

The Median Is Not the Only Message: A Clinician's Perspective on Mathematical Analysis of Glycemic Variability and Modeling in Diabetes Mellitus

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Abstract

Hemoglobin A1c (HbA1c), a long-term, integrated average of tissue exposure to hyperglycemia, is the best reflection of average glucose concentrations and the best proven predictor of microvascular complications of diabetes mellitus. However, HbA1c fails to capture glycemic variability and the risks associated with extremes of hypoglycemia and hyperglycemia.

These risks are the primary barrier to achieving the level of average glucose control that will minimize both the microvascular and the long-term macrovascular complications of type 1 diabetes. High blood glucose levels largely due to prandial excursions produce oxidative and inflammatory stress with potential acceleration of preexisting atherosclerosis and increased cardiovascular risk. Moreover, some temporal aspects of glycemic variation, including the rates of rise and fall of glucose, are associated with adverse cognitive and mood symptoms in those with diabetes.

Methods to quantify the risk of glycemic extremes, both high and low, and the variability including its temporal aspects are now more precise than ever. These important endpoints should be included for use in clinical trials as useful metrics and recognized by regulatory agencies, which has not been the case in the past. Precise evaluation of glycemic variability and its attendant risks are essential in the design of optimal therapies; for these reasons, inclusion of these metrics and the pulsatile hormone patterns in mathematical models may be essential. For the clinician, the incursion of mathematical models that simulate normal and pathophysiological mechanisms of glycemic control is a reality and should be also gradually incorporated into clinical practice.

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Abbreviations: (ACCORD) Action to Control Cardiovascular Risk in Diabetes, (ADRR) average daily risk range, (BG) blood glucose, (CGM) continuous glucose monitoring, (DCCT) Diabetes Control and Complications Trial, (HbA1c) hemoglobin A1c, (HBGI) high blood glucose index, (LBGI) low blood glucose index, (ROC) rate of change, (SMBG) self-monitored blood glucose, (UKPDS) United Kingdom Prospective Diabetes Study, (VADT) Veterans Affairs Diabetes Trial

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