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Maple-Brown, Louise; Ye, C; Retnakaran, R

Published in:
Diabetic Medicine

DOI:
10.1111/dme.12004

Published: 01/01/2013

Document Version
Peer reviewed version

Received Date : 25-Apr-2012
Revised Date : 23-Jul-2012
Accepted Date : 28-Aug-2012
Article type : Short Report

Technical Editor DRH

Short Report: Complications

Area-under-the-HbA_{1c}-curve above the normal range and the prediction of microvascular outcomes: an analysis of data from the Diabetes Control and Complications Trial

L. J. Maple-Brown[1,2,3], C. Ye[1] and R. Retnakaran[1,4]

[1]Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, ON, Canada, [2]Menzies School of Health Research, Charles Darwin University, [3]Division of Medicine, Royal Darwin Hospital, Darwin, NT, Australia and [4]Division of Endocrinology, University of Toronto, Toronto, ON, Canada

Correspondence to: Ravi Retnakaran. E-mail: rretnakaran@mtsinai.on.ca

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Abstract

Aims In the Diabetes Control and Complications Trial, mean updated HbA_{1c} 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 hyperglycaemic exposure may be the incremental area-under-the-HbA_{1c}-curve above the Diabetes Control and Complications Trial-standardized normal range for HbA_{1c} ($iAUC_{HbA1c>norm}$).

Methods Using the Principal Diabetes Control and Complications Trial data set, we compared the following three measures of chronic glycaemic exposure for their capacity to predict retinopathy, nephropathy and neuropathy during the Diabetes Control and Complications Trial: mean updated HbA_{1c}, $iAUC_{HbA1c>norm}$, and total area-under-the-HbA_{1c}-curve ($tAUC_{HbA1c}$). For each outcome, models using each of these three glycaemic measures were compared in the following three ways: hazard or odds ratio, χ^2 statistic, and Akaike information criterion.

Results The three glycaemic measures did not differ in their prediction of neuropathy. $iAUC_{HbA1c>norm}$ was modestly superior to mean updated HbA_{1c} for predicting nephropathy (χ^2 $P = 0.017$, Akaike $P = 0.032$). In contrast, for predicting retinopathy, both $iAUC_{HbA1c>norm}$ (χ^2 $P = 0.0005$, Akaike $P = 0.0005$) and $tAUC_{HbA1c}$ (χ^2 $P = 0.004$, Akaike $P = 0.0004$) were significantly better than mean updated HbA_{1c}. Varying its HbA_{1c} threshold incrementally between 37 and 53 mmol/mol (5.5–7.0%), inclusive, did not improve the prediction of retinopathy by $iAUC_{HbA1c>threshold}$ beyond that of $tAUC_{HbA1c,}$ consistent with the concept of a continuous relationship between glycaemia and retinopathy, with no glycaemic threshold.

Conclusions Both $iAUC_{HbA1c>norm}$ and $tAUC_{HbA1c}$ were superior to mean updated HbA_{1c} for predicting retinopathy. Optimal assessment of chronic glycaemic exposure as a determinant of

retinopathic risk may require consideration of both the degree of hyperglycaemia and its duration.

Abbreviations $iAUC_{HbA1c}$, incremental area-under-the-HbA_{1c}-curve; $iAUC_{HbA1c>norm}$, incremental area-under-the-HbA_{1c}-curve above the normal range for the DCCT-standardized HbA_{1c} assay; $tAUC_{HbA1c}$, total area-under-the-HbA_{1c}-curve; DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine

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, with glycaemic exposure (as determined by mean updated HbA_{1c}) 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 hyperglycaemia as a determinant of microvascular complications in patients with Type 1 diabetes. Although assessed by the mean updated HbA_{1c} in the DCCT, we hypothesized that a more precise measure of chronic hyperglycaemic exposure would be the incremental area-under-the-HbA_{1c}-curve above the DCCT-standardized normal range for HbA_{1c} ($iAUC_{HbA1c>norm}$). Indeed, this measure provides a way of integrating both the degree of glycaemia and the time spent above the normoglycaemic range, and hence could capture the cumulative exposure to hyperglycaemia. 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 HbA_{1c}. Thus, we sought to evaluate the predictive capacity of $iAUC_{HbA1c>norm}$ as a determinant of microvascular complications in the DCCT, as compared with mean updated HbA_{1c}.

Methods

The DCCT has been previously described in detail [4,5]. In brief, 1441 participants with Type 1 diabetes were randomized to intensive or conventional insulin therapy and followed for a mean 6.5 years, with quarterly measurement of HbA_{1c} and regular assessment for microvascular complications. Using the publicly available Principal DCCT data set (National Technical Information Service, Alexandria, VA, USA), we evaluated the following three measures of chronic glycaemic exposure: mean updated HbA_{1c}, mean $iAUC_{HbA1c>norm}$ and mean total area-under-the-HbA_{1c}-curve ($tAUC_{HbA1c}$).

These measures were assessed because, while mean updated HbA_{1c} will reflect the actual mean value for HbA_{1c} over follow-up, it does not account for duration of time spent above a particular glycaemic threshold [such as the upper-limit-of-normal for the DCCT-standardized HbA_{1c} assay (IFCC 42 mmol/mol or DCCT 6.0%)]. In contrast, $iAUC_{HbA1c>norm}$ provides a measure of glycaemic exposure that incorporates not only the degree of glycaemia, but also the time spent above the normal range. To illustrate this difference, consider the hypothetical example of two patients with the following quarterly HbA_{1c} 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 HbA_{1c} will be the same for both patients, but only $iAUC_{HbA1c>norm}$ will capture the fact that patient B spent time with HbA_{1c} over the normal range. Finally, we also assessed $tAUC_{HbA1c}$, as it is similar to $iAUC_{HbA1c>norm}$ 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 glycaemic exposure does not contribute to microvascular risk.

Mean updated HbA_{1c} was calculated as the mean of all quarterly HbA_{1c} measures up to the visit under study, computed at 6-monthly intervals [3]. Mean AUC_{HbA1c} was calculated by trapezoidal rule as a mean of the number of visits under study. For example, AUC_{HbA1c} at year 3 (12 visits) was calculated as:

$0.5 \times [H_0 + (2 \times H_1) + (2 \times H_2) + (2 \times H_3) + (2 \times H_4) + (2 \times H_5) + (2 \times H_6) + (2 \times H_7) + (2 \times H_8) + (2 \times H_9) + (2 \times H_{10}) + (2 \times H_{11}) + H_{12}]/12$, where H_0 is baseline HbA_{1c}, H_1 is first-quarterly visit HbA_{1c}, H_2 is second-quarterly visit HbA_{1c}, etc. Calculations for each 6-monthly or annual interval included all preceding quarterly HbA_{1c} measurements since the start of the DCCT.

For each measure of glycaemic 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 analysed by time-dependent proportional hazards models and neuropathy by logistic regression model. For each outcome, models using each of the three HbA_{1c} measures were compared in three ways: hazard or odds ratio, χ^2 statistic, and Akaike information criterion (Table 1). For both the χ^2 and Akaike information criterion statistics, pairwise comparisons were conducted using bootstrap

methods (2000 bootstrap samples were drawn from the original data set with replacement). The pairwise differences of the estimated χ^2 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 χ^2 or Akaike information criterion statistic. Based on this non-parametric 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 χ^2 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 HbA_{1c} thresholds between 37 and 53 mmol/mol (5.5–7.0%) for comparison of $iAUC_{HbA1c>threshold}$ vs. $tAUC_{HbA1c}$ (Table 2). The purpose of this analysis was to see if there was a particular HbA_{1c} threshold where $iAUC_{HbA1c>threshold}$ was superior to $tAUC_{HbA1c}$ for predicting retinopathy by both χ^2 and Akaike information criterion. All statistical analyses were performed using Stata 10.0 (StataCorp., College Station, TX, USA) and SAS 9.2 (SSA Institute, Cary, NC, USA).

Results

All three HbA_{1c} measures (mean updated HbA_{1c}, $tAUC_{HbA1c}$, $iAUC_{HbA1c>norm}$) were significantly associated with each microvascular outcome (Table 1). However, their comparative predictive capacities differed for each complication. While the three measures did not differ in their prediction of neuropathy, $iAUC_{HbA1c>norm}$ (but not $tAUC_{HbA1c}$) was superior to mean updated HbA_{1c} for prediction of nephropathy (χ^2 bootstrap $P = 0.017$, Akaike bootstrap $P = 0.032$). In contrast, both $iAUC_{HbA1c>norm}$ (χ^2 bootstrap $P = 0.0005$, Akaike bootstrap

$P = 0.0005$) and $tAUC_{HbA1c}$ (χ^2 bootstrap $P = 0.004$, Akaike bootstrap $P = 0.0004$) were superior to mean updated HbA_{1c} for the prediction of retinopathy, with no significant difference between $iAUC_{HbA1c>norm}$ and $tAUC_{HbA1c}$. Varying its HbA_{1c} 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 $iAUC_{HbA1c>threshold}$ beyond that of $tAUC_{HbA1c}$ (Table 2). Specifically, the χ^2 statistic did not reveal a significant difference between these two measures at any threshold, although the Akaike information criterion statistic found $tAUC_{HbA1c}$ to be superior to $iAUC_{HbA1c>threshold}$ at HbA_{1c} thresholds > 48 mmol/mol (6.5%). Lastly, after adjustment for covariates (baseline HbA_{1c}, age, gender, BMI, duration of diabetes, treatment group and baseline value of the outcome variable), both $iAUC_{HbA1c>norm}$ and $tAUC_{HbA1c}$ remained superior to mean updated HbA_{1c} for the prediction of retinopathy but not nephropathy or neuropathy (see also Supporting Information, Table S1).

Discussion

In this analysis, all three HbA_{1c} indices yielded comparable hazard or odds ratios for the prediction of each microvascular outcome, and the overall benefits of the AUC_{HbA1c} measures over mean updated HbA_{1c} were modest. Furthermore, it is recognized that neither the AUC_{HbA1c} indices nor mean updated HbA_{1c} 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_{HbA1c} measures can provide insight on the impact of glycaemic 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 $iAUC_{HbA1c>norm}$ and $tAUC_{HbA1c}$ were superior to mean updated HbA_{1c} for the prediction of retinopathy supports the concept that optimal assessment of chronic glycaemic exposure as a determinant of microvascular risk may require consideration of both the degree of hyperglycaemia and its duration. Interestingly, Orchard and colleagues previously explored this general concept with their construct of A_1months, defined as the product of HbA_{1c} above the normal range and months of 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 HbA_{1c}), it should be noted that its calculation from biennial HbA_{1c} assessments would have rendered A_1months a less precise measure of chronic glycaemic exposure than the AUC_{HbA1c} indices obtained from the more frequent HbA_{1c} measurements in the DCCT. Thus, the AUC_{HbA1c} measures in the current study may have been better able to demonstrate the predictive capacity of a cumulative glycaemic exposure variable that incorporates both duration and degree of glycaemia.

Secondly, it is noted that $iAUC_{HbA1c>norm}$ and $tAUC_{HbA1c}$ were both consistently superior to mean updated $HbA_{1c}$for the prediction of retinopathy, but not nephropathy and neuropathy. This difference may relate to methodologic features (e.g. 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 glycaemic exposure on risk of retinopathy, as compared with the other outcomes. Thirdly, we did not detect an HbA_{1c} level above which $iAUC_{HbA1c}$ surpasses $tAUC_{HbA1c}$ for predicting retinopathy, consistent with the concept of a continuous relationship between glycaemia and retinopathy, with no glycaemic threshold [3].

Finally, it should be noted that, although non-glycaemic factors may also be relevant [7], the unmeasured effect of glycaemic exposure in the years prior to the DCCT may have limited the achievable predictive capacity of all three HbA_{1c}-based measures obtained during the trial. Thus, $iAUC_{HbA1c>norm}$ and $tAUC_{HbA1c}$ from the time of diagnosis ultimately warrant study for the evaluation of total cumulative glycaemic exposure as a determinant of microvascular risk in Type 1 diabetes.

Competing interests

Nothing to declare.

Acknowledgements

The authors thank Dr Bernard Zinman (University of Toronto and Leadership Sinai Centre for Diabetes, Toronto, Canada) for advice and helpful discussion. The authors thank DCCT Investigators and participants for their landmark contributions to the understanding of diabetes control and complications. LMB is supported by an Australian National Health and Medical Research Council Early Career Fellowship no. 605837. RR is supported by a Canadian Institutes of Health Research New Investigator award, Canadian Diabetes Association Clinician Scientist incentive funding, and an Ontario Ministry of Research and Innovation Early Researcher Award.

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Supporting Information

Additional Supporting Information may be found in the online version of this article;

Table S1. Comparative performance of each measure of glycaemic exposure for the prediction of microvascular outcomes, adjusted for baseline HbA_{1c}, age, gender, BMI, duration of diabetes, treatment group and baseline value of the outcome variable.

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

	Mean updated HbA_{1c}	$tAUC_{HbA1c}$	$iAUC_{HbA1c>norm}$	*P*-values for pairwise comparisons§		
				Mean updated HbA_{1c} vs. $tAUC_{HbA1c}$	Mean updated HbA_{1c} vs. $iAUC_{HbA1c>norm}$	$tAUC_{HbA1c}$ vs. $iAUC_{HbA1c>norm}$
Retinopathy* (n = 1440)						
Hazard ratio (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
χ^2†	161.65	174.54	171.71	0.004	0.0005	0.170
Akaike information criterion‡	2847.83	2837.39	2839.22	0.004	0.0005	0.264
Nephropathy* (n = 1365)						
Hazard ratio (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
χ^2†	50.18	52.18	53.21	0.068	0.017	0.039
Akaike information criterion‡	3517.83	3516.15	3515.45	0.076	0.032	0.077
Neuropathy* (n = 1161)						
Odds ratio (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
χ^2†	41.91	42.05	42.17	0.368	0.328	0.256
Akaike information criterion‡	662.35	662.26	662.31	0.412	0.474	0.424

*Retinopathy 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 ≥ 40 mg/24 h. Neuropathy was defined on clinical examination at 5 years with concurrent/prior abnormalities in nerve conduction or autonomic nervous system testing. Retinopathy and nephropathy were analysed by time-dependent proportional hazards models as they were assessed regularly during the DCCT. Neuropathy was analysed by logistic regression model because it was assessed only at 5 years. Patients with urine albumin excretion rate > 40 mg/24 h at baseline were excluded from nephropathy models and those with neuropathy at baseline were excluded from neuropathy models.

†A larger χ^2 statistic indicates stronger evidence of an increasing trend over time in the effect of a measure of glycaemic exposure on the hazard or risk of an outcome.

‡The 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 glycaemic exposure for each outcome, the preferred model is the one with the minimum Akaike information criterion value, as least information is lost.

§The pairwise comparisons were conducted using bootstrap methods (2000 bootstrap samples were drawn from the original data set with replacement). The pairwise differences of the estimated χ^2 and Akaike information criterion statistics were obtained for each bootstrap sample. The bootstrap *P*-values were estimated by the proportion of those bootstrapped χ^2 or Akaike values at greater than or equal to the observed pairwise difference from the original data.

$iAUC_{HbA1c>norm}$, incremental area-under-the-HbA_{1c}-curve above the normal range for the DCCT-standardized HbA_{1c} assay; $tAUC_{HbA1c}$, total area-under-the-HbA_{1c}-curve; N/A, not applicable.

Table 2 Comparison of $iAUC_{HbA1c>threshold}$ and $tAUC_{HbA1c}$ for the prediction of the risk of retinopathy, for sequential incremental HbA_{1c} thresholds (T) from 37 to 53 mmol/mol (5.5 to 7.0%) inclusive

HbA_{1c} threshold (T)		Hazard ratio	χ^2-test		Akaike information criterion	
IFCC (mmol/mol)	DCCT (%)		Value	*P*-value for $iAUC_{HbA1c>T}$ vs. $tAUC_{HbA1c}$	Value	*P*-value for $iAUC_{HbA1c>T}$ vs. $tAUC_{HbA1c}$
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

$iAUC_{HbA1c}$, incremental area-under-the-HbA_{1c}-curve; $tAUC_{HbA1c}$, total area-under-the-HbA_{1c}-curve; DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.