COMMENTS AND RESPONSES

Comment on: Rizzo et al. Reduction of Oxidative Stress and Inflammation by Blunting Daily Acute Glucose Fluctuations in Patients With Type 2 Diabetes: Role of Dipeptidyl Peptidase-IV Inhibition. Diabetes Care 2012;35:2076–2082

In their interesting study on the concomitant reduction in inflammatory and oxidative stress and mean amplitude of glycemic excursions (MAGE) following treatment with dipeptidyl peptidase-IV (DPP-4) inhibitors, sitagliptin and vildagliptin, in patients with type 2 diabetes, Rizzo et al. (1) propose that the reduction in MAGE leads to the reduction in indices of oxidative and inflammatory stress. However, the recent demonstration that sitagliptin exerts a rapid and potent anti-inflammatory effect commencing within 2 h of the intake of the first dose of 100 mg suggests that the anti-inflammatory effect is a direct one and not secondary to a reduction in MAGE, which would take longer (2).

It is noteworthy that within 2 h of the intake of sitagliptin, there is a >90% inhibition of the DPP-4 enzyme, a reduction in nuclear factor-κB binding, and the expression of several inflammatory mediators, including inhibitory κB kinase β, chemokine receptor 2, and Toll-like receptor 2 (2). In addition, there was a reduction in the expression of CD26 in mononuclear cells. CD26 is essentially DPP-4 bound to cell membranes. Thus, sitagliptin not only inhibits DPP-4 activity in plasma, it also suppresses the expression of cellular CD26. It is also noteworthy that the concentration of glucagon-like peptide 1 (GLP-1) increases significantly within 2 h of the intake of sitagliptin and that exenatide, a GLP-1 agonist, also exerts a rapid anti-inflammatory effect (3). Thus, GLP-1 may also contribute to the anti-inflammatory effect by DPP-4 inhibitors in the long term. These anti-inflammatory effects of DPP-4 inhibitors and GLP-1 agonists are important since they could contribute to potential antiatherogenic effects in the long term and thus reduce cardiovascular events. Indeed, in the retrospective analyses of various trials carried out with DPP-4 inhibitors, there is a strong signal showing a reduction in cardiovascular events (4).

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