Editorial

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Candidate Dipeptidyl Peptidase-4 Inhibitors for the Treatment of Type 2 Diabetes

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Type 2 diabetes mellitus (T2DM) is a progressive disease that is characterized by insulin resistance and decreased insulin secretion [1]. Based on data from the UK Prospective Diabetes Study (UKPDS), there is consensus regarding the importance of glycemic control in patients with T2DM [2]. The American Diabetes Association (ADA) considers general glycemic control to be represented by HbA1c below 7.0% [3]. The ADA and European Association for the Study of Diabetes (EASD) statement on the management of hyperglycemia in T2DM patients recommends metformin intervention at the time of diagnosis in combination with lifestyle changes, and continuing timely augmentation of therapy with additional agents to achieve and maintain the recommended levels of glycemic control [4].

Sitagliptin is an oral, selective dipeptidyl peptidase-4 (DPP-4) inhibitor that is used for the treatment of patients with T2DM [5]. Sitagliptin delays the enzymatic degradation and inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), the major incretins involved in glucose homeostasis, thereby increasing insulin release and lowering glucagon secretion in a glucose-dependent manner [5,6]. Incretin-based therapies are currently recommended as add-on therapy, when metformin treatment alone is not sufficient to reach the ADA/EASD HbA1c target.

Treatment with sitagliptin 100 mg once daily leads to improvements in glycemic control in patients with T2DM, including reductions in HbA1c 0.6 to 0.7% [7]. The combined use of sitagliptin and metformin is an effective method of lowering glucose levels in T2DM. The reduction in HbA1c was 1.1% with metformin (2,000 mg/day) alone, and 1.9% with sitagliptin/metformin (100 mg/2,000 mg) [8]. When sitagliptin (100 mg) was added to ongoing sulfonylurea therapy alone or to a combination of sulfonylurea/metformin, HbA1c levels were reduced by only 0.3% and 0.6%, respectively, whereas only 11% and 23% of patients, respectively, achieved HbA1c <7% at the end of 24 weeks [9].

However, some studies have attempted to identify which patients respond to sitagliptin with better glycemic control among Korean T2DM patients. In this issue, 'Predictive clinical parameters for the therapeutic efficacy of sitagliptin in Korean type 2 diabetes mellitus' by Kim et al. [10] evaluates clinical factors associated with the therapeutic efficacy of sitagliptin when added to on oing metformin or metformin and sulfonylurea combination therapies. Kim et al. found that patients with more than a 20% decrease in fasting glucose and over 10% decrease in glycated hemoglobin after 24 weeks of sitagliptin administration, were younger and had lower body mass index (BMI) compared to non-responders. Treatment with 100 mg sitagliptin with metformin, or metformin and sulfonyurea for 24 weeks, led to additional reduction of mean HbA1c to 1.23±1.15%. This glycemic lowering effect is more potent than that observed in other previous studies [8,9]. In addition, the HbA1c lowering effect of sitagliptin was better in

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non-obese patients and in patients with decreased insulin secretion compared with the non-responder group.

Recently, beta cell dysfunction and reduction in maximal capacity to secrete insulin were demonstrated to be primary metabolic defects in patients with T2DM [11]. In particular, studies have suggested that beta cell dysfunction may be especially important in the development of T2DM in Korean patients [12]. These findings suggest that greater response to sitagliptin is expected in Korean T2DM patients with relative pancreatic secretory dysfunction in early phases of disease.

Sitagliptin is reported to be weight-neutral in clinical trials, and incidences of hypoglycemia and gastrointestinal adverse experiences in response to sitagliptin are similar to placebo [13]. In addition to its beneficial effects on glycemic control, sitagiptin, or combination treatment with sitagliptin and metformin, preserved beta cell function and beta cell integrity in Zucker diabetic fatty rats [14].

Kim et al.'s study was retrospective, and did not control for other factors that affect glucose control. Despite these limitations, their study is meaningful because it shows that early DPP-4 inhibitor initiation is a potential treatment option in younger, non-obese Korean T2DM patients whose glucose is not well controlled by metformin. As Kim et al. noted, further randomized, controlled prospective studies are needed.

We would like to express our gratitude to Kim et al. for conducting this study, and expect that expansion on these findings will yield even more useful results.

REFERENCES

1. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988;37:667-87.
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352: 837-53.
3. American Diabetes Association. Standards of medical care in diabetes--2011. Diabetes Care 2011;34 Suppl 1:S11-61.
4. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B; Professional Practice Committee, American Diabetes Association; European Association for the Study of Diabetes. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2006;49:1711–21.
5. Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes 1998; 47:1663-70.
6. Deacon CF, Ahren B, Holst JJ. Inhibitors of dipeptidyl peptidase IV: a novel approach for the prevention and treatment of type 2 diabetes? Expert Opin Investig Drugs 2004;13:1091-102.
7. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE; Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 2006;29:2632-7.
8. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care 2006;29:2638-43.
9. Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P; Sitagliptin Study 019 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2006;28:1556-68.
10. Kim SA, Shim WH, Lee EH, Lee YM, Beom SH, Kim ES, Yoo JS, Nam JS, Cho MH, Park JS, Ahn CW, Kim KR. Predictive clinical parameters for the therapeutic efficacy of sitagliptin in Korean type 2 diabetes mellitus. Diabetes Metab J 2011;35: 159-65.
11. Gerich JE. Redefining the clinical management of type 2 diabetes: matching therapy to pathophysiology. Eur J Clin Invest 2002;32 Suppl 3:46-53.
12. Kim DJ, Lee MS, Kim KW, Lee MK. Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. Metabolism 2001;50:590-3.
13. Karasik A, Aschner P, Katzeff H, Davies MJ, Stein PP. Sitagliptin, a DPP-4 inhibitor for the treatment of patients with type 2 diabetes: a review of recent clinical trials. Curr Med Res Opin 2008;24:489–96.
14. Han SJ, Choi SE, Kang Y, Jung JG, Yi SA, Kim HJ, Lee KW, Kim DJ. Effect of sitagliptin plus metforminon β-cell function, islet integrity and islet gene expression in Zucker diabetic fatty rats. Diabetes Res Clin Pract. Epub 2011 Feb 21. DOI: 10.1016/j.diabres.2011.01.016.