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Glycemic variability – the danger of a physiologically stable metric

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“Variatio delectat” - variety delights – wrote Cicero (106-43 B.C.) – and old view that perhaps reflects the nonchalance towards glycemic variability (GV) sometimes noted in modern diabetes management. Recent studies with continuous glucose monitoring (CGM) in healthy individuals clearly confirm a remarkable stability of glucose concentrations over days and weeks (1). Physiologically, it is the concentration of insulin that varies rapidly in order to maintain glucose concentrations stable. As the evidence demonstrating the potential harm caused by GV started to emerge only recently, nobody seems to be seriously concerned with this metric.

Some researchers relentlessly generated evidence demonstrating detrimental effects of postprandial hyperglycemia and GV for quite some time (2), and most learned were convinced (3). Recently, the amount of published evidence becomes overwhelming. An analysis reported by J.A. Critchley and colleagues from the Clinical Practice Research Datalink, a large primary care database representative of the United Kingdom population, included almost 59.000 individuals with type 2 diabetes (T2D): in models adjusted for variability, average, and trajectory of glycated hemoglobin A1c (HbA1c), HbA1c variability expressed as coefficient of variation (CV) showed a consistent dose-response relationship with all-cause mortality. Individuals with the most variable (top 10% - CV>16.64%) were almost twice as likely to die than were those with the most constant HbA1c (bottom 10% - CV< 3.14%). This association weakened but was not eliminated by the history of hypoglycemia, with CV remaining more strongly associated with mortality than average HbA1c, essentially confirming results from another large independent T2D registry for older individuals from the United Kingdom. Interestingly, for coronary artery diseases and ischemic stroke, increasing average HbA1c rather than CV was prognostic. Another recent report from S. Li and colleagues on almost 20.000 individuals with newly onset T2D from the

Scottish Care Information–Diabetes Collaboration associates HbA1c variability with increased risks of all outcomes in a fully adjusted proportional hazards model: in the highest HbA1c variability quintile participants have more than double risk of major adverse cardiovascular events, all-cause mortality, atherosclerotic cardiovascular death, coronary artery disease and ischemic stroke, more than triple risk for heart failure, diabetic peripheral neuropathy and chronic kidney disease, more than five-fold risk for diabetic foot ulcer, and more than seven-fold risk for diabetic retinopathy; adjustment for time-weighted average HbA1c and other confounders did not significantly influence these results. In a recent post-hoc analysis from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial C.S. Sheng and colleagues demonstrate a significant association between long-term variability of HbA1c with all-cause mortality in all participants of the trial; interestingly, cross-tabulation analysis showed the highest tertiles of HbA1c mean and variability combined have significantly higher (double) all-cause mortality only in the intensive-therapy group. Putting these results together with numerous similar older reports, long term glucose variability, evaluated either with HbA1c or fasting blood glucose (FBG), clearly is associated with considerable morbidity and mortality in diabetes.

In the present issue of the Journal of Clinical Endocrinology and Metabolism, Dr. Emma S. Scott and colleagues present a post-hoc analysis from almost 10.000 participants of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, investigating whether long-term GV, evaluated by both HbA1c and FPG, is associated with the subsequent development of chronic diabetes complications (4). Associations between the initial two years of GV and subsequent vascular outcomes were analyzed using a two-year landmark logistic and Cox proportional hazards regression analyses with increasing adjustments for pre-specified variables. Individuals with a younger age, male gender and

longer known diabetes duration were more likely to be in a higher quartile of GV. There was an increased risk of complications by increasing quartile of HbA1c and glucose CV for all endpoints. In the fully adjusted model, all GV parameters were independently associated with an increased risk of microvascular complications, albuminuria, major cardiovascular disease, total mortality and non-cardiovascular mortality. In a number-needed-to-treat analysis, for every 21, 43, 100, and 50 persons achieving an HbA1c CV below the median, one composite microvascular, one composite macrovascular, one stroke, and one death would be prevented, respectively (4).

The underlying mechanisms for the observed associations between GV and chronic complications are not clear: increased inflammation, oxidative stress, and epigenetic changes may be implicated (2). There is a difference between short-term and long-term GV: long-term GV is based on visit-to-visit measurements of HbA1c and/or fasting plasma glucose and partially reflects ambient hyperglycemia, correlating with mean blood glucose concentrations or mean HbA1c, while short-term GV expresses the potential risk of episodes of either acute hypoglycemia and/or hyperglycemia (2). Short-term GV is gaining increasing attention as evidence linking both hypoglycemia (2) and hyperglycemia (5) to diabetes complications accumulates with an unprecedented pace. Although it is not clear whether the long-term GV directly relates to the short-term GV assessed with CGM, we clearly have novel technologies helping individuals with diabetes increasing Time in Range (TIR) and reducing short-term GV (6). Dr. Scott and co-authors argue “there are no guidelines for long-term GV”. Indeed, it is not easy to imagine guidelines for long-term GV, however, it does seem likely that when guidance from the consensus for TIR and GV targets (7) are successfully implemented, reducing short-term GV will eventually result in less variable long-term glycemia.

In our opinion, endocrinologist and diabetes teams are facing an important decision: are we willing to and capable of adopting the new evidence-based reality of day-to-day glucose management - increasing TIR, minimizing hypoglycemia or Time Below Range and Time Above Range, thus reducing short-term GV with the clear goal of improving long-term diabetes outcomes (7), or we decide to wait for further evidence and linger with the HbA1c, helplessly observing the recently reported resurgence in diabetes-related complications (8).

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