Association of Estimated Time-in-Range Capillary Glucose Levels Versus HbA_{1c} With Progression of Microvascular Complications in the Diabetes Control and Complications Trial

*John M. Lachin,[1] Ionut Bebu,[1] Xiaoyu Gao,[1] David M. Nathan,[2] Bernard Zinman,[3] and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group**

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OBJECTIVE

Estimated time in range (eTIR) obtained from DCCT glucose profiles (pre- and postprandial and bedtime) was recently reported to be associated with microvascular outcomes and was recommended as a clinical trial outcome, but without consideration of HbA_{1c}.

RESEARCH DESIGN AND METHODS

The associations of eTIR with diabetic retinopathy and microalbuminuria were assessed without and with adjustment for HbA_{1c} and baseline covariates.

RESULTS

Adjusted for HbA_{1c} and covariates, eTIR was marginally significantly associated with retinopathy in the full cohort (hazard ratio [HR] 1.12 per 10% lower eTIR [95% CI 1.0, 1.26], $P = 0.042$). Conversely, HbA_{1c} was significantly associated with both outcomes (HR ≥1.19 per 0.5% higher HbA_{1c}, $P \leq 0.0002$) in five of six adjusted analyses.

CONCLUSIONS

The association of eTIR with complications is largely explained by its correlation with HbA_{1c}. HbA_{1c}, not eTIR or continuous glucose monitoring TIR, remains the preferred outcome in clinical studies of type 1 diabetes complications.

The time-in-range (TIR) glucose from continuous glucose monitoring (CGM), generally defined as the percentage of time in the ∼70–180 mg/dL range, is commonly used to guide diabetes care (1,2). Beck et al. (3) recently used seven-point fingerstick blood glucose profiles (before and after meals and at bedtime) obtained in the Diabetes Control and Complications Trial (DCCT), as measured by the DCCT central biochemistry laboratory (4), to calculate an estimated TIR (eTIR). These eTIR values were associated with DCCT complications, and Beck et al. concluded that TIR measured from CGM could be "an acceptable end point for clinical trials."

While eTIR is an imperfect measure of mean glucose, it is still correlated with HbA_{1c}, which, in turn, is strongly associated with microvascular outcomes (5,6). Therefore, some, if not all, of the association of eTIR with outcomes may just reflect the role of mean HbA_{1c} rather than that of eTIR per se. To determine whether

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

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

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the eTIR has an independent association with outcomes beyond that of HbA_{1c} and could substitute for, or provide added value to, HbA_{1c} in future clinical investigations, we have replicated the analyses of Beck et al. (3) by including both eTIR and HbA_{1c} together.

RESEARCH DESIGN AND METHODS

The DCCT showed that HbA_{1c} was a major determinant of the risk of progression of complications (7). The 1,441 participants were randomly assigned to intensive or conventional diabetes therapy and followed for an average of 6.5 years. Of these, the primary prevention cohort ($n = 726$) had no preexisting microvascular complications and 1–5 years duration of type 1 diabetes (T1D), and the secondary intervention cohort ($n = 715$) had mild preexisting complications and 1–15 years duration of T1D.

Average follow-up was 6.5 years with 6 monthly assessments of diabetic retinopathy on fundus photographs. The primary outcome was sustained progression of retinopathy at two successive visits. The albumin excretion rate was measured annually, with a secondary outcome being the onset of microalbuminuria (albumin excretion rate $\geq$30 mg/24 h) also sustained.

HbA_{1c} and the blood glucose profiles were measured quarterly by the central laboratory. Complete glucose profiles were obtained in 67% of the ~37,000 expected quarterly collections. As previously described (8), multiple imputation (9) generated 10 complete data sets using the multiple imputation by chained equations algorithm (10), and the Rubin-Schenker average was obtained (11). The same data and programs were used by Beck et al. (3) and herein. The quarterly eTIR was the percentage of the seven glucose values in the 70–180 mg/dL range. The mean eTIR and mean HbA_{1c} up to each visit (every 3 months) were then used as time-dependent factors in discrete-time Cox proportional hazards models of the outcome event (visit) times with and without adjustment for other covariates. Simple *P* values without correction for multiple tests are presented.

RESULTS

Table 1 presents the hazard ratio (HR) for each outcome per 10% lower eTIR with no adjustment for other covariates as in the Beck et al. (3) analyses, then

Table 1—Development of retinopathy or microalbuminuria outcomes as a function of eTIR and/or HbA_{1c}

	Per 10% lower eTIR*			Per 0.5% higher HbA_{1c}+		
Cohort and statistics	Unadjusted	Adjusted for HbA_{1c} alone	Adjusted for HbA_{1c} and other covariates#	Unadjusted	Adjusted for eTIR alone	Adjusted for eTIR and other covariates#
Retinopathy: three or more steps sustained progression						
All, $n = 271$ cases of 1,441						
HR (95% CI)	1.58 (1.46, 1.71)	1.11 (1, 1.24)	1.12 (1.00, 1.26)	1.32 (1.27, 1.37)	1.27 (1.21, 1.34)	1.31 (1.24, 1.39)
χ^2 (*P*)	139.8 (<0.001)	3.7 (0.059)	4.3 (0.042)	229.2 (<0.001)	77.4 (<0.001)	89.3 (<0.001)
Primary, $n = 107$ cases of 726						
HR (95% CI)	1.71 (1.5, 1.94)	1.12 (0.94, 1.33)	1.10 (0.92, 1.31)	1.38 (1.30, 1.46)	1.33 (1.22, 1.45)	1.36 (1.25, 1.49)
χ^2 (*P*)	68.8 (<0.001)	1.7 (0.206)	1.2 (0.283)	112.5 (<0.001)	43.2 (<0.001)	49.9 (<0.001)
Secondary, $n = 164$ cases of 715						
HR (95% CI)	1.53 (1.39, 1.69)	1.12 (0.97, 1.29)	1.14 (0.99, 1.32)	1.30 (1.24, 1.37)	1.25 (1.16, 1.34)	1.27 (1.18, 1.37)
χ^2 (*P*)	74.2 (<0.001)	2.6 (0.113)	3.4 (0.072)	119.8 (<0.001)	37.6 (<0.001)	41.7 (<0.001)
Nephropathy: sustained microalbuminuria						
All, $n = 116$ cases of 1,441						
HR (95% CI)	1.37 (1.23, 1.53)	1.11 (0.95, 1.30)	1.11 (0.95, 1.30)	1.22 (1.15, 1.28)	1.17 (1.07, 1.27)	1.19 (1.09, 1.29)
χ^2 (*P*)	33.7 (<0.001)	1.7 (0.202)	1.8 (0.191)	49.3 (<0.001)	13.5 (0.003)	15.7 (<0.001)
Primary, $n = 36$ cases of 726						
HR (95% CI)	1.61 (1.31, 1.97)	1.40 (1.04, 1.89)	1.39 (1.03, 1.88)	1.25 (1.13, 1.37)	1.10 (0.95, 1.28)	1.11 (0.95, 1.28)
χ^2 (*P*)	21.3 (<0.001)	5.0 (0.027)	4.7 (0.032)	21.3 (<0.001)	1.6 (0.217)	1.7 (0.193)
Secondary, $n = 80$ cases of 715						
HR (95% CI)	1.31 (1.15, 1.50)	0.99 (0.81, 1.20)	1.01 (0.83, 1.22)	1.24 (1.15, 1.33)	1.24 (1.12, 1.38)	1.22 (1.10, 1.36)
χ^2 (*P*)	16.4 (<0.001)	0.1 (0.901)	0.1 (0.926)	34.7 (<0.001)	16.6 (<0.001)	14.2 (<0.001)

Coefficient β-estimate, SE of the estimate, 95% with limits β_L and β_U, and *P* value for each factor (eTIR or HbA_{1c}) from a Cox proportional hazards model for sustained progression of retinopathy (three or more steps of progression on the Early Treatment of Diabetic Retinopathy Study [ETDRS] scale) and for sustained onset of nephropathy (microalbuminuria). For each factor (eTIR or HbA_{1c}), the corresponding HR and its 95% confidence limits per the designated change in the factor (C), where C = 10 for eTIR and 0.5 for HbA_{1c}, were obtained as exp(Cβ), exp(Cβ_L), and exp(Cβ_U), with β_L and β_U being the 95% confidence limits on the coefficient estimate. For each factor, models were fit with no adjustment for other covariates, adjusted for the other factor alone, and adjusted for the other factor plus other covariates. The β-coefficient for a factor is obtained as ln(HR)/ln(C). *P* values are not corrected for multiple tests. *HR computed per 10% lower eTIR from discrete-time Cox proportional hazards regression models as in Beck et al. (3). +HR per 0.5% higher HbA_{1c} as in Beck et al. (3). #Cox proportional hazards regression models stratified by the ETDRS level of retinopathy at baseline (no retinopathy, 10, 20, or 30 in worse eye) and adjusted for the preexisting duration of diabetes, retinopathy cohort, and duration by cohort interaction, as performed previously (3).

with adjustment for HbA_{1c} alone and adjustment for both HbA_{1c} and other covariates (3). Table 1 also presents the HR per 0.5% higher HbA_{1c} when adjusted for eTIR and other covariates. Analyses are presented for the full DCCT cohort and separately for the primary and secondary cohorts.

In unadjusted analyses, as in Beck et al. (3), eTIR was significantly associated with the six outcomes. However, when adjusted for HbA_{1c} alone, these associations were substantially diminished (HR closer to 1.00), and only the association of eTIR with nephropathy in the primary cohort reached significance (HR 1.40 per 10% lower eTIR, $P = 0.027$). When adjusted for HbA_{1c} and other covariates, this eTIR association remained unchanged (HR 1.39, $P = 0.032$), and the association with retinopathy in the full cohort was barely significant (HR 1.12, $P = 0.042$).

Conversely, HbA_{1c} had a statistically significant association with all outcomes when unadjusted, when adjusted for eTIR, and when adjusted for eTIR and other covariates (each $P < 0.003$), except for microalbuminuria in the primary cohort where $P = 0.193$. However, only 36 primary cohort subjects developed microalbuminuria, inadequate for a definitive conclusion.

CONCLUSIONS

In the analyses by Beck et al. (3), a higher eTIR was significantly associated with a decreased risk of progression of retinopathy and nephropathy in the DCCT cohort. However, in the analyses herein, those associations are largely eliminated with adjustment for HbA_{1c}, whereas the association of HbA_{1c} with outcomes remains largely significant when adjusted for eTIR. Therefore, these results do not provide direct evidence that higher TIR computed from CGM, or the DCCT eTIR, contributes to the risk of progression of complications beyond that conferred by, or independent from, HbA_{1c} levels.

The analyses herein address these issues by fitting models with eTIR and HbA_{1c} separately and together. Adjusted for HbA_{1c} alone, eTIR was not significantly associated with the outcome in five of the six analyses. When also adjusted for other covariates, eTIR was no longer nominally significant in four of the six analyses. After correcting for six multiple tests (data not shown), all eTIR P values became nonsignificant. Likewise, HbA_{1c} had a significant association in five of the six analyses when adjusted for eTIR (all $P < 0.001$). These associations also remained significant ($P < 0.006$) when corrected for multiple tests. Thus, eTIR fails to replace or negate the association of HbA_{1c} with outcomes and does not augment the association of HbA_{1c} with outcomes.

The analyses by Beck et al. (3) showed that eTIR by itself was associated with outcomes, whereas the current analyses show that those associations are largely negated when adjusted for HbA_{1c}. Conversely, the HbA_{1c} associations are not affected by adjustment for eTIR. Thus, if a treatment were to increase the eTIR, it is possible that it might show a beneficial association with outcomes. However, that benefit will depend to a greater extent on the treatment's effects on HbA_{1c}, not eTIR. The potential benefit of a treatment's effect on CGM-measured TIR is not known.

Clearly, the DCCT eTIR is an imperfect representation of TIR as would be provided by CGM. Furthermore, a substantial fraction of the profile data was missing and replaced using multiple imputation. While previous analyses validated this approach (3,8), the missing data are a weakness. Nevertheless, the quarterly DCCT seven-point profiles provide the best-available opportunity to assess the association of eTIR with progression of retinopathy and nephropathy during the DCCT, since it is unlikely that a DCCT-like study using CGM will ever be performed. Thus, the eTIR serves as a surrogate for a bona fide measure of TIR obtained from CGM.

In conclusion, our analyses with eTIR do not support the conclusion by Beck et al. (3) that "a compelling case can be made that TIR is strongly associated with the risk of microvascular complications and should be an acceptable end point for clinical trials."

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