Influence of age at diagnosis on glycaemic control evolution in patients with type 1 diabetes

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Abstract

\textbf{Aim.} – The objective of this study was to describe the relationship between age at onset, with no age limits, and glycaemic control evolution from the time of onset in patients with type 1 diabetes (T1D).

\textbf{Methods.} – This observational retrospective follow-up study included 716 patients with T1D onset between 1990 and 2008 treated at the Navarre Hospital Complex. The mean (SD) follow-up lasted 10.1 (5.3) years. Information on their HbA\textsubscript{1c} levels was collected at onset and every year thereafter. Generalized additive mixed models and linear models were used, with patients’ annual HbA\textsubscript{1c} levels as the response variable and the number of years since onset together with age at onset as covariates.

\textbf{Results.} – The evolution of glycaemic control is not linear and differs across all age groups. Children reach their highest values in adolescence, while patients with onset at ages 10–15 years stabilize their HbA\textsubscript{1c} values after 7 or 8 years. In adults, it is notable that an age of onset ≥ 45 years is associated with the worst control.

\textbf{Conclusion.} – A non-linear increase in HbA\textsubscript{1c} levels can be observed from the time of T1D diagnosis, with significant differences across all age groups.

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\textbf{Keywords:} Age of onset; Glycaemic control; Type 1 diabetes

Résumé

Influence de l’âge au diagnostic sur l’évolution du contrôle glycémique chez les patients atteints de diabète type 1.

\textbf{Objectif.} – L’objectif de cette étude est de décrire la relation entre l’âge d’apparition de la maladie, sans limite d’âge, et l’évolution du contrôle glycémique, dès le diagnostic, chez les patients atteints de diabète type 1.

\textbf{Méthodes.} – Il s’agit d’une étude d’observation rétrospective. Au total, nous avons étudié 716 patients ayant développé la maladie pendant la période 1980–2008. Tous ces patients ont été traités dans le complexe hospitalier de Navarre. Le suivi à long terme a été en moyenne de 10,1 ± 5,3 années. Les taux de HbA\textsubscript{1c} ont été obtenus au début de la maladie et annuellement. Nous avons utilisé des modèles mixtes additifs généralisés (GAMM) et des modèles linéaires, en choisissant d’utiliser les taux annuels d’HbA\textsubscript{1c} des patients comme variable réponse et le nombre d’années écoulées depuis le début de la maladie ainsi que l’âge des patients au début de la maladie comme covariables.

\textbf{Résultats.} – L’évolution du contrôle glycémique ne présente pas de linéarité et elle est différente dans tous les groupes d’âge. Les enfants atteignent leurs taux les plus élevés lors de l’adolescence. Les patients tombés malade entre les dix et les 15 ans, stabilisent leurs taux d’HbA\textsubscript{1c} après sept à huit ans. À noter que, quand la maladie apparaît chez les adultes ayant dépassé 45 ans, cette apparition est liée, notamment, à un mauvais contrôle.

\textbf{Conclusions.} – Une altération de non-linéarité des taux d’HbA\textsubscript{1c} peut être observée dès le diagnostic avec des différences significatives entre les différents groupes d’âge.

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\textbf{Mots clés :} Âge d’apparition; Contrôle glycémique; Diabète type 1

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1. Introduction

Type 1 diabetes (T1D) is usually characterized by an abrupt onset, a variable remission phase and evolution towards absolute insulin deficiency at 5–10 years from the time of diagnosis [1]. This means that metabolic control essentially depends on the best possible insulin replacement therapy regimen [2]. However, other components of treatment (diet, physical exercise, self-control and support from the therapeutic team) are also essential for achieving the proposed objectives [3,4]. Nevertheless, several additional factors may be associated with glycaemic control throughout the course of the disease. In children and adolescents under 20 years of age, it has been reported that the age of diagnosis, characteristics at onset, gender, the presence or not of pancreatic autoantibodies, body mass index (BMI), socioeconomic status, family structure, mean glycated haemoglobin (HbA1c) levels during the first year and duration of diabetes all influence HbA1c levels throughout the course of the disease [5–13]. Regarding age at diagnosis, multicentre data from Germany and Austria [7], France [8], Scotland [9], Denmark [10] and Sweden [11] all agree that, in children and adolescents, the greater the age, the poorer the glycaemic control during follow-up. However, to the best of our knowledge, there are no published reports providing data for adults on this issue.

Our objective was to determine the relationship between age at T1D onset and evolution of glycaemic control, as evaluated by HbA1c levels, not only in children but also in adults that would represent an advance over previously published findings. For this reason, the evolution of glycaemic control was analyzed in a cohort of 716 T1D patients followed for an average of 10 years between 1990 and 2010.

2. Patients and methods

In this observational retrospective follow-up study, the subjects were all patients with T1D onset between 1990 and 2008 who had been treated at the Navarre Hospital Complex. T1D was diagnosed according to the clinical criteria recommended by the World Health Organization (WHO) [14] that had also been previously validated by Molbak et al. [15]. Anti-GAD65 and anti-IA2 antibodies were analyzed by radioimmunoassay (RIA; Medipan Diagnostica, Selchow, Germany; reference ranges: anti-GAD65: 0–0.9 kU/L; anti-IA2: 0–1 kU/L). Positivity was detected in 83% of our patients. The intake for the Hospital Complex averaged 477,008 people during the study recruitment period.

According to the medical protocol followed at the Navarre Hospital Complex, all patients had at least one scheduled outpatients appointment per year. Data used in the study were obtained from the electronic health records of the Navarre Health Service. For all patients, the collected information included age, gender, physical characteristics and complete analytical data such as HbA1c at T1D onset. The type of insulin treatment (conventional, intensive with multiple doses or continuous subcutaneous insulin infusion) was chosen to achieve the best control for every patient at every moment. HbA1c levels were recorded at every appointment and when patients had more than one measurement available in a year, the arithmetic mean was computed. From 1990 to 1997, HbA1c was measured using various techniques (Abbott IMX, Ciba Corning Glycomat, and Merck and Menarini HPLC), but after 1997, HbA1c was determined in all patients by high-performance liquid chromatography (HPLC; Adams A1c HA, Menarini Diagnostics, Florence, Italy; reference range: 4.1–6.2%). In 2005, the Hospital Complex obtained level II laboratory certification of traceability to the Diabetes Control and Complications Trial (DCCT) reference method through the National Glycohemoglobin Standardization Program. Previous HbA1c determinations had also been standardized to the DCCT reference range (4.05–6.05%) [2].

2.1. Statistical methods

To assess the evolution of HbA1c since the onset of T1D, generalized additive mixed models (GAMMs) were used, as these are flexible models with no restrictions that can therefore properly reflect the true relationship between variables and also account for intraindividual correlation of the observations. The GAMMs were first fitted with the patients’ annual HbA1c levels as the response variable and two explanatory variables, the number of years since disease onset and age at onset, using different specifications. The model with the best goodness of fit was the one with plate regression splines for variables and their interaction terms, and an autoregressive temporal structure of order 1 (AR(1)) for error terms within each patient. The surface of the predicted HbA1c levels was then depicted in three-dimensional (3D) graphs. As a second step based on visual assessment of this graph, seven age groups were selected (0–4, 5–9, 10–14, 15–19, 20–29, 30–44 and 45–59 years) to fit the age-stratified GAMMs with time since disease onset as the only explanatory variable. Again, predictions made with these models were depicted in 3D graphs along with means and 95% confidence intervals (CI) of the observed levels of HbA1c for each year of follow-up. However, as the number of observations beyond 16 years of follow-up was relatively small and the precision of the estimates low, the study was limited to up to 15 years of follow-up from disease onset. GAMM diagnostics were performed using standard graphical methods for deviation residuals.

The study had the approval of the regional ethics review board of Navarre.

3. Results

The number of patients enrolled in the study was 716, with a total of 6115 HbA1c determinations and an overall mean (SD) follow-up duration of 10.1 (5.3) years. In the tenth year of follow-up, the number of observations in the 0–4, 5–9, 10–14, 15–19, 20–29, 30–44 and 45–59 years of age groups was 20, 32, 57, 42, 82, 48 and 12, respectively. The demographic and clinical characteristics of all patients are shown in Table 1.

Regarding the age at T1D onset and evolution of HbA1c, results of the GAMM predictions with age at onset and follow-up time as variables suggested that the worst evolution was in
patients who were aged < 20 years at disease onset—especially adolescents—and in adults aged > 40 years (Fig. 1).

Children with ages at onset between 0–4 years had higher levels in the first year of follow-up than those whose onset was between age 5–9 and 10–14 years. Their evolution, however, was similar to that of those aged 5–9 years from the third year of follow-up onwards. In contrast, the disease course of the group aged 10–14 years was markedly different. From a level in the first year similar to those aged 5–9 years, their mean values showed a sharp increase that plateaued at around 8.4% in the seventh year of follow-up; thereafter, a mild descent was observed (Fig. 2).

In patients with T1D onset after age 15, glycaemic control was worse in those aged ≥ 45 years than in those aged 15–19, 20–29 and 30–44. Patients with onsets at < 30 years of age showed a rapid rise in mean levels of HbA1c during the first 3 or 4 years, then reached an HbA1c plateau of just over 8% from the fifth year onwards. However, in the group aged 30–44 years, the rate of increase was not as quick in the first years of follow-up, but was more sustained over time. Patients with a later age of onset, between 45 and 59 years, started with a mean HbA1c level in the first year that was higher than those aged 30–34 years and then also experienced a rapid rise in HbA1c to surpass the 8% threshold from the third year of follow-up onwards, reaching values closer to 9% by the end of follow-up (Fig. 2).

No gender differences were observed in glycaemic control evolution in any of our age groups.

4. Discussion

The evolution of glycaemic control in patients with T1D was related to age at onset: the greater the age, the poorer the glycaemic control in both adolescents and adults.

However, some limitations of the present study were its retrospective nature and the small number of patients in some age groups during the later years of follow-up. Also, differences in the evolution of glycaemic control were described according to age at disease onset, with no assessment of the aetiological causes that might have explained the observed differences, such as socioeconomic status, compliance with treatment, antibody positivity and residual insulin, among others.

However, whatever the factors beyond age, our study nevertheless presented an accurate picture of the evolution of HbA1c in all age groups and, for the first time, in patients with T1D onset after age 15. This is valuable information that may help to improve the management of diabetic patients, as it is now clearer as to who needs closer care. Other strengths of this study are the long follow-up periods beginning at the time of onset and that all our hospital data were collected in a standardized form for the past 20 years, making them highly reliable.
Our study also noted how children with ages at onset of < 5 years initially showed poor glycaemic control. This was probably due to the less stringent HbA1c targets at this age in efforts to avoid hypoglycaemia. Although the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends the same target HbA1c (7.5%) in children independent of age [16], the American Diabetes Association (ADA) recommends a higher target (< 8.5%) for children aged 0–6 years [17], and paediatricians at our hospital have generally preferred to follow the ADA recommendations. On the other hand, impaired metabolic control during adolescence in patients with T1D is a frequent finding regardless of the type of insulin regimen used [5]. It has also been reported that patients with an onset close to adolescence and puberty (age 10–15 years) show poorer metabolic control in their disease evolution [4, 7, 9] than the rest of the children. Those years of adolescence with their conflicts and hormonal changes probably account for such behaviour [4–11, 18]. The Danish Registry quantifies impaired glycaemic control in relation to age at diagnosis as an HbA1c of 0.06% per year in patients aged 0 to 18 years [10].

It is more difficult to assess disease evolution in the different age groups at later ages. There are only two reports covering those aged 15–20 years at diagnosis [7, 8] and, in line with our present results, both agreed that their glycaemic control was worse than in children of younger ages, including those aged 10–15 years. They attributed this to differences in sensitivity to insulin and treatment adherence, as well as variations in the insulin dosis due to these factors.

T1D patients with an onset age between ages 30 and 44 worsened slowly, but consistently throughout the follow-up, and those with an age at onset ≥ 45 years had the worst control of all age groups during the entire follow-up. This is a remarkable finding that cannot be explained by differences in treatment regimens, as the therapeutic options for these patients were the same as those for younger patients. To the best of our knowledge, there are no published reports describing glycaemic control evolution in patients with T1D onset at ages > 20 years to allow comparison with our findings or to provide satisfactory explanations. Moreover, better, not worse, metabolic control might have been expected, as it has been reported that beta-cells are better preserved when T1D begins in adulthood [19]. Our present findings, however, do not support this idea in adults with later T1D onset.

Looking at the relationship between duration of diabetes and metabolic control, several national registries agree that control worsens as duration of diabetes increases [4–9]. The Danish Registry notes that the increase in HbA1c is 0.051% for each year of evolution, while the Swedish Registry’s rate is lower at 0.045%. Our present results reflect progressive impairment of metabolic control, but do not support a linear relationship with time. On the contrary, curves were noted for all age groups in which HbA1c levels increased more rapidly in the first years after onset to later reach a plateau.

In conclusion, healthcare professionals need to be aware that, in T1D patients, the age at onset influences the evolution of glycaemic control, and that closer monitoring and more intensive treatment may be warranted for certain age groups, especially adolescents and patients with onset at age ≥ 45 years.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.
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