



COMMENT ON THE FLAT-SUGAR TRIAL INVESTIGATORS

Glucose Variability in a 26-Week Randomized Comparison of Mealtime Treatment With Rapid-Acting Insulin Versus GLP-1 Agonist in Participants With Type 2 Diabetes at High Cardiovascular Risk. *Diabetes Care* 2016;39:973–981

Diabetes Care 2016;39:e186–e187 | DOI: 10.2337/dc16-1133

Louis Monnier,¹ Claude Colette,¹ and David R. Owens²

Achieving near-normal glucose homeostasis infers that all components of dysglycemia that are present in diabetic states should be eradicated. At present, there is incontrovertible evidence that controlling chronic glucose exposure exerts consistent benefit on the incidence of all related diabetes complications (1,2). However, we are sadly lacking similar evidence for implicating glucose variability (GV) as an independent causative factor for vascular complications in those with diabetes. In an attempt to answer this question, the investigators of the FLuctuATion reduction with inSULin and GLP-1 Added together (FLAT-SUGAR) trial (3) have randomly assigned patients with insulin-requiring type 2 diabetes to two basal-prandial therapeutic protocols. The first one was the classic basal-bolus insulin regimen (BBI group) and the second one consisted of a basal insulin (glargine) with exenatide (GLIPULIN group), a short-acting (prandial) glucagon-like peptide-1 receptor agonist, with the addition of metformin in both arms. As expected, the long-term glycemic outcome (HbA_{1c} levels) at 26 weeks was similar with both treatment modalities. In addition, significant reductions in GV, body weight, levels of alanine aminotransferase,

and serum amyloid A were observed in the GLIPULIN group. However, there was a lack of statistically significant improvements in the other cardiovascular risk biomarkers: serum CRP, microalbuminuria, serum interleukin-6, and urinary 8-iso-prostaglandin F_{2α} (8-iso-PGF_{2α}). The authors attributed the lack of differences in the majority of the secondary end points to the fact that the reduction in GV was relatively modest and that the duration of the study was relatively short. However, we would like to draw the attention of the investigators of this study to their data on 8-iso-PGF_{2α}, a marker of the oxidative stress. First, we were surprised to note the extremely high levels of urinary 8-iso-PGF_{2α} normally expressed as pg/mg of creatinine and not as ng/mg (3), which contrasts with previous reports (4). However, the concentrations were computed both at baseline and end point, which revealed a slight increment of 8-iso-PGF_{2α} in the GLIPULIN group in contrast to a more marked but not statistically significant decrement in the BBI group (3). This seemingly unexpected result may be explainable by the fact that oxidative stress is activated by acute glucose fluctuations (4) and inhibited by exogenous insulin (5). Despite both

arms being treated with insulin, we can assume that the plasma insulin profiles were more physiological in those who were treated with the BBI regimen. Superimposition of the glucose profiles for the two treatment groups at 26 weeks would have been valuable for the reader to aid comparison. A possible interpretation of the findings related to the urinary isoprostane differences between the comparative treatment arms might be that reducing GV with therapies such as glucagon-like peptide-1 receptor agonists is insufficient to lower the oxidative stress when the concomitant insulin treatment does not mimic both the basal and prandial periods. In conclusion, the results of the FLAT-SUGAR trial (3) suggest that a reduction in GV combined with more physiological insulin delivery may be necessary in order to normalize the main cardiovascular risk markers and perhaps over a longer period prevent diabetes complications.

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

References

1. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and

¹Laboratory of Human Nutrition and Atherogenesis, University Institute of Clinical Research, University of Montpellier, Montpellier, France

²Diabetes Research Group, Swansea University, Swansea, Wales, U.K.

Corresponding author: Louis Monnier, louis.monnier@inserm.fr.

© 2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–412

2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589

3. The FLAT-SUGAR Trial Investigators. Glucose variability in a 26-week randomized comparison of meal-time treatment with rapid-acting insulin versus GLP-1 agonist in participants with type 2 diabetes at high cardiovascular risk. *Diabetes Care* 2016;39:973–981

4. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations

compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006;295:1681–1687

5. Monnier L, Colette C, Mas E, et al. Regulation of oxidative stress by glycaemic control: evidence for an independent inhibitory effect of insulin therapy. *Diabetologia* 2010;53:562–571