RESPONSE TO 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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Carr and Alexander (1) raise the question as to why we have classified dipeptidyl peptidase-4 (DPP-4) inhibitors as insulin secretagogues and not taken into account the features that differentiate DPP-4 inhibitors from older insulin secretagogues. First, there is cogent evidence that the actions of DPP-4 inhibitors are not solely restricted to a stimulatory effect on the insulin release by β-cells and that these agents also act through several additional effects, such as their inhibitory action on glucagon release (2). As a consequence, these drugs represent a new class of antidiabetes agents; for that reason, we agree that the true terminology is incretin enhancers. Second, these new drugs are also well-recognized insulinotropic glucose-dependent agents, which is why they have been simply classified as insulin secretagogues in our study (3).

Reverting to the main objective of our study, which was to investigate the impact of the dawn phenomenon on the overall glucose exposure in type 2 diabetes, the main message is that the contribution of the dawn phenomenon cannot be neglected, i.e., 0.4% (4 mmol/mol) in terms of percentage points of HbA_{1c}, which approximates one-half of the decrement in HbA_{1c} (0.8% [8 mmol/mol]) commonly observed after several weeks of treatment when these drugs are used as add-on therapy to metformin (2).

The data that we have reported in our article (3) indicate that none of the currently marketed oral antidiabetes medications are capable of adequately controlling the dawn phenomenon even when given as combined therapies. Porcellati et al. (4) suggested in their commentary to our article that regimens with long-acting insulin injected once daily in the evening seem the most appropriate therapies for reducing or abolishing the dawn phenomenon. However, as an excessive rise in the glucagon in the early morning is probably one of the main causative factors of the dawn phenomenon, it is not unrealistic to hypothesize that DPP-4 inhibitors, which exert an inhibitory effect on the glucagon release, can be an alternative option to combat this glycemic disorder. Furthermore, it is highly likely that the dawn phenomenon appears in the early stages in the time course of type 2 diabetes, and therefore it seems eminently reasonable to give due consideration to this disorder. To date, the impact of DPP-4 inhibitors has never been tested in a randomized trial. However, should such a study be undertaken and the results are confirmatory that DPP-4 inhibitors have a blunting effect on the dawn phenomenon, this would support the suggestion that DPP-4 inhibitors be prescribed earlier in the natural history of type 2 diabetes (3,5).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Carr RD, Alexander CM. 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 (Letter). Diabetes Care 2014;37:e161–e162. DOI: 10.2337/dc14-0352
2. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–1705
3. Monnier L, Colette C, Dejager S, Owens D. 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
4. Porcellati F, Lucidi P, Bolli GB, Fanelli CG. Thirty years of research on the dawn phenomenon: lessons to optimize blood glucose control in diabetes. Diabetes Care 2013;36:3860–3862
5. Monnier L, Colette C, Sardinoux M, Baptista G, Regnier-Zerbib A, Owens D. Frequency and severity of the dawn phenomenon in type 2 diabetes: relationship to age. Diabetes Care 2012; 35:2597–2599

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