

Glucose Variability and Complications

In this issue of the *Diabetes Care*, Kilpatrick et al. (1) report their analysis of the large Diabetes Control and Complications Trial (DCCT) database on the relationship between glucose variability and relative risk of developing microangiopathic complications in type 1 diabetes. They find that glucose variability (intraday blood glucose excursions) does not play a role and conclude that only elevation of mean blood glucose over time (as expressed by its integrated measure over the previous ~8 weeks' A1C) associates with proportionally greater risk of developing microangiopathy long term.

This result translates into an important, practical message for subjects with type 1 diabetes and people delivering diabetes care (doctors, nurses, educators, dietitians, etc.). Consider the following example: two young subjects with newly diagnosed type 1 diabetes initiate intensive insulin treatment and are both able to maintain similar A1C <7.0% over the years. However, one subject exhibits minor intraday excursions in blood glucose, whereas the other has large peaks of hyperglycemia, for example after meals, but still maintains A1C <7.0% by compensatory prolonged plateaus of low blood glucose between meals. According to the results of Kilpatrick et al., the latter subject with elevated variability in intraday blood glucose, but A1C <7.0%, has no additional risk of developing microangiopathic complications compared with the former subject with greater stability of blood glucose and similar A1C. This conclusion indicated by the study of Kilpatrick et al. deserves some comments.

First, the conclusion is unexpected. The current, prevalent hypothesis based on in vitro data is that glucose variability might play an important role in the risk for long-term microangiopathic complications of type 1 diabetes (2). According to this view (2), intraday glucose variability would explain the epidemiological observation of the DCCT of greater risk for retinopathy progression in the conventional compared with intensive treatment when subjects are matched for similar A1C (3). Decades ago, several indexes of glucose stability were proposed to quantify this phenomenon in the belief it was implicated in pathogenesis of microangi-

opathy (4,5). The introduction of A1C as a measure of long-term blood glucose control in the early 1980s and the results of the DCCT in 1993 (6) gave great emphasis to the role of A1C as a surrogate marker for subsequent development of microangiopathic complications. The indexes of glucose variability were forgotten. However, extensive discussion has continued about glucose variability as a risk factor for complications independent of A1C in type 1 diabetes (2,3) as well as in type 2 diabetes (7,8). Clearly, it has not been possible to answer the question about variability of blood glucose and risk for microangiopathy before the DCCT study (6) because the end point "development of complications" was needed to validate the predictive value of A1C and of mean blood glucose and of its intraday variability. In this regard, the extraordinary large database for the DCCT is a solid guarantee of the findings of Kilpatrick et al.

Second, how is the conclusion of Kilpatrick et al. going to change our approach to treatment of type 1 diabetes? The study strongly emphasizes the role of A1C as the "sole" marker for future development of microangiopathic complications, and we are increasingly left with the concept that it is the mean blood glucose and the percentage of A1C that predict the future risk of microangiopathic complications in subjects with type 1 diabetes. In this regard, the instant blood glucose at a given time of day is not important, and it does not matter if it is high or low either before or after meals (or vice versa) as long as A1C is at the target value <7.0%. What really matters for development of complications is the overall exposition of endothelium, tissues, and whole body to blood glucose over time, as indicated for example by the percentage of A1C. One might also comment that the study by Kilpatrick et al. is an additional appropriate example that attractive observations in vitro or in small animals (rev. in 2) do not necessarily predict the more complex in vivo situation in human subjects and might give expectations opposite to what occurs in real life of people.

The conclusions by Kilpatrick et al. are good news for subjects with type 1 diabetes because the goals of treatment are going to be simplified. Until today, the large intraday swings in blood glu-

ucose have often caused a feeling of impotence, frustration, and even inability to exert efficient control on regulation of blood glucose in subjects with type 1 diabetes. The idea of difficulty in controlling blood glucose at each time point adequately, i.e., in the fasting state, before and after meals, and at night, has sometimes resulted in loss of faith in treatment and lead to nonadherence to continuing intensive therapy. After the study by Kilpatrick et al., subjects with type 1 diabetes should be more concentrated in keeping A1C at the recommended target rather than worrying because of intraday ups and downs in blood glucose. This is not to say that the everyday fundamental work of selecting the appropriate dose of insulin based on blood glucose monitoring, diet, and physical activity is not important. On the contrary, it is this everyday effort to match the actual needs by the multiple doses of injected or infused insulin that is the key to success for the long-term maintenance of near normoglycemia as indicated by the DCCT (6). What the message of Kilpatrick et al. says is that doctors (and the entire diabetes team including the type 1 diabetic patient) should not be worried if intraday variability in blood glucose remains elevated in some subjects compared with others, as long as A1C is at the target. A corollary to the conclusion of the study is that a change in the model of insulin treatment might be not necessary if the goal of A1C at target is satisfied but glucose variability remains high with current treatment. For example, increasing the number of daily injections of insulin or moving to continuous subcutaneous insulin infusion in place of multiple daily injections might be not necessary if the current treatment results in A1C consistently <7.0% over time. Neither is it recommended to complicate the management of diabetes and life of subjects with the burden of software analysis of blood glucose monitoring to assess the SD of blood glucose values as recently proposed (2).

Should we then disregard the concept of glucose variability completely? The answer is no because in type 1 diabetes, fluctuations of blood glucose result into hyper- and hypoglycemia as well. We need to limit the intraday glucose variabil-

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