EDITORIAL (SEE KILPATRICK ET AL., P. 1486)

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 exibits 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 quantitate this phenomenon in the belief it was implicated in pathogenesis of microangiopathy (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 glucose 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 maintainance 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-

ity to help subjects to minimize the number of blood glucose values <70 mg/dl (4.0 mmol/l), a threshold of plasma glucose concentration that was initially proposed as the definition of hypoglycemia in type 1 diabetes (9), subsequently accepted in type 2 diabetes (10) and later accepted by the American Diabetes Association (11). Hypoglycemia is not only unpleasant for the subject but it is the leading cause of the syndrome of hypoglycemia unawareness, loss of counterregulatory hormonal responses, and is a major risk factor for severe hypoglycemia (12). Physiological insulin replacement is needed to limit the frequency of hypoglycemia in intensive treatment of type 1 diabetes (13), and one justification to switch from multiple daily injections to continuous subcutaneous insulin infusion may be better prevention of hypoglycemia (14). Thus, the glucose variability in the analysis of Kilpatrick et al. is not important for development of long-term microvascular complications but does remain important to prevent hypoglycemia. Glucose variability should be reduced as much as possible to limit hypoglycemia unawareness and severe hypoglycemia. After the article by Kilpatrick et al., two therapeutic goals in treatment of type 1 diabetes remain: *1*) keep A1C <7.0% and *2*) reduce the risk for minor hypoglycemia as much as possible. As said, the latter requires careful blood glucose management, which itself considerably reduces glucose variability. However, if A1C is maintained <7.0% and hypoglycemia is prevented, the remaining fluctuations of blood glucose are unlikely to play a role in long-term complications according to the conclusions of Kilpatrick et al.

Kilpatrick et al. have answered a long-awaited question. Other questions remain open: What about glucose variability and risk of macroangiopathy in type 1 diabetes? Do the results obtained for microangiopathy (1) apply to macrovascular disease as well, which in type 1 diabetes has recently been shown to respond to A1C similarly to microangiopathy (15)? Most importantly, what about type 2 diabetes? Can we extrapolate the concept of Kilpatrick et al. in type 1 to type 2 diabetic subjects and their micro- and macroangiopathic complications? Should we value only A1C in type 2 diabetes and not intraday glucose variability as some studies indicate (10,16), thus neglecting the postprandial hyperglycemia (17) and glycemic excursions (18)? At present, we have no answers. We should use the conclusions of Kilpatrick et al. for what they are good for, i.e., type 1 diabetes and microangiopathy and refrain from extending those conclusions to situations not examined in the study. For example, the conclusion that postprandial hyperglycemia in type 1 diabetes does not play a role as risk factor for long-term complications might be extended to type 2 diabetes regarding microangiopathy, but we cannot exclude a role of postprandial hyperglycemia in macroangiopathy (16). However, in the future, the methodology of Kilpatrick et al. could be applied to the database of the U.K. Prospective Diabetes Study and hopefully generate interesting results.

For the time being, we are left with the reassuring therapeutic message for subjects with type 1 diabetes that the primary goals remain to keep A1C <7.0% over the years to prevent hypoglycemia and not to worry about instant escapes of blood glucose, as long as the two goals are successfully met.

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