COMMENT ON MILLER AND ORCHARD

Understanding Metabolic Memory: A Tale of Two Studies. Diabetes 2020;69:291–299

John M. Lachin,[1] David M. Nathan,[2] Bernard Zinman,[3] and Ionut Bebu[1]

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In "Understanding Metabolic Memory: A Tale of Two Studies," Miller and Orchard (1) purportedly disprove "metabolic memory." However, their analyses do not directly address metabolic memory and their interpretations are flawed.

The Diabetes Control and Complications Trial (DCCT) (2) demonstrated that randomly assigned intensive therapy, with mean HbA_{1c} of ~7%, dramatically reduced microvascular complications compared with conventional therapy, with mean HbA_{1c} of ~9%, an effect entirely attributable to the separation in HbA_{1c} levels between the two groups (3). Afterward, all participants were taught intensive therapy and referred to their physicians for care, resulting in similar HbA_{1c} levels of ~8% in the two original groups. This would have been predicted to narrow the rate of complications between the original groups. However, with further follow-up, the original DCCT conventional group experienced substantially higher risks of *further* progression of retinopathy, nephropathy, and neuropathy for 4–8 years (4,5). We coined "metabolic memory" to describe the impact of early glycemic separation on complications even after the glycemic differences had disappeared. Metabolic memory appears to last up to 12–15 years, after which waning or "metabolic amnesia" occurs.

Miller and Orchard present analyses based on "A1c months," the sum of the incremental HbA_{1c} above normal (6.1%) at a visit multiplied by the number of months elapsed from the last HbA_{1c}. Algebraically, the mean HbA_{1c} is proportional to the A1c months and the two are highly correlated. However, Miller and Orchard do not present analyses of the observational Pittsburgh Epidemiology of Diabetes Complications study to explore metabolic memory. Nor do they reanalyze DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) data to show that the difference in A1c months between groups during the DCCT explains metabolic memory during EDIC.

Nevertheless, Miller and Orchard state: "There is no need to invoke a 'metabolic memory' phenomenon to explain the persistence of a lower incidence of complications in the DCCT intensive therapy group compared with conventional therapy group, which can be fully explained by cumulative glycemic exposure." However, they fail to recognize that cumulative glycemic exposure includes long-term effects, such as metabolic memory.

Miller and Orchard then conclude that the order of glycemic exposure doesn't matter: "…on average, the development of complications increases with greater glycemic exposure, irrespective of whether this results from a high exposure for a short time or a lower exposure for a longer time."

The association of A1c months, a measure of glycemic exposure, with complications is expected based on the strong association of complications with mean HbA_{1c} in DCCT/EDIC (3). However, the fundamental issue is whether the pattern of glucose exposure makes a difference. Miller and Orchard suggest that 20 years' duration at an HbA_{1c} of 8% [(8% – 6.1%) × 240 months = 456 A1c months] yields the same risk of outcomes as 10 years at 9.0% followed by 10 years at 7% (also 456 A1c months), or vice versa. DCCT/EDIC results (4,5) clearly demonstrate that this is not the case. No analysis shows that A1c months explains the metabolic memory phenomenon.

Metabolic memory supports a particularly pernicious effect of elevated levels of HbA_{1c} early in the course of type 1 diabetes. We continue to recommend that intensive therapy be initiated as early as possible in the

[1]The Biostatistics Center, The George Washington University, Rockville, MD
[2]Massachusetts General Hospital and Harvard Medical School, Boston, MA
[3]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada

Corresponding author: John M. Lachin, jml@bsc.gwu.edu

course of type 1 diabetes to minimize the risk of long-term complications.

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References

1. Miller RG, Orchard TJ. Understanding metabolic memory: a tale of two studies. Diabetes 2020;69:291–299

2. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986

3. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN; DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial–revisited. Diabetes 2008;57:995–1001

4. The DCCT Research Group. The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. Diabetes 1995;44:968–983

5. Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–389