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Area-under-the-A1c-Curve above the Normal Range and the Prediction of Microvascular Outcomes: An analysis of data from the Diabetes Control and Complications Trial

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Abstract

Aims—In the Diabetes Control and Complications Trial (DCCT), mean updated A1c accounted for most of the differential risk of microvascular complications between intensive and conventional insulin therapy. We hypothesized, however, that a more precise measure of chronic hyperglycemic exposure may be the incremental area-under-the-A1c-curve above the DCCT-standardized normal range for A1c (iAUC_{A1c>norm}).

Methods—Using the Principal DCCT Dataset, we compared the following 3 measures of chronic glycemic exposure for their capacity to predict retinopathy, nephropathy, and neuropathy during the DCCT: mean updated A1c, iAUC_{A1c>norm}, and total area-under-the-A1c-curve (tAUC_{A1c}). For each outcome, models using each of these 3 glycemic measures were compared in the following 3 ways: hazard or odds ratio, chi-square statistic, and Akaike information criterion.

Results—The 3 glycemic measures did not differ in their prediction of neuropathy. iAUC_{A1c>norm} was modestly superior to mean updated A1c for predicting nephropathy (chi-square p=0.017, Akaike p=0.032). In contrast, for predicting retinopathy, both iAUC_{A1c>norm} (chi-square p=0.0005, Akaike p=0.0005) and tAUC_{A1c} (chi-square p=0.004, Akaike p=0.0004) were significantly better than mean updated A1c. Varying its A1c threshold incrementally between 37 and 53 mmol/mol (5.5% - 7.0%) inclusive did not improve the prediction of retinopathy by iAUC_{A1c>threshold} beyond that of tAUC_{A1c}, consistent with the concept of a continuous relationship between glycemia and retinopathy with no glycemic threshold.

Conclusions—Both iAUC_{A1c>norm} and tAUC_{A1c} were superior to mean updated A1c for predicting retinopathy. Optimal assessment of chronic glycemic exposure as a determinant of retinopathic risk may require consideration of both the degree of hyperglycemia and its duration.

Keywords

A1c; glycated hemoglobin; glycemic exposure; retinopathy; DCCT; Diabetes Control and Complications Trial

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Introduction

The Diabetes Control and Complications Trial (DCCT) study group reported that intensive insulin therapy can reduce the development and progression of retinopathy, nephropathy and neuropathy in type 1 diabetes (T1DM), with glycemic exposure (as determined by mean updated A1c) explaining virtually all of the difference in risk of these complications between the intensive and conventional therapy groups [1-3]. These data highlight the central importance of chronic exposure to hyperglycemia as a determinant of microvascular complications in patients with T1DM. Though assessed by the mean updated A1c in the DCCT, we hypothesized that a more precise measure of chronic hyperglycemic exposure would be the incremental area-under-the-A1c-curve above the DCCT-standardized normal range for A1c ($iAUC_{A1c>norm}$). Indeed, this measure provides a way of integrating both the degree of glycemia and the time spent above the normoglycemic range, and hence could capture the cumulative exposure to hyperglycemia. As such, by reflecting the presumed key biologic risk determinant relevant to the development of microvascular complications, it may be a stronger predictor of these outcomes than mean updated A1c. Thus, we sought to evaluate the predictive capacity of $iAUC_{A1c>norm}$ as a determinant of microvascular complications in the DCCT, as compared to mean updated A1c.

Methods

The DCCT has been previously described in detail [4,5]. In brief, 1441 participants with T1DM were randomized to intensive or conventional insulin therapy and followed for mean 6.5 years, with quarterly measurement of A1c and regular assessment for microvascular complications. Using the publicly-available Principal DCCT dataset (National Technical Information Service, Alexandria, VA), we evaluated the following 3 measures of chronic glycemic exposure: mean updated A1c, mean $iAUC_{A1c>norm}$, and mean total area-under-the-A1c-curve ($tAUC_{A1c}$).

These measures were assessed because, while mean updated A1c will reflect the actual mean value for A1c over follow-up, it does not account for duration of time spent above a particular glycemic threshold (such as the upper-limit-of-normal for the DCCT-standardized A1c assay (IFCC 42 mmol/mol or DCCT 6.0%)). In contrast, $iAUC_{A1c>norm}$ provides a measure of glycemic exposure that incorporates not only the degree of glycemia but also the time spent above the normal range. To illustrate this difference, consider the hypothetical example of 2 patients with the following quarterly A1c measurements: Patient A has measurements of 42 mmol/mol (6.0%), 42 mmol/mol, 42 mmol/mol, and 42 mmol/mol, while Patient B has measurements of 42 mmol/mol, 46 mmol/mol (6.4%), 38 mmol/mol (5.6%) and 42 mmol/mol. Mean updated A1c will be the same for both patients, but only $iAUC_{A1c>norm}$ will capture the fact that Patient B spent time with A1c over the normal range. Finally, we also assessed $tAUC_{A1c}$ since it is similar to $iAUC_{A1c>norm}$ but does not assume that the upper-limit-of-normal for the DCCT-standardized assay (IFCC 42 mmol/mol or DCCT 6.0%) is an absolute threshold below which glycemic exposure does not contribute to microvascular risk.

Mean updated A1c was calculated as the mean of all quarterly A1c measures up to the visit under study, **computed at 6-monthly intervals** (3). Mean AUC_{A1c} was calculated by trapezoidal rule as a mean of the number of visits under study. For example, AUC_{A1c} at year 3 (12 visits) was calculated as:

$0.5*[H_0+(2*H_1)+(2*H_2)+(2*H_3)+(2*H_4)+(2*H_5)+(2*H_6)+(2*H_7)+(2*H_8)+(2*H_9)+(2*H_{10})+(2*H_{11})+H_{12}]/12$, where H_0 is baseline A1c, H_1 is first-quarterly visit A1c, H_2 is second-quarterly visit A1c, etc. Calculations for each 6-monthly or annual interval included all preceding quarterly A1c measurements since the start of the DCCT.

For each measure of glycemic exposure, we determined its predictive capacity for incidence of the following DCCT-defined [3] microvascular outcomes: persistent 3-step change in retinopathy, microalbuminuria, and neuropathy. Retinopathy and nephropathy were analyzed by time-dependent proportional hazards models and neuropathy by logistic regression model. For each outcome, models using each of the 3 A1c measures were compared in 3 ways: hazard or odds ratio, chi-square statistic, and Akaike information criterion (Table 1). For both the chi-square and Akaike information criterion statistics, pairwise comparisons were conducted using bootstrap methods (2,000 bootstrap samples were drawn from the original data set with replacement). The pairwise differences of the estimated chi-square and Akaike information criterion statistics were obtained for each bootstrap sample. The bootstrap method made it possible to estimate the sampling distribution of the pairwise difference of the chi-square or Akaike information criterion statistic. Based on this nonparametric method and the observed pairwise differences, we calculated bootstrap p-values to control type I error and determine the significance of pairwise differences. The bootstrap p-values were estimated by the proportion of those bootstrapped chi-square or Akaike values at greater than or equal to the observed pairwise difference from the original data.

Models for the prediction of retinopathy were repeated at different A1c thresholds between 37–53 mmol/mol (5.5–7.0%) for comparison of $iAUC_{A1c>threshold}$ versus $tAUC_{A1c}$ (Table 2). The purpose of this analysis was to see if there was a particular A1c threshold where $iAUC_{A1c>threshold}$ was superior to $tAUC_{A1c}$ for predicting retinopathy by both Chi-square and Akaike information criterion. All statistical analyses were performed using Stata10.0 (College Station, TX) and SAS9.2 (Cary, NC).

Results

All 3 A1c measures (mean updated A1c, $tAUC_{A1c}$, $iAUC_{A1c>norm}$) were significantly associated with each microvascular outcome (Table 1). However, their comparative predictive capacities differed for each complication. While the 3 measures did not differ in their prediction of neuropathy, $iAUC_{A1c>norm}$ (but not $tAUC_{A1c}$) was superior to mean updated A1c for prediction of nephropathy (chi-square **bootstrap** $p=0.017$, Akaike **bootstrap** $p=0.032$). In contrast, both $iAUC_{A1c>norm}$ (chi-square **bootstrap** $p=0.0005$, Akaike **bootstrap** $p=0.0005$) and $tAUC_{A1c}$ (chi-square **bootstrap** $p=0.004$, Akaike **bootstrap** $p=0.0004$) were superior to mean updated A1c for the prediction of retinopathy, with no significant difference between $iAUC_{A1c>norm}$ and $tAUC_{A1c}$. Varying its A1c threshold above or below 42 mmol/mol (6.0%) from 37–53 mmol/mol (5.5–7.0%) did not improve the prediction of retinopathy by $iAUC_{A1c>threshold}$ beyond that of $tAUC_{A1c}$ (Table 2). Specifically, the chi-square statistic did not reveal a significant difference between these two measures at any threshold, although the Akaike information criterion statistic found $tAUC_{A1c}$ to be superior to $iAUC_{A1c>threshold}$ at A1c thresholds >48 mmol/mol (6.5%). Lastly, after adjustment for covariates (baseline A1c, age, gender, BMI, duration of diabetes, treatment group, and baseline value of the outcome variable), both $iAUC_{A1c>norm}$ and $tAUC_{A1c}$ remained superior to mean updated A1c for the prediction of retinopathy but not nephropathy or neuropathy (Online Table).

Discussion

In this analysis, all 3 A1c indices yielded comparable hazard or odds ratios for the prediction of each microvascular outcome and the overall benefits of the AUC_{A1c} measures over mean updated A1c were modest. Furthermore, it is recognized that neither the AUC_{A1c} indices nor mean updated A1c are practical measures for calculation in clinical practice. Instead, however, these indices are more relevant as research tools in clinical studies. Indeed, as

shown in this analysis, AUC_{A1c} measures can provide insight on the impact of glycemic exposure on risk of microvascular complications, and potentially the biology underlying these relationships. In this context, three key findings emerge from the current data.

First, the demonstration that both $iAUC_{A1c>norm}$ and $tAUC_{A1c}$ were superior to mean updated $A1c$ for the prediction of retinopathy supports the concept that optimal assessment of chronic glycemic exposure as a determinant of microvascular risk may require consideration of both the degree of hyperglycemia and its duration. Interestingly, Orchard and colleagues previously explored this general concept with their construct of A_1 months, defined as the product of $A1c$ above the normal range and months exposure as determined from biennial assessment in the Pittsburgh Epidemiology of Diabetes Complications study [6]. While they found that this measure was not a better predictor of microvascular complications than its components (duration and mean $A1c$), it should be noted that its calculation from biennial $A1c$ assessments would have rendered A_1 months a less precise measure of chronic glycemic exposure than the AUC_{A1c} indices obtained from the more frequent $A1c$ measurements in the DCCT. Thus, the AUC_{A1c} measures in the current study may have been better able to demonstrate the predictive capacity of a cumulative glycemic exposure variable that incorporates both duration and degree of glycemia.

Secondly, it is noted that $iAUC_{A1c>norm}$ and $tAUC_{A1c}$ were both consistently superior to mean updated $A1c$ for the prediction of retinopathy, but not nephropathy and neuropathy. This difference may relate to methodologic features (eg. neuropathy was assessed only at 5 years while retinopathy was assessed every 6 months) or limitations in the measurement of nephropathy and neuropathy outcomes, but also may reflect a comparatively greater influence of glycemic exposure on risk of retinopathy, as compared to the other outcomes. Thirdly, we did not detect an $A1c$ level above which $iAUC_{A1c}$ surpasses $tAUC_{A1c}$ for predicting retinopathy, consistent with the concept of a continuous relationship between glycemia and retinopathy, with no glycemic threshold [3].

Finally, it should be noted that, although non-glycemic factors may also be relevant [7], the unmeasured effect of glycemic exposure in the years prior to the DCCT may have limited the achievable predictive capacity of all three $A1c$ -based measures obtained during the trial. Thus, $iAUC_{A1c>norm}$ and $tAUC_{A1c}$ from the time of diagnosis ultimately warrant study for the evaluation of total cumulative glycemic exposure as a determinant of microvascular risk in T1DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. DCCT 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. [PubMed: 8366922]

2. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial--revisited. *Diabetes*. 2008; 57:995–1001. [PubMed: 18223010]
3. DCCT Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes*. 1995; 44:968–983. [PubMed: 7622004]
4. DCCT Research Group. The Diabetes Control and Complications Trial (DCCT): Design and methodologic considerations for the feasibility phase. *Diabetes*. 1986; 35:530–545. [PubMed: 2869996]
5. DCCT Research Group. Diabetes Control and Complications Trial (DCCT). Update. *Diabetes Care*. 1990; 13:427–433. [PubMed: 2180661]
6. Orchard TJ, Forrest KY, Ellis D, Becker DJ. Cumulative glycemic exposure and microvascular complications in insulin-dependent diabetes mellitus. The glycemic threshold revisited *Arch Intern Med*. 1997; 157:1851–1856.
7. Hirsch IB, Brownlee M. Beyond hemoglobin A1c--need for additional markers of risk for diabetic microvascular complications. *JAMA*. 2010; 303:2291–2292. [PubMed: 20530784]

List of Abbreviations

AER	albumin excretion rate
DCCT	Diabetes Control and Complications Trial
iAUC_{A1c}	incremental area-under-the-A1c-curve
iAUC_{A1c>norm}	incremental area-under-the-A1c-curve above the normal range for the DCCT-standardized A1c assay
tAUC_{A1c}	total area-under-the-A1c-curve

Table 1
Comparative performance of each measure of glycemic exposure for the prediction of microvascular outcomes.

	Mean Updated A1c	tAUC _{A1c}	iAUC _{A1c>norm}	p values for pairwise comparisons ^d		
				Mean Updated A1c versus tAUC _{A1c}	Mean Updated A1c versus iAUC _{A1c>norm}	tAUC _{A1c} versus iAUC _{A1c>norm}
Retinopathy^a (n=1440)						
HR (95% CI)	1.64 (1.52, 1.77)	1.69 (1.57, 1.83)	1.68 (1.56, 1.82)	n/a	n/a	n/a
Chi-square ^b	161.65	174.54	171.71	0.004	0.0005	0.170
Akaike Information Criterion ^c	2847.83	2837.39	2839.22	0.004	0.0005	0.264
Nephropathy^a (n=1365)						
HR (95% CI)	1.31 (1.22, 1.41)	1.33 (1.23, 1.43)	1.33 (1.23, 1.44)	n/a	n/a	n/a
Chi-square ^b	50.18	52.18	53.21	0.068	0.017	0.039
Akaike Information Criterion ^c	3517.83	3516.15	3515.45	0.076	0.032	0.077
Neuropathy^a (n=1161)						
OR (95% CI)	1.53 (1.34, 1.74)	1.53 (1.35, 1.75)	1.54 (1.35, 1.75)	n/a	n/a	n/a
Chi-square ^b	41.91	42.05	42.17	0.368	0.328	0.256
Akaike Information Criterion ^c	662.35	662.26	662.31	0.412	0.474	0.424

Abbreviations: HR, Hazard Ratio; OR, Odds Ratio; CI, confidence interval; n/a, not applicable

^aRetinopathy was defined as persistent 3-step change from baseline, graded according to the Early Treatment Diabetic Retinopathy Study scale. Nephropathy was defined as urine albumin excretion rate (AER) 40mg/24hr. Neuropathy was defined on clinical examination at 5 years with concurrent/prior abnormalities in nerve conduction or autonomic nervous system testing. Retinopathy and neuropathy were analyzed by time-dependent proportional hazards models since they were assessed regularly during the DCCT. Neuropathy was analyzed by logistic regression model because it was assessed only at 5 years. Patients with urine AER >40mg/24h at baseline were excluded from nephropathy models and those with neuropathy at baseline were excluded from neuropathy models.

^bA larger chi-square statistic indicates stronger evidence of an increasing trend over time in the effect of a measure of glycemic exposure on the hazard or risk of an outcome.

^cThe Akaike information criterion offers a measure of the information lost when a statistical model is used to describe reality. Thus, in this study, given a set of models using three measures of glycemic exposure for each outcome, the preferred model is the one with the minimum Akaike information criterion value, as least information is lost.

^dThe pairwise comparisons were conducted using bootstrap methods (2,000 bootstrap samples were drawn from the original data set with replacement). The pairwise differences of the estimated chi-square and Akaike information criterion statistics were obtained for each bootstrap sample. The bootstrap p-values were estimated by the proportion of those bootstrapped chi-square or Akaike values at greater than or equal to the observed pairwise difference from the original data.

Table 2

Comparison of $iAUC_{A1c>threshold}$ and $tAUC_{A1c}$ for the prediction of the risk of retinopathy, for sequential incremental $A1c$ thresholds (T) from 37 to 53 mmol/mol (5.5 to 7.0%) inclusive.

IFCC(mmol/mol)	A1c Threshold (T)		HR	Chi-square test		Akaike Information Criterion	
	DCCT(%)			Value	<i>p</i> value for $iAUC_{A1c>T}$ vs $tAUC_{A1c}$	Value	<i>p</i> value for $iAUC_{A1c>T}$ vs $tAUC_{A1c}$
37	5.5	1.682	171.50	0.166		2838.74	0.316
38	5.6	1.682	171.55	0.169		2838.77	0.313
39	5.7	1.682	171.58	0.171		2838.85	0.293
40	5.8	1.683	171.64	0.175		2838.93	0.294
41	5.9	1.683	171.62	0.163		2839.05	0.278
43	6.1	1.684	171.81	0.180		2839.44	0.240
44	6.2	1.686	171.90	0.190		2839.74	0.205
45	6.3	1.687	171.95	0.200		2840.15	0.158
46	6.4	1.689	171.98	0.204		2840.70	0.109
48	6.5	1.690	171.94	0.202		2841.36	0.078
49	6.6	1.693	171.96	0.211		2842.08	0.047
50	6.7	1.696	172.05	0.225		2842.86	0.024
51	6.8	1.700	172.06	0.237		2843.76	0.014
52	6.9	1.705	172.29	0.264		2844.59	0.008
53	7.0	1.710	172.40	0.281		2845.56	0.005