Metabolic Memory in the Autonomic Neuropathy of Diabetes
Implications for Pathogenesis and Patient Care

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Metabolic memory, the concept that historical glycemic control is a major determinant of diabetes complications, is of considerable interest not only to those involved in the care of people with diabetes mellitus but also to a wider audience, those wishing to understand the pathogenesis of hyperglycemia-related target organ damage. This phenomenon has been popularized clinically by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC), which has repeatedly demonstrated the long-term impact of metabolic memory on nephropathy, retinopathy, cardiovascular disease, and peripheral neuropathy in type 1 diabetes mellitus. An article in this issue of Circulation from the DCCT/EDIC Research Group demonstrates the same phenomenon for cardiac autonomic neuropathy (CAN). In the DCCT, intensive glycemic control over an average of 6.5 years achieved a marked reduction in hemoglobin A1c, 1.7% lower than that achieved on conventional therapy, and a reduction in CAN incidence of 53%. At the termination of DCCT, all participants were encouraged to adopt intensive glycemic control such that 5 years after DCCT termination, there was no significant difference in hemoglobin A1c between the originally randomized groups. At 13 to 14 years of follow up, CAN incidence subsequent to DCCT termination in those initially randomized to intensive control was reduced by a third compared with those randomized to conventional therapy, even though glycemic control had been identical in these groups for decade before the CAN assessment. Statistical adjustment for historical glycemic control, specifically that achieved during the DCCT itself, abolished the group difference in CAN, supporting the assertion that metabolic memory explained the persistent lower risk of CAN in those originally randomized to intensive glycemic control.

CAN is frequently observed in diabetes mellitus. The majority of previous studies identify diabetes duration and glycemic control as major risk factors for the development and progression of CAN. Observational data have also indicated a key role for historical glycemic status, independent of current control. Thus, this latest DCCT/EDIC demonstration of a continued beneficial influence of previous tight glycemic control on CAN incidence, independent of current control, is not unexpected but nevertheless of clinical and etiological importance.

So what are the implications of these findings for diabetes care and for our understanding of the mechanisms underlying hyperglycemia-related vascular target organ damage in general? It is thought that metabolic memory is due to long-term molecular and cellular changes that are a consequence of hyperglycemia. Key to all these is the oxidative stress that occurs as a consequence of hyperglycemia, initiating a sequence of adverse changes in metabolic pathways, including increased flux through the hexosamine and polyol pathways, activation of protein kinase C-β, and generation of advanced glycation end products, which in turn themselves increase oxidative stress, creating a vicious cycle of insult and damage. A recent review summarizing findings from experimental studies supports this mechanistic concept in the pathogenesis of diabetes complications. Clinically, the DCCT also provides mechanistic evidence for this pathway; the amount of skin advanced glycation end products correlated with the degree of glycemic control and also predicted complications.

Experimental models further suggest that institution of tight control once diabetes mellitus is long established has substantially less of a beneficial impact, both on metabolic pathways and on downstream complications, than early intervention. Is this true clinically? The DCCT consisted of 2 trial populations, a primary prevention cohort with no retinopathy at baseline and mean diabetes duration of 2.6 years and a secondary prevention cohort with minimal retinopathy at baseline and mean diabetes duration of ≈8.7 years. If the experimental data are correct, beneficial effects of metabolic memory should be more pronounced in the primary than in the secondary prevention cohort. Although findings for each of the cohorts are rarely reported separately in the EDIC follow-up, there does not appear to be a clinical difference in impact of metabolic memory by severity or duration of disease at baseline. Specifically, although findings by treatment cohort for objective CAN measures are not presented here, long-term treatment effects on CAN symptoms did not appreciably differ by cohort.

However, intensive control, even according to the rigorous DCCT protocol, does not eliminate complications. Incident CAN occurred in around a quarter of the DCCT/EDIC...
population over more than a decade. The proposed mechanisms underlying the metabolic memory phenomenon provide additional support for exploration of therapeutic agents that favorably alter the downstream effects of hyperglycemia, such as advanced glycation end products cross-link breakers, aldose reductase inhibitors, and protein kinase C-β inhibitors. A disadvantage of the metabolic memory concept is that it risks focusing attention exclusively on interventions associated with glycemic control. Epidemiological studies demonstrate the strong and independent predictive power of other cardiovascular risk factors such as smoking, blood pressure, and hyperlipidemia in the development of autonomic neuropathy, and experimental studies highlight the role of local alterations in blood flow as a consequence of both metabolic and hemodynamic disturbances. These upstream risk factors may either directly or, via the metabolic pathways described above, adversely affect a final common pathway in the genesis of diabetes complications that includes endothelial dysfunction, inflammation, and cytokine and growth factor expression. Agents that favorably alter these upstream and downstream pathways may therefore also be of benefit in reducing the risk of complications. For example, blockers of the renin-angiotensin system are shown to reduce both advanced glycation end products production and oxidative stress and may thus have a beneficial effect on neuropathy in addition to any direct hemodynamic effects.

Compared with the wealth and quality of trials exploring the role of such agents in nephropathy and retinopathy, trials in neuropathy and specifically CAN are lacking. The authors of this article state that “CAN may be the most overlooked complication of diabetes.” Why is this? In part, this is due to challenges inherent in measuring CAN. There is no widely used gold standard for CAN assessment. A diversity of measures, from subjective symptom reporting to a complex array of more objective measures, which include resting heart rate, heart rate variability and baroreflex sensitivity, are used. Each of these measures reflects a slightly different aspect of the autonomic system, so that abnormalities may be observed in some measures and not others, correlations between measures may not be strong, and associations with risk factors and outcomes may be inconsistent, a difficulty that is also present in this report where metabolic memory does not have an equivalent or statistically significant effect on all outcomes measured. In addition, the incomplete understanding of the role of CAN in the pathogenesis of cardiovascular disease, and the mechanisms underlying any association may further contribute to the poor prominence of CAN in diabetes research.

The marked reduction in severe microvascular complications in the last few decades has contributed to the increased survival time of people with type 1 diabetes mellitus. As in type 2 diabetes mellitus, cardiovascular disease (CVD) is now the main cause of morbidity and mortality in type 1 diabetes mellitus, and people with type 1 diabetes mellitus are at markedly increased risk of CVD compared with the general population for reasons which are not entirely clear. Dysfunction of the autonomic system strongly predicts cardiovascular outcomes in people with and without diabetes mellitus. This predictive power is often as strong as, and may even be independent of, other cardiovascular risk factors. Specifically in type 1 diabetes mellitus, a 4-fold increased risk of death was observed in the presence of CAN. Strategies to reduce or postpone CVD are therefore of increasing importance. These new data from the DCCT/EDIC follow-up provide additional support for the need to intensify glycemic control in order to reduce the total burden of diabetes complications. Importantly, Pop-Busui et al demonstrate that tight control for even a few years remains of long-term benefit for CAN, an important clinical message. Some important questions remain. More recent reports from the DCCT/EDIC group suggest that the impact of metabolic memory, observed in the early years of the EDIC follow up, begins to wane after about 10 years. The role of CAN in predicting the risk of CVD, and the mechanisms underlying this risk, are unclear and require further exploration. The DCCT is a large well-designed trial that has been invaluable in providing the definitive evidence base for recommending tight glycemic control to reduce complication risk in people with type 1 diabetes mellitus. Importantly, government-funded support for continued follow-up and the willingness of the majority of participants (>90%) to remain in the study provide a unique opportunity to assess the long-term effects of these few years of intensive control and will help address these further questions. But unlike type 2 diabetes mellitus where the notion of simultaneous multifactorial intervention, as the most appropriate measure to reduce both the early risks of microvascular complications and the later risks of CVD, is established in guidelines, clinical practice, and clinical trials, type 1 diabetes has seen such models only rarely employed, to the extent that the evidence base for multifactorial intervention and the appropriate time point at which to intervene are not known. More recent trials such as the Adolescent Diabetes Intervention Trial, a multifactorial intervention in high-risk adolescents with type 1 diabetes mellitus (http://www.controlled-trials.com/ISRCTN91419926), due to report in 2012 to 2013, may help to address this deficiency, and, like the DCCT, may have a marked impact on clinical guidelines for people with type 1 diabetes mellitus and on mechanistic insights underlying hyperglycemia-related vascular target organ damage.

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References


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