

## Effects of Sitagliptin on Insulin and Glucagon Levels in Type 2 Diabetes Mellitus

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Recently, the use of dipeptidyl peptidase-4 (DPP4) inhibitors in the management of type 2 diabetes mellitus (T2DM) has been widespread. This class drug control the fasting and postprandial glucose (PPG) levels in a glucose dependent manner. By slowing incretin degradation, DPP4 inhibitors increase the levels of active glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, and thereby stimulate insulin secretion and suppress glucagon release based on blood glucose level [1]. Sitagliptin, a highly selective DPP4 inhibitor, also has been demonstrated to control glucose levels through the similar mode of action [2].

Since several studies have reported that DPP4 inhibitors exhibit a better glucose lowering efficacy in Asian populations than in non-Asians with T2DM [3], sitagliptin may be one of appropriate treatment for T2DM in Asian patients. Most studies showed that sitagliptin treatment leads to significant improvements in  $\beta$ -cell function [4]. In Asian patients,  $\beta$ -cell dysfunction is major pathophysiology of T2DM. Furthermore, insulin secretory defect is more prominent in Asian than in Caucasian patients [5]. The changes of plasma insulin levels and glucagon levels during oral glucose tolerance test (OGTT) could be differed by ethnic groups and could partly elucidate the response of DPP4 inhibitors.

In Western patients with T2DM, there were many studies evaluating the effect of DPP4 inhibitors on blood insulin and glucagon levels. Herman et al. [1] showed that single doses of sitagliptin increased insulin (21% to 22%) and C-peptide (13%

to 21%) levels, reduced plasma glucagon levels (7% to 14%), and reduced glycemic excursion following an OGTT. In short-term clinical study of 2 weeks, sitagliptin reduced mean postprandial plasma glucagon concentration relative to baseline [6]. Relatively long-term clinical studies also evaluated markers of  $\beta$ -cell function such as homeostasis model of assessment of  $\beta$ -cell function (HOMA- $\beta$ ), fasting proinsulin-to-insulin ratio, fasting insulin secretion and the insulinogenic index, an index of early insulin release in response to a meal [7]. It has been reported that sitagliptin significantly improve these indices related to  $\beta$ -cell function in patients with T2DM [8-10].

However, clinical studies aimed to evaluate  $\beta$ -cell function by DPP4 inhibitor treatment in Asian patients are uncommon. In a couple of studies conducted in China, India, and Korea, sitagliptin did lead to significant improvement of indices of  $\beta$ -cell function, 2-hour postprandial insulin, C-peptide and the insulinogenic index [11] and saxagliptin increased HOMA- $\beta$  assessment [12]. In other study, which was to evaluate the effects of sitagliptin in Japanese patients with T2DM, 3-day treatment with sitagliptin showed significant decrease of PPG and the area under the curve<sub>0 to 2 hour</sub> for glucagon throughout the meal tolerance test [13]. Moreover, it improved the insulinogenic index and suppressed glucagon responses significantly for 12 weeks [14,15].

There are few data available to assess the effect of DPP4 inhibitors on insulin or glucagon in Korean patients with T2DM. Considering already proven the stronger effect of DPP4 inhibi-

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tors on glycosylated hemoglobin (HbA1c) reduction in Asians [3,14], we can expect that a marked change of insulin or glucagon levels after the use of DPP4 inhibitors in Korean patients with reduced pancreatic insulin secretion. A subset of study on Asian type 2 diabetic patients showed that the treatment with sitagliptin for 18 weeks significantly reduced HbA1c by 1.4% in Korean compared with placebo. Significant improvements of indices of  $\beta$ -cell function were also observed in this study [11]. Another DPP4 inhibitor, gemigliptin had been reported to significantly improve insulin secretory function, as assessed using HOMA- $\beta$ , proinsulin/insulin ratio and the insulinogenic index with 2-hour post-OGTT insulin and C-peptide levels in Korean patients with T2DM, as well [16].

In this issue, Yang et al. [17] investigated the effect of sitagliptin on plasma glucose, insulin and glucagon responses in Korean patients with T2DM. The insulinogenic index increased after treatment with sitagliptin for 6 months, especially in patients with higher body mass index (BMI) and higher HbA1c level. Although no significant differences in the levels of glucagon and glucagon/insulin ratio were observed, there was a significant reduction in the percentile change of glucagon/insulin ratio. In this study, indices of  $\beta$ -cell function were measured during a 75-g OGTT and the 3-day washout period was used to obviate any acute effect of sitagliptin on  $\beta$ -cell insulin or  $\alpha$ -cell glucagon secretion during testing. As a result, they could investigate the long-term effect of sitagliptin without any acute effects of the study drugs, so these findings were novel. In addition, it was interesting that the insulinogenic index significantly increased especially in subgroup of the higher BMI group. Most Korean and Japanese oriented studies reported that sitagliptin is expected to be more effective in patients with lower baseline BMI [18,19], because BMI is highly correlated with insulin sensitivity. On the contrary, other conflicting data suggested that the DPP4 inhibitors were also effective for glycemic control in patients with a high BMI. It was speculated that a high BMI might reflect sustained insulin secretory function [20]. More clinical studies are needed to find accurate predictive parameters for the therapeutic efficacy of DPP4 inhibitors.

However, this study had several limitations. First, there was no control group and combined anti-diabetic drugs were not fully described. The results can be varied depend on formulation and/or dose of insulin or regimen combined. Also, neither diet nor exercise were evaluated while the participants of this study were receiving treatment. Finally, although this study was designed to eliminate any acute effects of the study

drugs, the increase of the insulinogenic index could be influenced by secondary effects of improvement of glucose toxicity for long follow-up period of 6 months. Therefore, direct effect of DPP4 inhibitors on insulin and glucagon levels could be elucidated by well-controlled prospective study using OGTT. It is also expected that a direct comparison with other ethnic groups to show the response of insulin and glucagon in Asian patients will be contributed to understand the effect of DPP4 inhibitors.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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