



COMMENT ON MONNIER ET AL.

Magnitude of the Dawn Phenomenon and Its Impact on the Overall Glucose Exposure in Type 2 Diabetes: Is This of Concern? *Diabetes Care* 2013;36:4057–4062

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The recent publication by Monnier et al. (1) on the magnitude of the dawn phenomenon in patients with type 2 diabetes highlights the need to effectively treat early morning hyperglycemia. However, we wish to comment on the authors' classification system for oral antihyperglycemic agents. The authors categorized dipeptidyl peptidase-4 (DPP-4) inhibitors, along with sulfonylureas and glinides, as insulin secretagogues and metformin and thiazolidinediones as insulin sensitizers. While others have also used this approach, we feel that this classification may be misleading as it does not fully reflect the mechanism of action of incretin agents, including GLP-1 receptor agonists and DPP-4 inhibitors, and may erroneously lead some readers to believe that the mechanism of action of DPP-4 inhibitors is similar to that of sulfonylureas. Whereas it is true that one element of the efficacy of DPP-4 inhibitors is mediated via increased insulin secretion, the mechanism of action of DPP-4 inhibitors is much broader than the effect on insulin secretion alone.

The differences between mechanisms of action of DPP-4 inhibitors and sulfonylureas include the following:

1. Glucagon suppression. DPP-4 inhibitors reduce glucagon release from pancreatic α -cells, whereas sulfonylureas have little overall impact or

may actually increase glucagon levels (2). This important difference between the mechanisms of action of DPP-4 inhibitors and sulfonylureas has consequences in that DPP-4 inhibitors reduce hepatic glucose output, and thus, unlike sulfonylureas, address a pathophysiologic aspect of type 2 diabetes (elevated hepatic glucose output) often categorized as insulin resistance. Based on a study using native GLP-1 (3), it has been proposed that glucagon suppression and insulin secretion contribute equally to the blood glucose-lowering effect of DPP-4 inhibitors.

2. Insulin synthesis and secretion. DPP-4 inhibitors increase insulin synthesis and release from pancreatic β -cells. However, circulating insulin levels are often barely changed (4), possibly due to hepatic uptake of portal vein insulin and/or reduction of concomitant glucose-stimulated insulin release.

3. Glucose dependency. DPP-4 inhibitors increase levels of intact (biologically active) GLP-1, leading to increased occupancy of GLP-1 at GLP-1 receptors on β -cells, whereas sulfonylureas close ATP-dependent potassium channels and cause insulin release via cellular depolarization. DPP-4 inhibitor-mediated insulin release results from GLP-1 receptor-linked increases in cyclic

AMP and subsequent amplification of glucose-mediated insulin release. Accordingly, insulin is not released and glucagon is not suppressed at low glucose levels, and the pancreatic effects of DPP-4 inhibitors are therefore described as being glucose-dependent and thus different from that of sulfonylureas. This key difference in mechanism accounts for the low incidence of hypoglycemic events for DPP-4 inhibitors in contrast to sulfonylureas.

Don't the authors agree that the classification of DPP-4 inhibitors as insulin secretagogues does not take fully into account the important features that differentiate DPP-4 inhibitors from sulfonylureas and other insulin secretagogues?

Duality of Interest. R.D.C. and C.M.A. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, and may own stock or hold stock options in the company. No other potential conflicts of interest relevant to this article were reported.

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