabetes 2009; 58: 726–731.

62. Bergman RN, Philips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 1981; 68: 1456–1467.

63. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 1993; 42: 1663–1672.

64. Weyer C, Bogardus C, Mott DM, et al. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999; 104: 787–794.

65. Ahren B. Glucagon-like peptide-1 receptor agonists for type 2 diabetes: a rational drug development. J Diabet Invest 2019; 10: 196–201.

66. Ahren B. Creative use of novel glucose-lowering drugs for type 2 diabetes: where will we head in the next 50 years? Diabetologia 2015; 58: 1740–1744.

67. Dennis JM, Shields BM, Hill AV, et al. Precision medicine in type 2 diabetes: Clinical markers of insulin resistance are associated with altered short- and long-term glycemic response to DPP4-inhibitor therapy. Diabetes Care 2018; 41: 705–712.

68. Bihan H, Ng LW, Magliano DJ, et al. Predictors of efficacy of GLP-1 agonists and DPP-4 inhibitors: a systematic review. Diabet Res Clin Pract 2016; 121: 27–34.

69. Monami M, Cremasco F, Lamanna C, et al. Predictors of response to dipeptidyl peptidase-4 inhibitors: evidence from randomized clinical trials. Diabet Metab Syndr Obes 2011; 4: 362–372.

70. Esposito K, Chiodini P, Maiorino M, et al. A nomogram to estimate the HbA1c response to different DPP-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of 98 trials with 24 163 patients. BMJ Open 2015; 5: e005892.

71. Ahren B, Mathieu C, Bader G, et al. Efficacy of vildagliptin versus sulfonylurea as add-on therapy to metformin: comparison of results from randomized controlled and observational studies. Diabetologia 2014; 57: 1304–1307.

72. Del Prato S, Patel S, Crowe S, et al. Efficacy and safety of linagliptin accounting to patient baseline characteristics; a pooled analysis of three phase 3 trials. Nutr Metab Cardiovas Dis 2016; 26: 886–892.

73. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: focus on East Asian perspectives. J Diabet Investig 2016; 7: 102–109.

74. Seino Y, Taminato T, Kurahachi H, et al. Comparative and therapeutic implications. J Diabet Investig 2016; 7: 102–109.

75. Kodama K, Tojjar D, Yamada S, et al. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. Diabetes Care 2013; 36: 1789–1796.

76. Moller JB, Dalla Man C, Overgaard RV, et al. Ethnic differences in insulin sensitivity, beta-cell function, and hepatic extraction between Japanese and Caucasians: a minimal model analysis. J Clin Endocrinol Metab 2014; 99: 4273–4280.

77. Ohn JH, Kwak SH, Cho YM, et al. 10-year trajectory of beta cell function and insulin sensitivity in the development of type 2 diabetes: a community-based prospective cohort study. Lancet Diabetes Endocrinol 2016; 4: 27–34.

78. Kim JD, Lee WY. Insulin secretory capacity and insulin resistance in Korean type 2 diabetes mellitus patients. Endocrinol Metab 2016; 31: 354–360.

79. Kuwata H, Okamoto S, Seino Y, et al. Relationship between deterioration of glycated hemoglobin-lowering effects in dipeptidyl peptidase-4 inhibitor monotherapy and dietary habits: retrospective analysis of Japanese individuals with type 2 diabetes. J Diabet Investig 2018; 9: 12153–21158.

80. Seino Y, Yabe D. Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: incretin actions beyond the pancreas. J Diabet Investig 2013; 4: 108–130.

81. Kozawa J, Kitamura T, Nishizawa H, et al. Dipeptidyl peptidase-4 inhibitors are effective in Japanese type 2 diabetic patients with sustained endogenous insulin-secreting capacity, a higher body mass index and insulin resistance. J Diabet Investig 2013; 4: 1900–1904.

82. Umezawa S, Kubota A, Maeda H, et al. Two-year assessment of the safety and efficacy of sitagliptin in elderly patients with type 2 diabetes: post hoc analysis of the ASSET-K study. BMC Med Res 2015; 15: 34.

83. Chen TY, Hsieh CJ. Efficacy and safety of sitagliptin in patients with type 2 diabetes mellitus. Postgrad Med 2014; 126: 205–215.

84. Ohmura H, Mita T, Taneda Y, et al. Efficacy and safety of sitagliptin in Japanese patients with type 2 diabetes. J Clin Med Res 2015; 7: 211–219.

85. Kim YG, Hahn S, Oh TJ, et al. Differences in the glucose lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and Non-Asians: a systematic review and meta-analysis. Diabetes 2013; 56: 696–708.
86. Park H, Park C, Kim Y, et al. Efficacy and safety of dipeptidyl peptidase-4 inhibitors in type 2 diabetes: meta-analysis. Ann Pharmacother 2012; 46: 1453–1469.

87. Ito Y, Ambe K, Hayase T, et al. Comparison of efficacy of dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter 2 inhibitors between Japanese and non-Japanese patient: a meta analysis. Clin Transl Sci 2020; 13: 498–508.

88. Kim YG, Hahn S, Oh TJ, et al. Differences in the HbA1c lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab 2014; 16: 900–909.