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Diabetic retinopathy in well-controlled type 2 diabetes: role of glycaemic memory

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Abstract

Aims. – As diabetic retinopathy (DR) can occur even in well-controlled patients with type 2 diabetes (T2D), our study sought to determine whether it might be related to 'glucose memory' by evaluating patients' HbA1c over previous years and their skin autofluorescence (SAF).

Methods. – In 334 patients with T2D and HbA1c levels ≤ 8%, their available values of HbA1c from previous years were collected, and their SAF measured by an advanced glycation end-product (AGE) reader. Binary logistic regression analysis was then used to correlate DR with previously recorded HbA1c levels and to SAF, with adjustment for DR risk factors [age, gender, BMI, duration of diabetes, arterial hypertension, diabetic kidney disease (DKD), blood lipid levels and statin treatment].

Results. – Our patients were mostly men (58.4%) aged 63 ± 10 years, with a duration of diabetes of 13 ± 10 years and HbA1c = 7.1 ± 0.7%. Of these patients, 84 (25.1%) had DR, which was associated with longer duration of diabetes and greater prevalence of DKD. A total of 605 HbA1c values from previous years were collected for time periods -4 ± 3 months (n = 255), -16 ± 4 months (n = 152), -30 ± 4 months (n = 93) and -62 ± 26 months (n = 105). After adjustment, the association between DR and having an HbA1c higher than the median was significant only for the oldest previous HbA1c values: OR = 6.75, 95% CI: 1.90–23.90. Moreover, SAF values were higher in those with DR [2.95 ± 0.67 arbitrary units (AU)] *vs* 2.65 ± 0.65 AU with no DR ($P < 0.01$) and were also associated with the oldest previous HbA1c values ($P < 0.01$).

Conclusion. – Our study found that 25.1% of our well-controlled T2D patients had DR, which was related to both their HbA1c levels from 5 years prior to study admission and their SAF values, a marker of glucose memory.

Keywords: Advanced glycation end products; Diabetes complications; Diabetic retinopathy; Glycaemic memory; Microangiopathy; Skin autofluoresence

Introduction

Diabetic retinopathy (DR) is the most frequent cause of blindness in adults before the age of 50 years in developed countries [1]. Even though the risk of DR is increased in patients with type 2 diabetes (T2D) and diabetic nephropathy [2], arterial hypertension and dyslipidaemia, its most consistent risk factor is, in fact, chronic hyperglycaemia [3]. Yet, glucose control is not commonly recommended for reducing the risk and progression of DR [4]. Moreover, DR can occur and progress even in well-controlled T2D patients [5]. This observation led to our hypothesis that a 'glycaemic memory' phenomenon, referring to exposure to a hyperglycaemic environment in the past together with an increased risk of later complications despite metabolic improvement, as reported for both type 1 (T1D) [6] and T2D, could be contributing to cases of unexpected DR.

For our 334 patients with well-controlled T2D (HbA1c ≤ 8%), their available HbA1c values from previous years were systematically collected, and the first, second and third years of HbA1c values and the oldest recorded values were registered. These data were then used to analyze the relationship between HbA1c values at each previous time point and the presence or absence of DR. Our study also tested whether DR and these ancient HbA1c values were related to skin autofluorescence (SAF) as a marker of glycaemic memory [7].

Subjects and methods

Subjects

Patients with T2D were included if they had HbA1c levels ≤ 8%. All qualifying patients gave their informed consent to participate in the study, which was approved by the local ethics committee.

Data collection

The following data were collected for each participant: age; gender; duration of diabetes; body mass index (BMI); arterial hypertension (blood pressure = 140/90 mmHg, or use of antihypertensive treatment); statin medication use; and a history of macroangiopathy (myocardial infarction, stroke, gangrene, revascularization).

DR was diagnosed either during hospitalization or the year before by an ophthalmologist based on fundus examination or retinal imaging (photography) after dilation and, if required, by optical coherence tomography (OCT) examination. Blood and urine analyses included

HbA1c, blood lipid levels, albumin excretion rates (AER) and serum creatinine to allow estimated glomerular filtration rates (eGFR), which were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Diabetic kidney disease (DKD) was defined as an eGFR < 60 mL/min/1.73 m^2 and/or AER > 30 mg/24 h. All available HbA1c values from each of the 3 years prior to admission were retrospectively registered, as well as each patient's oldest recorded HbA1c.

Skin autofluorescence

Cutaneous accumulation of advanced glycation end-products (AGEs) was measured on the forearm for SAF values, expressed in arbitrary units (AU), using an AGE Reader (Diagnoptics Technologies B.V., Groningen, The Netherlands). Patients with Fitzpatrick skin phototypes V and VI were excluded, as their levels of skin pigmentation do not allow reliable measurement. Indeed, Meerwaldt et al. [7] had previously demonstrated that SAF correlates with concentrations of AGEs in skin biopsies.

Statistical analysis

In our present study, results for continuous variables are expressed as means ± standard deviation (SD) and as percentages for categorical variables. Subjects with *vs* without DR were compared using analysis of variance (ANOVA) for continuous variables, and chi-squared tests for non-continuous variables. Also, a non-parametric test was used to compare continuous variables with asymmetrical distributions (triglycerides), and binary logistic regression analysis was performed to search for correlations between DR and age, gender and its other known risk factors (BMI, blood lipids, statin treatment, arterial hypertension, DKD, duration of diabetes). These analyses were repeated after introducing HbA1c values from each previous time period into the model, first as a continuous variable and then after categorizing HbA1c values as being either above or below the median.

Results

Characteristics of the patient population

As detailed in Table S1 (see supplementary materials associated with this article online), our 334 patients were mostly men (58.4%) aged 63 ± 10 years, with a 13 ± 10-year duration of diabetes. Their BMI was 31.5 ± 6.2 kg/m^2; 64% had arterial hypertension, and 59.3% were

being treated with a statin. Macroangiopathy was present in 40.7% of our patients, 43.7% had DKD and all were well controlled with HbA1c = 7.1 ± 0.7%.

DR and its risk factors

A total of 84 participants (25.1%) had DR: 9.58% (n=32) had proliferative retinopathy; 15.58% (n=52) had non-proliferative retinopathy; and 11.67% (n=39) had macular oedema. These patients differed from the others in their duration of diabetes (DR: 18 ± 11 years, no DR: 12 ± 9; $P < 0.001$) and prevalence of DKD (DR: 66.7%, no DR: 36%; $P < 0.001$). In addition, their age, BMI and prevalence of arterial hypertension were higher but non-significant, they did not differ significantly according to gender and their blood lipid profiles also did not differ, although there was a tendency for more statin-treated patients to be among the DR cases (66.7% *vs* 56.8% of those not taking statins; $P = 0.07$). Moreover, two explicative variables were significantly related to DR according to binary logistic regression including all of the above-mentioned factors: duration of diabetes odds ratio (OR): 1.048, 95% confidence interval (CI): 1.019–1.078; and DKD OR: 3.592, 95% CI: 2.016–6.401. However, HbA1c did not differ according to DR (with DR: 7.1 ± 0.5%, without DR: 7.0 ± 0.7%; $P = 0.15$).

Previous HbA1c and DR

A total of 605 HbA1c values from previous years were collected for the following time periods: -4 ± 3 months (n = 255); -16 ± 4 months (n = 152); -30 ± 4 months (n = 93); and -62 ± 26 months (n = 105). In addition, the oldest previous HbA1c values registered were higher in cases with DR, whereas values with moderate differences (0.5–0.6%) never reached significance: HbA1c at time 0 (T0): 7.1 ± 0.5% with DR *vs* 7.0 ± 0.7% without DR ($P = 0.15$); previous HbA1c (-4 months): 8.0 ± 1.7% with DR *vs* 8.2 ± 1.7% without DR ($P = 0.56$); previous HbA1c (-16 months): 8.5 ± 0.7% with DR *vs* 8.2 ± 0.5% without DR ($P = 0.32$); previous HbA1c (-30 months): 8.5 ± 1.9% with DR *vs* 7.9 ± 1.4% without DR ($P = 0.10$); and oldest HbA1c (-62 months): 9.3 ± 2.5% with DR *vs* 8.7 ± 2.4% without DR ($P = 0.19$). The coefficient of variation of consecutive HbA1c values did not differ according to DR: 15.9 ± 12.3% with DR *vs* 14.8 ± 11.6% without DR ($P = 0.49$).

When introduced as a continuous variable in the binary logistic regression model, only the oldest HbA1c recorded correlated with the presence of DR [Exp(B) = 1.027 (1.005–1.050)], whereas the other HbA1c values taken at different times did not. Also, the association

between having an HbA1c higher than the median at each time period and the presence of DR, depicted in Fig. 1, was significant only when the oldest previous HbA1c values were analyzed.

Skin autofluorescence

SAF, used as a marker of glycaemic memory in our study patients, was not related to HbA1c at either T0 or previous time periods except for the oldest HbA1c values collected ($P < 0.01$), which had a relationship that remained significant [variance inflation factor (VIF) = +0.24, $P < 0.01$] even after adjusting for the two explicative variables related to SAF: age and DKD. SAF values were higher in DR cases (2.95 ± 0.67 AU) *vs* no DR (2.65 ± 0.65 AU; $P < 0.01$) and remained significant even after adjustment for other DR risk factors ($P < 0.05$). In addition, in those with DR, 67.9% had SAF values higher than the median *vs* 44.4% in those without DR ($P < 0.005$), and this relationship remained significant even after multiple adjustments: OR: 2.23, 95% CI: 1.22–4.07.

Discussion

Glucose control is the cornerstone of DR prevention in T2D [1], based on the results of randomized controlled trials. However, some residual risk of DR persisted in the intensively treated arms of those trials, and has also been confirmed by studies focusing on well-controlled T2D.

In line with the 25.1% presence of DR seen in our present study, Brown et al. [5] found a DR rate of 22.7% in 396 subjects whose mean HbA1c was 7.8 ± 1.2% after 9 years of diabetes, while around 20% of those DR cases continued to progress over the following 5 years despite HbA1c values < 6.5%, further underscoring the limits of glucose control. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study, which targetted those with HbA1c < 6%, led to a one-third reduction in the progression of DR, yet DR still occurred in 7.3% of the intensively treated participants [8]. In fact, such an ambitious goal may not have been safe for all of our patients, 40% of whom had various macroangiopathies.

Intensive treatment of both arterial hypertension and dyslipidaemia are also recommended to prevent DR [1]. However, while most of our patients were treated for arterial hypertension, their high frequency of DKD (40.7%) suggests that blood pressure control was not always optimal. Nevertheless, intensive blood pressure control to < 120 mmHg systolic

did not reduce progression of DR in the ACCORD Eye Study [8]. Furthermore, despite most of our patients being treated with statins, their blood lipid levels [low-density lipoprotein (LDL) cholesterol: 101 mg/dL; triglycerides: 155 mg/dL] were not within the range of secondary prevention. Finally, although the ACCORD Eye [8] and Fenofibrate Intervention and Event-Lowering in Diabetes (FIELD) Studies [9] both reported a benefit of fibrates in DR, this would require its co-prescription with statins that, in many cases, may not be safe.

Thus, the medical treatment of patients with DR despite good glucose control is evidently not simple. Our work thus far suggests there is important room for improvement in the prevention of DR, which correlated more closely with higher previous rather than current levels of HbA1c in our patients (Fig. 1). In line with the glucose memory concept, such an association with previous glucose control has already been described in T1D [6], but not as yet, to our knowledge, in T2D. According to previous trials [3] and prospective studies [5], DR would probably have been less frequent if our patients had been better controlled over the previous 5 years as well as more closely followed [10]. However, there are striking disparities in the situations and treatments that can have an impact on diabetes complications, especially retinopathy [10].

Accordingly, regular follow-ups of patients with T2D are associated with a lower glycaemic burden and half as many retinopathies [11]. Nevertheless, in real-world clinical practice, patients are often treated with no awareness of their previous HbA1c levels, which may not even have been measured in all cases. However, our present study shows that SAF can provide information on glucose control during previous years in a simple and non-invasive manner. This can be expected because SAF relies on the fluorescent properties of accumulated AGEs in tissues, a long-term process. In fact, SAF proved to be related to HbA1c levels 10 years earlier in elderly participants from the general population in the Three-City (3C) Study cohort [12]. Other authors have correlated SAF with DR in T2D, but did not demonstrate such a relationship with earlier previous levels of HbA1c [13]. Also, in the longitudinal Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC) cohort, SAF failed to predict DR [14], which was infrequent as those participants were young and had T2D of recent onset. Thus, further work is still necessary to better assess the relationship between SAF and DR.

Study limitations

Our present study has some limitations. As DR may have been diagnosed during the year prior to hospitalization, it is not possible to exclude the idea that some patients may have developed DR between the ophthalmological examination and later collection of current HbA1c values. In addition, as previous HbA1c values were higher than the current ones, some DR cases may have been due to early worsening despite better diabetes control, a notion that cannot be ruled out, given the lack of results for previous ophthalmological examinations. Finally, the use of fibrates was not registered in our present study patients as this treatment was, in fact, uncommon.

Appendix supplementary material

Supplementary material (Table S1) associated with this article can be found at http://www.scincedirect.com at doi . . .

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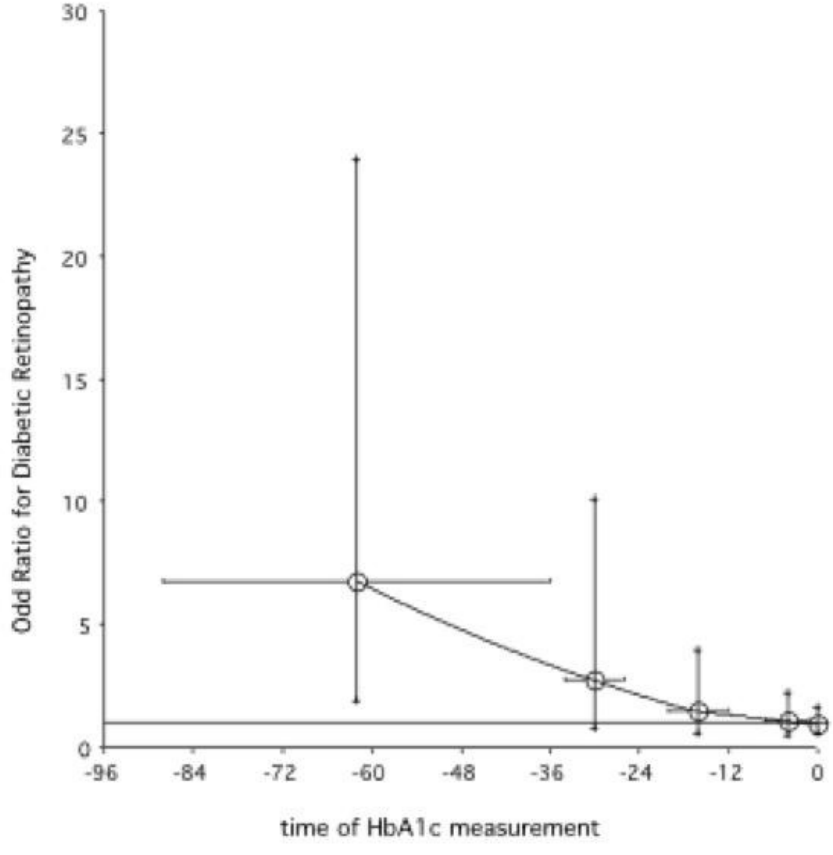
Figure legend

Fig. 1. Relationship between an HbA1c level higher than the median at each time point and diabetic retinopathy (DR). x-axis: time in months before diagnosis of DR (horizontal extensions); y-axis: odds ratio with 95% CI (vertical extensions).


30
25
20
15
10
5
0
Odd Ratio for Diabetic Retinopathy
-96
-84
-72
-60
-48
-36
-24
-12
0
time of HbA1c measurement