RESPONSE TO COMMENT ON KOVATCHEV AND COBELLI

Glucose Variability: Timing, Risk Analysis, and Relationship to Hypoglycemia in Diabetes. Diabetes Care 2016;39:502–510

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We thank Dr. Service (1) for critically reviewing our Perspective (2) on glucose variability (GV) in diabetes, and, in response, we would like to point out certain distinctions between our view of GV and the definition of the mean amplitude of glucose excursions (MAGE)—a widely used statistical metric of GV that Service introduced in 1970 (3). However, before explaining these distinctions, we must first address Service's specific criticism of our mentioning of MAGE.

1) The formula we presented for the calculation of MAGE is correct and so is our assessment that MAGE is "inherently biased toward hyperglycemia and has a relatively weak association with hypoglycemia" (2). This assessment has been confirmed in many analyses (4) and stems from the definition of MAGE, which is based on a blood glucose scale that is inherently numerically biased toward hyperglycemia (5). Over the past 20 years we had numerous occasions to confirm this fact, which is now not only at the base of the risk analysis of GV (6) but also embedded in the design of closed-loop control (artificial pancreas) algorithms (7).
2) The statement that our article "repeats an error that has been perpetuated in the literature" (1) is made out of the context of our article. We state only that "among the many criticisms of MAGE, it was noted that MAGE was originally developed using 1-h data spacing but was then used with 7-point glucose profiles and with CGM data" (2). Thus, we simply mean that the use of MAGE with 7-point glucose profiles does not correspond to its original development; we do not discuss the original data used to introduce MAGE.

With these points clarified, we shall now move to a philosophical difference in the interpretation of GV that is evidenced by Service's letter—the conflation of glycemic variability with glucose exposure. We indeed disagree fundamentally with the statement "to avoid distortion of variability to that of glycemic exposure, its calculation should be devoid of a time component" (8), and here is why:

1) We view GV from an engineering process-control perspective: in our opinion, GV is a measurable component of the action of a complex dynamical system that evolves in time.
2) In contrast, Service's approach is purely statistical and static, quote, "glycemic variability is a normal biologic function manifested by glycemic excursions during a 24-h period. Any parameter measured over days. . .is subject to variation, but that variability is of exposure" (1).

Although a statistical approach to the assessment of GV may have its use, in our Perspective we specifically focus on risk and time—the manifestations of GV that are important for real-time control of diabetes and are critical for the contemporary concepts of pattern recognition, predictive alarms, and closed-loop control. None of these new methods would work if devoid of time component; thus we must insist that GV is not only a statistical property of an assembly of glucose readings but a manifestation of a process in time that should be appropriately measured.

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