

The Need for Identifying Standardized Indices for Measuring Glucose Variability

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We read the article by Siegelaar and colleagues,¹ which clearly suggests the lack of association between glycemic variability (GV) and oxidative stress estimated by 8-iso-prostaglandin F_{2α} (8-iso-PGF_{2α}) excretion rate in patients with type 2 diabetes mellitus (T2DM) with good metabolic control by oral glucose lowering agents. We have, however, some concerns.

As an index of GV, mean amplitude of glycemic excursions (MAGE), one of the most widely used indexes for measuring GV, was chosen; although a gold-standard procedure is still lacking. In our article,² we observed a positive correlation between 8-iso-PGF_{2α} and GV, measured as continuous overall net glycemic action (CONGA-2), in diabetic patients with short-term disease and optimal metabolic control. However, we were unable to show a significant correlation between MAGE and 8-iso-PGF_{2α}. The observation of a different behavior between CONGA-2 and MAGE, in terms of association with oxidative stress, is possibly due to the metabolic characteristics of our patients. In fact, CONGA-2 is known to detect small glycemic swings, occurring over short-time intervals,³ thus appropriately describing the glycemic fluctuations of patients in optimal metabolic balance, without peaks and valleys. On the other side, MAGE displays several limitations, the most important being the arbitrary definition of significant peaks and nadirs in units of standard deviations. Moreover, the raw glycemic data, obtained by continuous glucose monitoring, are usually asymmetric (hypoglycemic is much narrower than hyperglycemic range). Hence we believe that because MAGE analysis is based on the standard deviation value, as a consequence, we can predict that MAGE will preferentially look at hyperglycemic peaks and will be relatively insensitive to hypoglycemic nadirs.³ Therefore, we suggest applying different indices for the measurement of GV, depending on the aim of the study and the metabolic characteristics of the studied population.

We should also consider the possible confounding effect of insulin secretagogues and of the various drugs used in the population studied by Siegelaar and colleagues¹ on GV and on oxidative stress parameters.⁴

In our study, in order to avoid these important confounding factors, we selected patients treated only by either diet alone or diet plus metformin. On the other side, it should be noted that, in agreement with our data, the population studied by Siegelaar and associates¹ showed an optimal glycemic control, thus excluding the possible interference of glucotoxicity⁵ on the results observed.

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Abbreviations: (8-iso-PGF_{2α}) 8-iso-prostaglandin F_{2α}, (CONGA) continuous overall net glycemic action, (GV) glycemic variability, (MAGE) mean amplitude of glycemic excursions, (T2DM) type 2 diabetes mellitus

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Noteworthy is the utilization of high-performance liquid chromatography tandem mass spectrometry for the quantification of oxidative stress, which is known to represent the reference method for isoprostane measurement.⁶

In conclusion, the impact of GV on oxidative stress activation in T2DM patients is still under debate. We believe that most of the discrepancies between different findings could be largely overcome by standardizing the use of different GV indices according to clinical characteristics and specific aims. This could help in choosing the most appropriate GV index, measuring the different facets of glucose change over time, in different settings.

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