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The shape of the metabolic memory of HbA_{1c}: re-analysing the DCCT with respect to time-dependent effects

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Abstract
Aims/hypothesis We determined the shape of the metabolic memory of HbA_{1c} and its contribution to retinopathy, as well as the importance of reducing HbA_{1c} to prevent progression of retinopathy.
Methods The relative risk contribution of HbA_{1c} values at different points in time to current progression of retinopathy was determined in the DCCT patients.
Results HbA_{1c} 2 to 3 years earlier had the greatest relative risk contribution to current progression of retinopathy. HbA_{1c} up to 5 years earlier made a greater contribution than current values, while values from 8 years earlier still had an important impact. When HbA_{1c} had been at 8% for a long period and was subsequently lowered to 7%, the salutary effects did not begin to appear until 2 to 3 years after lowering. The hazard function for a constant level of HbA_{1c} increased with time. The numbers needed to treat when reducing HbA_{1c} from 8.3% to 8% from diagnosis was estimated to be 1,688 for the first 3 years and 13 for the period 9 to 12 years. Survival functions when reducing HbA_{1c} from 8% to 7% show that pre-study glycaemic control dominates the effect on progression of retinopathy during the first years of a trial.
Conclusions/interpretation The most harmful effect of hyperglycaemia on progression of retinopathy in type 1 diabetes initially increases, but declines after roughly 5 years. The salutary effect of reducing HbA_{1c} accelerates with time and becomes greater in clinical practice than has been previously understood. Clinical trials should preferably be designed for long periods or include patients with low previous glycaemic exposure to distinguish trial effects from those of the metabolic memory.

Keywords Cost-effectiveness · Design · Diabetes · HbA_{1c} · Metabolic memory · Prognosis · Retinopathy · Risk · Risk engine

Abbreviations
AIC Akaike's information criterion
NNT Numbers needed to treat
SDIS Stockholm Diabetes Interventions Study

Introduction

Good glycaemic control is essential in preventing diabetic complications [1–3]. In the DCCT, type 1 diabetic patients randomised to intensive glycaemic control had substantially fewer lesions of retinopathy, nephropathy and neuropathy than patients receiving conventional therapy [3]. After the end of the DCCT the former intensively and conventionally

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treated groups had similar glycaemic control, but new lesions of diabetic complications developed to a much greater extent in the latter during the subsequent 4 to 11 years [4–7]. Hence, previously high levels of HbA_{1c} will have a strong effect on diabetic complications, even though glycaemic control is improved. This prolonged effect of glycaemic control on diabetic complications has been called 'metabolic memory' of glycaemic control, the molecular mechanisms and clinical evidence behind which were extensively reviewed recently [8].

Although there is evidence of a prolonged effect of glycaemic control on diabetic complications, the role of time and duration of glycaemic exposure is still unknown [1, 8]. If we understood the relative risk contribution of glycaemia measured as HbA_{1c} at different points in time, it would be possible to better understand the association between glycaemic control and diabetic complications in clinical practice and in trials, e.g. whether worsening complications during good glycaemic control is explained by the prolonged effect of previously impaired glycaemic control [9] or why there was a greater beneficial effect on complications for patients with different diabetes duration and HbA_{1c} at entry into recent clinical trials [10]. The predictive ability of HbA_{1c}, being of importance for risk gradients, health economical analyses and risk engines, would probably also increase, if the shape of the prolonged effect of HbA_{1c} were known [2].

We have recently developed a method to determine the temporal relationship between HbA_{1c} and diabetic complications [2]. The aim of this study was thus to determine the shape of the prolonged effect of HbA_{1c} on diabetic complications. We analysed data from the DCCT, including frequent HbA_{1c} measurements, and detailed grading of diabetic retinopathy [3].

Methods

We used publicly available data from the DCCT [11]. The aim of the 9-year DCCT study of 1,441 patients with type 1 diabetes was to compare the effects of intensive and conventional blood glucose treatment on the development and progression of diabetic complications. At the time of inclusion in the DCCT, the patients were 13 to 39 years old and duration of type 1 diabetes was 1 to 15 years. When randomised, the participants had no advanced micro- or macrovascular diabetic complications. The study was stopped in 1993 because of the beneficial effect of intensive treatment on retinal, renal and neurological complications. The design and outcome of the DCCT have been described in detail elsewhere [3].

Previous analyses have described the effect of the updated mean HbA_{1c} on the risk of progression of retinopathy. This assumes that each past value is equally important for the development of diabetic complications. We have developed an integral function of the history of HbA_{1c} values over time, which can weight past values differentially [2]. In this study we examined the relative risk contribution of HbA_{1c} values at different points in time before an event indicating progression of retinopathy occurred.

A basis for the model is to imitate the true HbA_{1c} curve for each diabetes patient from diagnosis and onwards to include possible impact of the prolonged effect of HbA_{1c} as early as from diagnosis. We constructed continuous HbA_{1c} curves for all patients in the DCCT from diagnosis, i.e. from before the start of the DCCT (median duration at entry 5.8 years). Since the pre-study level of HbA_{1c} was unknown, we defined the pre-study level from diagnosis to entry into the trial as equal to baseline HbA_{1c}. The pre-study HbA_{1c} level is hence not known in detail, but the model provides a correlation of a single HbA_{1c} value to the average level during several years [2]. The rest of the HbA_{1c} curves were constructed by linking the monthly HbA_{1c} values in the intensively treated group and the quarterly values in the conventionally treated group with straight lines. The HbA_{1c} curves lasted to progression of retinopathy or if no endpoint appeared to the end of the study. Hence, the mean exposure period to HbA_{1c} was the period before and during the DCCT, i.e. 12.3 years, whereas the observation time for progression of retinopathy was the 6.5 years duration of the DCCT itself.

The studied endpoint was a three-step progression on the Early treatment diabetic retinopathy study (ETDRS) scale, which comprises 23 steps of progression of retinopathy [12, 13]. In the HbA_{1c} integral, the continuous HbA_{1c} curve for each patient is included, as well as a function describing possible variations in the importance for retinopathy depending on the time of the HbA_{1c} value. We searched the values of three coefficients in this function to obtain optimal fit between the HbA_{1c} curves and events of progression of retinopathy. The influence of age, sex, diabetes duration and treatment group were studied. The fit and predictive ability of the model was compared with models that have been used earlier and worked with updated mean and baseline HbA_{1c}.

By using the estimated coefficients in the HbA_{1c} integral and the other coefficients, we were able to use the integral to calculate the hazard functions for different historical HbA_{1c} levels, accounting for different relative risk contributions from HbA_{1c} at different points in time. With knowledge of the hazard function for a series of HbA_{1c} values, the corresponding survival functions can be estimated, as well as numbers needed to treat (NNT). Hence, the HbA_{1c} integral makes it possible to study hazard functions, survival curves and NNT for any historical HbA_{1c} levels.

Statistics The HbA_{1c} integral is described in the Electronic supplementary material (ESM Main model and ESM Fig. 1). The integral was included as a time-dependent covariate in the hazard function of a Poisson model, together with age, sex, duration of diabetes, treatment group and time since entry into the DCCT (ESM) [14]. The maximum likelihood method was used to find the coefficients in the HbA_{1c} integral, which were solved simultaneously with the beta coefficients of the other variables in the hazard function (ESM). The mathematical methods to solve these equations, the coefficients in the HbA_{1c} integral and the beta coefficients found are also presented in the ESM, as are the beta coefficients for alternative models. Akaike's information criterion (AIC) was calculated as a measure to compare the fit of the present model with baseline and updated mean HbA_{1c} (ESM).

The survival curve $S(t)$ for a corresponding hazard function is calculated as exp(−area below the hazard function until time t). The probability, p, for an event before time, t, is given by $1 - S(t)$. NNT, e.g. for HbA_{1c} 8% vs HbA_{1c} 7% is given by $1/(p8-p7)$ where $p8$ and $p7$ represent the probabilities for events during a certain time period when HbA_{1c} was 8% and 7% respectively. Estimations of hazard and survival functions corresponding to a certain HbA_{1c} curve (ESM Fig. 2) are described in the ESM.

Results

HbA_{1c} values from 2 to 3 years earlier were associated with the greatest relative risk of contributing to current progression of retinopathy, whereas HbA_{1c} values from up to 5 years ago contributed more than current values (Fig. 1). Values from 6.5 years earlier had a relative risk contribution of 50% of the contribution of current values; the contribution of values from 8 years ago was 25%.

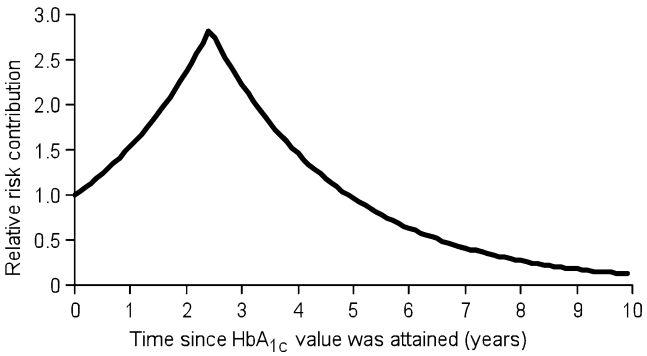

Fig. 1 The relative contribution of HbA_{1c} values at different points in time in the past to risk of current retinopathy progression. The relative contribution is largest from values 2.4 years ago, which is 2.8 times greater than the contribution from present values. The contribution is greater than that from present values for times up to 4.9 years ago. For values from 6.5 and 8.4 years ago, the contribution is 50% and 25% of present values, respectively

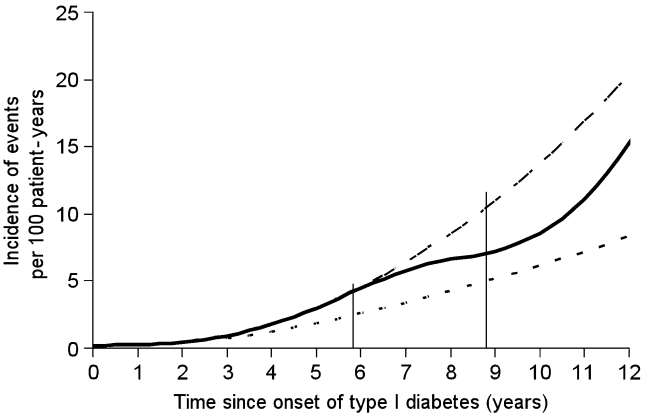

Fig. 2 The hazard functions of developing retinopathy for patients with different HbA_{1c} levels. Long-dashed curve, HbA_{1c} 8%; short-dashed curve, HbA_{1c} 7%; continuous curve, effect on risk after reduction from HbA_{1c} 8% to 7% for 3 years (vertical lines), followed by subsequent increase to HbA_{1c} 8%. Hazard functions were calculated using the HbA_{1c} integral and the beta coefficients of the Poisson model

The hazard functions for constant levels of HbA_{1c} increased with longer exposure time (Fig. 2). The hazard ratio for a higher level of HbA_{1c} increased with longer time and for HbA_{1c} 8% vs HbA_{1c} 7% was 1.05 at 1 year and 1.63 at 5 years, respectively. When HbA_{1c} had been 8% for a long period and was subsequently lowered to 7%, the hazard function did not approach that of HbA_{1c} 7% until 2 to 3 years later (Fig. 2).

The corresponding survival functions were estimated from these hazard functions of HbA_{1c} (Fig. 3). The survival functions when lowering HbA_{1c} from 8% to 7% over a period of 3 years were mainly influenced by the HbA_{1c} level before this improvement in glycaemic control.

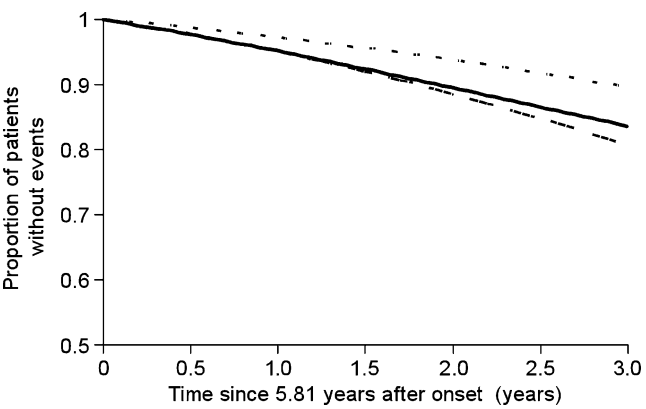

Fig. 3 Survival function of developing retinopathy for patients with different HbA_{1c} levels. Long-dashed curve, HbA_{1c} 8%; short-dashed curve, HbA_{1c} 7%; continuous curve, HbA_{1c} reduced from 8% to 7% for three years. Survival functions were calculated from the hazard functions in Fig. 2

From the hazard functions for constant levels of HbA_{1c}, NNT to prevent one event of progression of retinopathy were estimated (Table 1). The NNT when lowering HbA_{1c} from 8.3% to 8% from diagnosis was 1,688 for the first 3 years and 13 for the period 9–12 years after diagnosis.

The present model showed greater fit and predictive ability than previously used models based on baseline and updated mean HbA_{1c} values (ESM Tables 1–9). It had a higher log likelihood value of −2,809 compared with baseline HbA_{1c} of −2,918 and updated mean HbA_{1c} of −2,865. For HbA_{1c} values of 8% vs 7%, the present model predicted a 92% greater risk of retinopathy progressing over 6 years, while models using updated mean HbA_{1c} predicted a 50% and baseline HbA_{1c} predicted a 30% higher risk respectively. The number of events per time unit predicted by the present model for the DCCT was similar to the true number of events (ESM Tables 10–11).

Discussion

The shape of the metabolic memory of glycaemic control as measured by HbA_{1c} and its effects on the development of diabetic retinopathy show that the present HbA_{1c} value is not the most important. Instead, HbA_{1c} values from 2 to 3 years ago contribute the greatest risk to current progression of retinopathy, with values from up to 5 years earlier contributing more than current values. Values from up to 8 years ago still have an important impact on current progression of retinopathy. Thus when reducing HbA_{1c}, it will take several years before substantial preventive effects appear, since glycaemic control in the period before an improvement will initially have the main influence on complications. Similarly, in clinical trials, pre-study glycaemic control will have a greater impact on progression of retinopathy during the first years of the trial than any intervention. Hence, to distinguish a true beneficial effect, studies of the effects of glycaemic control on diabetic complications should probably be designed to run over extended time periods or to include patients with short previous exposure to hyperglycaemia. The harmful effect of a given HbA_{1c} level will accelerate with longer exposure time, since more previous HbA_{1c} values will exist, each leading to a risk contribution at the later point of time. Salutary effects, therefore, will continue to increase beyond the duration of clinical studies and are likely to have an even greater effect in clinical practice.

Table 1 Number needed to treat to prevent one event of retinopathy during different 3-year intervals when HbA_{1c} is reduced from level at diagnosis

HbA_{1c} level (%)	Time interval (years) since diagnosis			
	0–3	4–6	7–9	10–12
6 vs 7	721.5	59.7	19.2	10.1
7 vs 8	632.2	37.7	10.5	5.2
8 vs 9	482.6	24.1	6.3	3.5
7 vs 9	273.7	14.7	3.9	2.1
8 vs 8.3	1,687.8	94.3	24.9	12.7

Previous studies of HbA_{1c} and the development of diabetic complications have generally not examined the temporal relationships between exposure and its clinical effects [1]. Earlier studies have generally related baseline, mean or updated mean HbA_{1c} to diabetic complications. Baseline HbA_{1c} is a single value, while mean and updated mean HbA_{1c} imply that HbA_{1c} values at different points of time are of the same importance for the subsequent development of diabetic complications [1, 2]. However, one analysis of the DCCT concluded that there is an interaction between treatment effect and time [15]. It was also found that the highest predictive ability of HbA_{1c} was reached when pre-study glycaemic exposure, consisting of diabetes duration at entry into the DCCT multiplied by baseline HbA_{1c}, was included in the model in addition to the present values. In another study, Yoshida et al. have shown that the odds ratio for a higher level of HbA_{1c} to affect development of retinopathy increases with longer follow-up time [16]. In the 10-year follow-up of the Stockholm Diabetes Interventions Study (SDIS), the effects of a lower HbA_{1c} value were even greater although the HbA_{1c} difference between the intensively and conventionally treated groups was smaller during the last years [17]. Another publication from the SDIS concluded that the baseline and mean values of HbA_{1c} were correlated to retinopathy, but the final value was not [18]. Recently it has been shown that the standard deviation, contradicting results of previous studies, is important for predictive ability, in addition to updated mean HbA_{1c} [15, 19].

Although efforts have been made to study influence of time and different variations in HbA_{1c}, it has not previously been examined how the relative risk contribution of HbA_{1c} varies at different points in time [1]. The findings in the present study have several implications. Considering the prognosis of diabetes, the negative effects of hyperglycaemic exposure begin to disappear after 5 years, although harmful minor effects will persist for some years longer. Hence, a patient with previous poor glycaemic control can start to feel less anxious about future severe complications, if no complications have appeared 5 years after an improvement in HbA_{1c}. However, it was shown earlier that the absolute risk at HbA_{1c} 11% is more than ten times greater than that of HbA_{1c} at 6% [15]. Thus, an effect of an HbA_{1c} value of 11% will be considerable even 8 years later, when 25% of the effect still remains, whereas an HbA_{1c} level of 8% will by then be of minor importance. Due to the

shape of the metabolic memory of HbA_{1c}, elevated HbA_{1c} values from 5 to 10 years earlier can explain an ongoing development of diabetic complications. Hence, in most of the patients in the DCCT with progression of retinopathy despite having achieved good glycaemic control, the deterioration was probably due to impaired glycaemic control occurring at some time before the study [9]. However, it should be noted that besides the present and previous levels of HbA_{1c} a rapid lowering of HbA_{1c} from a previous high level also showed a transient effect on progression of retinopathy [3, 20, 21]. In the DCCT, patients on intensive therapy had a higher cumulative incidence for progression of retinopathy during the first year [3]. One possible explanation is increased levels of IGF-1 during rapid improvement of glycaemic control [22].

In diabetic patients after pancreas transplantation, normalisation of HbA_{1c} was not seen to have major beneficial effects on diabetic nephropathy until 5 to 10 years later [23, 24]. This is probably due to the prolonged effect of HbA_{1c}, which continued to exert harmful effects during the first years after normalisation of glucose levels [25]. Considering the shape of the prolonged effect of HbA_{1c}, we can now show that the current HbA_{1c} values during the first 3 years of a trial will only have a marginal influence on complications and that the main effect is derived from pre-study glycaemic control. Hence, it will probably be essential to have studies of long duration or to include patients with low previous hyperglycaemia exposure in order to reduce the influence of the metabolic memory of pre-study glycaemic control.

The shape of the metabolic memory of HbA_{1c} also influences risk estimations of HbA_{1c} and diabetic complications [2]. We have previously shown that meta-analyses of HbA_{1c} and diabetic complications, including several studies based on baseline HbA_{1c}, led to underestimations of the pooled risk [1, 26]. We have also shown that the use of updated mean HbA_{1c} which does not consider the prolonged effect of HbA_{1c}, probably leads to substantial underestimations of the predictive ability of HbA_{1c}, a finding that is important in health economical analyses and risk engines [2, 27]. We now confirm those results and further support those conclusions, and now it would be important to carry out analyses corresponding to those presented here for other diabetic complications. Such results could then be used in health economical analyses and risk engines to understand the full effects obtained by lowering HbA_{1c} in clinical practice. There are three main reasons why consideration of the prolonged effect of HbA_{1c} is crucial to risk estimations. First, the prolonged effect of pre-study glycaemic control explains several of the complications in a study. Second, HbA_{1c} at different points in a study is of different importance. And third, the beneficial effects of lowering HbA_{1c} during a certain time period increase with time beyond the time range of clinical studies. For example, the number of patients needed to be treated (NNT) in order to prevent progression of retinopathy in one patient is much lower for a similar time period at a later point of time when the treatment has been sustained for a longer period of time. For a reduction of HbA_{1c} from 8.3% to 8.0%, we estimated that 1,688 patients would have to be treated during the first 3 years after diagnosis, but only 13 patients during the 9 to 12 years post diagnosis at the similar glycaemic level.

A limitation of the present study is that only a few variables were used to reflect the temporal relationship between HbA_{1c} and retinopathy. The reason for this was that too many variables would make estimations more difficult and maybe even impossible. The shape of the temporal relationship could, in reality, be smoother in the increasing and decreasing phases and have a less pronounced peak than the relation described. The temporal relationship seems realistic from earlier evidence of HbA_{1c} and progression of retinopathy, where a prolonged effect of intensive treatment has been shown. Further on, the incidence curves in the DCCT did not start to diverge until after 2 to 3 years, which agrees with our finding that a beneficial effect of lowering HbA_{1c} did not begin to appear until after 2 to 3 years [3]. The present model had a better fit and predictive ability than baseline and updated mean HbA_{1c}, and the number of events per time unit agreed with the true number of events in the DCCT. It is unlikely that any other factor than glycaemic control described by HbA_{1c} underlies the associations, since outcomes were blinded to patients and investigators, and complications were strongly related to HbA_{1c}, but not to treatment modality when included in the same analysis.

In conclusion, our results strongly suggest that good glycaemic control is more important than earlier believed in preventing diabetic retinopathy. The momentary risk of retinopathy accelerates with time, although HbA_{1c} is constant, and the predictive ability is greater than earlier recognised. Patients with current good control can develop retinopathy due to earlier poor glycaemic control. The design of trials of HbA_{1c} and diabetic complications could probably be improved if their temporal relationship were first determined. In general, clinicians should analyse time-dependent effects of treatments and risk factors in epidemiological and clinical trials to understand the magnitude of the effects.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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