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RESEARCH LETTER

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# Glycated haemoglobin in the first year after diagnosis of type 1 diabetes is an independent risk factor for diabetic retinopathy: The IMDIAB 25 years follow-up study

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## 1 | BACKGROUND

Intensive glycaemic control lowers the risk of microvascular complications.[1] This effect has been shown to persist for up to 18 years of follow-up.[2–5] Whether the glycaemic control obtained during the first months after type 1 diabetes (T1D) onset has an impact on the future risk of chronic complications has not been clarified.

We aimed to understand if the long-term risk of complications in T1D may be influenced by the onset characteristics of the disease and by the glycaemic control obtained within the first year after diagnosis.

## 2 | METHODS

### 2.1 | Study design and population

We retrospectively evaluated a cohort of patients enrolled within 1 year of T1D diagnosis in any of the 10 intervention trials conducted by the IMmunotherapy DIABetes (IMDIAB) study group (Appendix S1) and followed-up for up to 37 years, for whom data about the presence of chronic complications were available at the time of study conduction, and who accepted to participate in this follow-up study. IMDIAB participants were reached by phone

**TABLE 1** Clinical and biochemical features of participants with and without a diagnosis of diabetic retinopathy at follow-up

| | Retinopathy | | |
|---|---|---|---|
| | No (n = 148) | Yes (n = 27) | *p*-Value |
| Male gender, n (%) | 83 (56.08) | 13 (48.15) | .45 |
| Features at diabetes diagnosis | | | |
| Age, years | 11 [8-18] | 13 [9-21] | .45 |
| Length of symptoms before diagnosis, days | 21 [11-40] | 25.5 [11-47.5] | .59 |
| HbA1c, % | | | |
| At onset | 9.70 [8.40-11.80] | 10.60 [8.20-11.80] | .45 |
| Updated first-year | 6.17 [5.65-7.10] | 6.80 [6.05-7.80] | .047 |
| Fasting C-peptide, ng/ml | | | |
| At onset | 0.60 [0.30-1.00] | 0.58 [0.3-1.20] | .79 |
| Updated first-year | 0.79 [0.52-1.66] | 0.73 [0.53-1.23] | .88 |
| Mean change over first-year (vs. baseline) | +0.18 [−0.10 to 0.42] | +0.11 [−0.26 to 0.52] | .90 |
| Presence of urine ketones, n/total (%)[a] | 75/95 (79.0) | 21/23 (91.3) | .23 |
| IMDIAB treatment arm | | | .34 |
| Insulin only, n (%) | 22 (14.9%) | 6 (22.22%) | |
| Insulin plus trial drug, n (%) | 126 (85.1%) | 21 (76.8%) | |
| Mean first-year insulin requirement, IU/kg/day | 0.47 [0.3-0.67] | 0.38 [0.28-0.66] | .68 |
| Features at last follow-up | | | |
| Age, years | 37 [32-43.5] | 43 [34-49] | .12 |
| Disease duration, years | 25 [22-27.5] | 28 [24-30] | .029 |
| BMI, kg/m$^2$ | 24 [21.8-26.5] | 25 [22.4-28.7] | .43 |
| HbA1c, % | 7.2 [6.7-7.8] | 8.0 [6.9-8.9] | .003 |
| Total cholesterol, mg/dl | 170 [155-191.5] | 179 [156-195] | .82 |
| HDL cholesterol, mg/dl | 57 [49.5-69.5] | 59 [51-73] | .78 |
| LDL, cholesterol, mg/dl | 100 [83-116.8] | 99.5 [77.3-115.4] | .80 |
| Triglycerides, mg/dl | 66 [50-79] | 66.5 [56-91] | .12 |
| eGFR, ml/min/1.73 m$^2$ | 109 [98.1-118] | 108 [98.8-117.4] | .099 |
| Insulin delivery method | | | .86 |
| MDI, n (%) | 85 (57.4) | 16 (59.3) | |
| CSII, n (%) | 63 (42.6) | 11 (40.7) | |
| Hypertension, n (%) | 15 (10.5) | 6 (22.2) | .084 |
| Dyslipidaemia, n (%) | 55 (37.5) | 9 (34.6) | .78 |
| Smoker, n (%) | | | .91 |
| Never | 61 (58.6) | 12 (66.7) | |
| Past | 20 (19.2) | 1 (5.56) | |
| Current | 23 (22.12) | 5 (27.78) | |
| Diabetic nephropathy, n (%) | 3 (2.0) | 5 (18.5) | <.001 |
| Peripheral neuropathy, n (%) | 4 (2.7) | 8 (29.6) | .002 |

Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; IMDIAB, IMmunotherapy DIABetes (study group); LDL, low-density lipoprotein; MDI, multiple daily insulin injections.

[a]Data for urine ketones were not available for 39 people.

between January 2020 and March 2023 and data for 175 of 628 IMDIAB participants meeting all the inclusion criteria were retrieved from the trial datasets and from clinical charts, as described in Appendix S1.

## 2.2 | Statistical analysis

Updated first-year glycated haemoglobin (HbA1c), C-peptide and mean first-year insulin requirement were calculated as the mean of

the available values at 3, 6, 9 and 12 months after diabetes onset. C-peptide change over the first year was calculated as the difference between the updated first-year C-peptide and baseline C-peptide.

Multiple imputation was used to impute missing values (Appendix S1).

Logistic regression models were used to test the association of baseline and follow-up features with diabetic retinopathy (DR). Multivariate models having the mean first-year HbA1c as the main exposure were used to adjust for confounders (list of variables tested in the model in Appendix S1). Variables associated with the outcome at a nominal $p < .1$ were retained in the final model. Linear regression models were used to test the presence of any association between HbA1c at diabetes onset, mean-first-year HbA1c and HbA1c measured at last follow-up and to test baseline features associated with first-year HbA1c. Multivariable analysis of variance was used to compare HbA1c values measured at multiple time points. $p < .05$ was considered statistically significant.

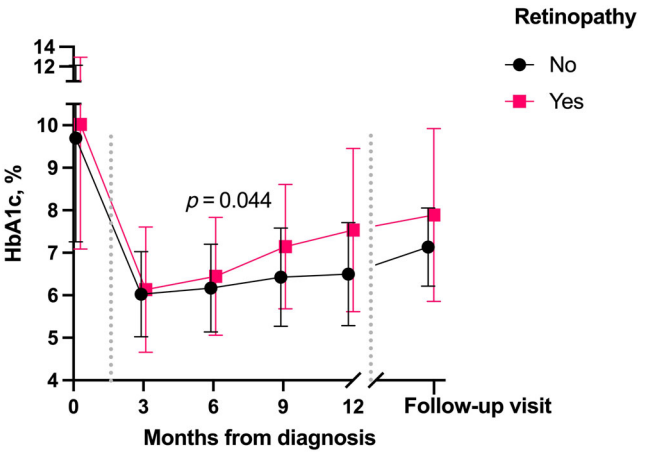


**FIGURE 1** Mean glycated haemoglobin (HbA1c) values during the first year after diabetes onset in IMmunotherapy DIABetes (IMDIAB) study group participants with available HbA1c measurements at all time-points with (n = 9) and without (n = 57) diabetic retinopathy. Most recent HbA1c in the same groups are also reported. The *p*-value is estimated with MANOVA for the difference in HbA1c values at 3, 6, 9 and 12 months between study groups. Error bars represent standard deviations.

## 3 | RESULTS

### 3.1 | Population features

The 175 people considered in this analysis were slightly younger at diabetes onset compared with the 453 IMDIAB participants not included in this study [11 (8-18) vs. 13 (9-21), $p = .046$]. No differences in terms of gender, baseline and first-year HbA1c and C-peptide was found (data not shown). At the time of the last follow-up, the population enrolled in this study was aged 37 (32-45) years, the median disease duration was 25 (22-28) years and the HbA1c was 7.3 (6.7-8.0)%. DR was diagnosed in 27 (17.3%) people (7 with proliferative DR), diabetic nephropathy in 8 (4.6%) and peripheral neuropathy in 12 (6.9%) people. Only one participant had a positive history of coronary heart disease and one had an ischaemic stroke.

### 3.2 | Glycaemic control and risk of retinopathy

Table 1 summarizes baseline and follow-up features of people with and without DR. People with DR, compared with those without, had a longer disease duration ($p = .036$), and were more frequently affected by nephropathy ($p < .001$) and peripheral neuropathy ($p < .001$). Although HbA1c at onset was similar between the two groups, people with DR showed a significantly higher updated first-year HbA1c ($p = .047$) and higher HbA1c at last follow-up ($p = .003$) compared with people free from DR (Figure S1). There was a nominal association between higher updated first-year HbA1c and higher HbA1c at follow-up, which was marginally non-statistically significant (beta-coefficient: 0.13, $p = .051$, Figure S2). The updated first-year HbA1c was slightly higher among women than among men [6.4 (5.8-7.6)% vs 6.3 (5.5-7.0)%, $p = .014$], although gender was not directly associated to an increased risk of DR or impacted on the association between the updated first-year HbA1c and DR. Age at diagnosis, length of symptoms before diagnosis, updated first-year C-peptide, mean first-year insulin requirement and randomization arm were not associated with the updated first-year HbA1c.

The updated first-year HbA1c remained significantly associated with DR also after adjusting for HbA1c at follow-up, disease duration and triglycerides, which were the only variables associated with the outcome at a nominal $p < .1$ in the final model (Table S1).

The trend of the HbA1c values measured every 3 months after T1D onset was evaluated among IMDIAB participants for whom HbA1c measurements were available at all time points (0, 3, 6, 9, 12 months). In this subgroup (n = 66), we observed an initial (at 3 months) improvement in HbA1c values in both participants who will develop DR (n = 9) and in those free of DR at follow-up (n = 57), with the former showing a subsequent significant worsening of glycaemic control starting 6 months after diabetes onset ($p = .044$ for the difference of HbA1c values at 3, 6, 9 and 12 months between groups) (Figure 1).

## 4 | CONCLUSIONS

Failure to keep a strict glycaemic control during the first year after T1D onset is associated with an increased risk of DR after a median 25 years of follow-up. Although similar results were available in people with type 2 diabetes,[6] such data were lacking for T1D, which has a shorter preclinical period than type 2 diabetes. Furthermore, our results expand the existing literature in that previous studies showing the effect of early intensive glycaemic control in T1D only enrolled people who had diabetes for >1 year, did not provide results about the specific impact of the peri-diagnosis period or did not control the association for confounders.[7–9] We did not find any association

between the insulin dose used during the first year after T1D diagnosis and DR, suggesting that an intensive insulin treatment may benefit on the long-term risk of DR only as means to obtain a strict glycaemic control. Similarly, fasting C-peptide values during the first year after the T1D diagnosis were not related to the future risk of DR, adding novel evidence in a debated field.[10–12]

We found a lower prevalence of DR than expected. The overall good metabolic control observed in our population and the decreasing incidence of DR observed globally[13,14] may in part explain this finding.

Some limitations of this study should be acknowledged, including the retrospective study design, low number of events, ascertainment of complications only through medical records and that we were not able to adjust for the cumulative effect of metabolic control over the years and to reach a high proportion of people participating the IMDIAB trials, which might cause a population bias. Nevertheless, the evaluation of complication risk in people participating in a randomized controlled trial immediately after T1D onset offered the unique opportunity to use data about early risk factors, which were rigorously collected by experienced investigators of the IMDIAB network according to the randomized controlled trial protocols.

In conclusion, glycaemic control obtained during the first year after T1D onset is associated with long-term risk of DR. This suggests that blood glucose monitoring immediately after diabetes onset may help for an early stratification of long-term complication risk, and prompt the intensification of blood glucose management immediately after a diagnosis of T1D.

## AUTHOR CONTRIBUTIONS

EM designed the study, analysed the data, interpreted results and wrote the first draft of the manuscript. AC researched the data and contributed to manuscript writing. DP researched data and helped in data interpretation. GL, CS, MA, MGC, IB, SM, CM, LC, NV, FT, RS and AC researched the data. RB helped in the study design and interpretation of results. PP designed the study, interpreted results, reviewed and edited the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript. EM is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## CONFLICT OF INTEREST STATEMENT

EM has received fees for consultancy, speaker service or advisory boards from Abbott, MTD, Novo Nordisk and PikDare; RB has received fees for consultancy, speaker service or advisory boards from Abbott, Astrazeneca, Lilly, Novo Nordisk and Sanofi. PP has received fees for consultancy from Dompè and Altheia. The other authors have no conflicts of interest to declare.

## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

The datasets generated for this work are available from the corresponding authors under reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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