Pre-pubertal onset of type 1 diabetes and appearance of retinopathy

M Porta¹, P Dalmasso², G Grassi¹, S Marena¹, M Maurino¹, P Passera¹, M Trento¹

SUMMARY

Objectives: It was suggested that the years of diabetes preceding puberty may not contribute to the development of retinopathy but evidence for this is conflicting. To verify the influence of pre-pubertal diabetes, we compared the correlations between prevalence of retinopathy and diabetes duration in patients who developed type 1 diabetes before and after puberty.

Methods: Six hundred and twenty-eight patients with diabetes onset at age ≤ 29, on insulin treatment and aged ≤ 60 at the time of screening for retinopathy were considered retrospectively. Pre-pubertal age was defined as 0-12 in males and 0-11 in females. Two hundred patients had developed diabetes before puberty and 428 after puberty. Screening was by ophthalmoscopy + 35 mm photography or digital photography.

Results: Prevalence of retinopathy was lower among patients with pre-pubertal onset and diabetes durations 10-14 and 15-19 years (p = 0.006 and p = 0.003, respectively) but prevalence rates became similar after 20 yrs duration.

Conclusion: That retinopathy is infrequent and mild during childhood, is probably due to the short duration of diabetes rather than a specific protective effect of pre-puberty. After 20 years’ duration, however, the prevalence of retinopathy is no longer influenced by age at onset, suggesting that, in the longer term, pre-pubertal years do contribute to the onset of retinopathy.

Key-words: Diabetes mellitus - Type 1 diabetes - Diabetic retinopathy - Pre-pubertal diabetes - Screening.

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RéSUMÉ

Apparition prépubertaire du diabète de type 1 et développement de la rétinopathie

Objectifs: Il a été suggéré que les années de diabète précédant la puberté pouvaient ne pas contribuer au développement de la rétinopathie, mais les preuves en sont conflictuelles. Pour vérifier l’influence du diabète prépubertaire, nous avons comparé les corrélations entre la prévalence de la rétinopathie et la durée du diabète chez des patients ayant développé un diabète de type 1 avant et après la puberté.

Méthodes: Six cent vingt-huit patients devenus diabétiques à l’âge de ≤ 29, sous insulinothérapie et âgés de ≤ 60 au moment du dépistage de la rétinopathie ont été étudiés rétrospectivement. L’âge prépubertaire était défini comme 0-12 chez les hommes et 0-11 chez les filles. Deux cents patients ont développé un diabète avant la puberté et 428 après puberté. Le dépistage s’est fait par ophtalmoscopie + photographie 35 mm ou photographie numérique.

Résultats: La prévalence de la rétinopathie était plus basse chez les patients avec début pré-pubertaire et durée de diabète de 10-14 ans et 15-19 ans (p = 0,006 et p = 0,003, respectivement) mais les taux de prévalence sont devenus similaires après une durée de 20 ans.

Conclusion: Le fait que la rétinopathie soit rare et modérée au cours de l’enfance est probablement liée à la courte ancienneté du diabète plutôt qu’à un effet protecteur spécifique de la pré-puberté. Après une ancienneté de 20 ans, la prévalence de la rétinopathie n’est plus influencée par l’âge au début, suggérant qu’à plus long terme, les années pré-pubertaires contribuent à l’apparition de la rétinopathie.

Mots-clés: Diabète sucré - Diabète de type 1 - Rétinopathie diabétique - Diabète pré-pubertaire - Dépistage.
Diabetic retinopathy (DR) develops in nearly all patients with type 1 diabetes mellitus (T1DM), duration of disease and metabolic control being the most important factors associated with its appearance and progression [1, 2]. DR is infrequent in children and it was suggested that the years of diabetes preceding puberty may not contribute to the development of microvascular complications [3]. Evidence for such period of grace is conflicting, though, with some authors supporting the notion that countdown may begin only at or after puberty [4-7] and others reporting that pre-pubertal diabetes does play a role in the onset of complications [8-10]. Differences in approach and in the populations studied may account for such inconsistencies.

To verify the influence of pre-pubertal diabetes in the onset of retinopathy, we assessed the data collected in all patients with T1DM screened for DR in our Centre between 1992 and 2002. The correlations between prevalence of DR and duration of diabetes were compared in patients who had developed diabetes before and after puberty.

**Patients and methods**

**Patients**

Patients with diabetes onset at age ≤ 29, on insulin treatment and aged 60 or younger at the time of screening were extracted from a database of 5510 patients who had been screened at least once in our Diabetic Retinopathy Centre. Patients on diet only (n = 18), oral hypoglycaemic agents (n = 24) or oral agents associated with insulin (n = 21) were excluded. In total, 628 patients were considered. Pre-pubertal age was defined as 0-12 in males and 0-11 in females. Two hundred patients had become diabetic before puberty and the remainder 428 later in their life. The clinical characteristics of the patients are summarised in Table I. The patients with pre-pubertal onset of T1DM were younger (p < 0.0001) and had longer duration of disease (p < 0.0001) at the time of screening. There were no differences in the prevalence of any DR or proliferative DR.

**Retinopathy assessment**

DR had been classified according to the Diabetic Retinopathy Working Party recommendations for screening [11]. For the purpose of this study, DR was classified as absent if no lesions were observed. Presence of at least one individual red lesion (dot or larger) or bright lesion (hard exudate, cotton wool spot) indicated the presence of DR. New vessels and/or fibrous tissue and/or advanced diabetic eye disease and/or previous panretinal photocoagulation indicated proliferative DR. The diagnosis in the worse affected eye was considered for each patient.

Screening had been performed by direct ophthalmoscopy, indirect ophthalmoscopy and color photography (2 × 45° fields, one centred on the macula and one nasal including the optic disc) on 35 mm slide film (Kodak Elite 200 ASA), using Kowa Pro-I and Kowa Pro-II fundus cameras (275 patients) until May 2000. As of June 2000, screening was by non mydriatic digital fundus photography (Canon NM45CR, Kawasaki, Japan) of the same 2x 45° fields (353 patients) and images were captured and assessed by the Eye-Cap software (Haag-Streit, Koeniz, Switzerland). In both cases, photographic fields were according to the above screening guidelines recommendations [11].

No formal trial was run to compare ophthalmoscopy + 35 mm photography versus digital photography in our setting. Hence, to assess the influence of the different screening methods on the outcome of DR grading, two approaches were taken: 1) all consecutive diagnoses of patients screened in our Centre for the first time 9 months before changing to digital photography (n = 544) were compared with those of all patients first screened over the 9 months after changeover (n = 622), and 2) the diagnoses of 332 patients who had been screened during the 9 months before and again during the 9 months after changeover were compared. No significant differences were observed between the detection rates of DR,

<table>
<thead>
<tr>
<th></th>
<th>Pre-pubertal (n = 200)</th>
<th>Post-pubertal (n = 428)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M)</td>
<td>104 (52.0%)</td>
<td>226 (52.8%)</td>
<td>0.851</td>
</tr>
<tr>
<td>Age at screening</td>
<td>26.3 ± 8.0 (9-48)</td>
<td>36.8 ± 10.5 (14-60)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% C.I.: 8.9-11.9)</td>
<td></td>
</tr>
<tr>
<td>Age at diabetes onset</td>
<td>7.7 ± 3.1 (1-12)</td>
<td>20.5 ± 5.3 (12-29)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% C.I.: 12.2-13.5)</td>
<td></td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>18.6 ± 8.1 (1-39)</td>
<td>16.2 ± 9.4 (0-38)</td>
<td>0.0008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% C.I.: 1.0-3.9)</td>
<td></td>
</tr>
<tr>
<td>RD (%)</td>
<td>117 (58.5)</td>
<td>264 (61.7)</td>
<td>0.447</td>
</tr>
<tr>
<td>Proliferative RD</td>
<td>27 (13.5)</td>
<td>54 (12.6)</td>
<td>0.636</td>
</tr>
</tbody>
</table>

suggesting consistency of the diagnoses obtained with the two methods (data unpublished).

Statistics
The patients, classified by age at the time of diabetes diagnosis, as described above, and presence of DR at the time of first screening (Table I), were stratified by 5-year periods of diabetes duration at the time of screening. Two-sample Student’s t test and chi-square test were utilized for continuous and categorical data, respectively. Prevalence Rate Ratios and 95% confidence intervals were computed to compare prevalences of DR between groups. Statistical analysis was carried out using the PC program Stata Statistical Software (Release 8.0 College Station, TX; Stata Corporation, 2002). Significance was set at 0.05.

Results
Table I shows the prevalence of all DR at first screening, subdivided by 5-yr categories of diabetes duration, among patients with onset of T1DM before or after puberty. There were no statistically significant differences during the first decade. When duration of diabetes was 10-14 and 15-19 years, the prevalences of DR were lower among the persons with pre-pubertal diabetes (p = 0.006 and p = 0.003, respectively). This difference disappeared after 20 yrs of duration, as prevalence rates became similar in the 2 groups.

Discussion
Kostraba et al. [3] compared prevalences of DR against duration of diabetes in people with pre- and post-pubertal onset of diabetes, using the same definition as in this paper, and showed that the curves became superimposable when only post-pubertal durations were considered. However, not all subsequent reports supported their conclusion that the years with diabetes before puberty do not contribute to the development of retinopathy [8-10]. Our study represents the larger case series so far addressing this problem and supports the hypothesis that DR may take longer to develop in patients who become diabetic before puberty. On the other hand, after 20 years’ duration, the prevalence of DR was no longer influenced by age at onset, suggesting that, in the longer term, pre-pubertal years, though delaying its appearance, do add up for the onset of retinopathy. This slow-down and catch-up effect of pre-pubertal onset suggests that differences in diabetes duration among the case series studied by other authors may account for their conflicting reports.

Klein et al. [4] retrospectively evaluated 200 insulin treated people with diabetes onset before age 30 and current age < 26, comparing patients with durations of disease that were similar but entirely contained within the pre-pubertal years (set at ≤ 12 for both sexes) and post-puberty, set at age 13-26. As expected, the prevalence of retinopathy was lower before (9.0%) than after puberty (33.6%) and the authors concluded that duration of diabetes was more strongly associated with DR in post-pubertal years. Kullberg et al. [5] studied 390 patients with T1DM of 6-13 years duration and observed higher prevalence of retinopathy, independent of duration and metabolic control, among patients with post-pubertal diabetes onset. Palmberg et al. [6], also reporting on a population of 461 insulin-requiring patients with diabetes onset before age 30, found that, after 4-6 years duration, DR prevalence was 13% among patients with diabetes onset before age 10 and 35% among those with later onset. Frank et al. [7] reported that, after 7-9 years duration, DR prevalence was 36% in patients with onset below age 7 and 66% in those with later onset.

On the other hand, Kalter-Leibovici et al. [8], studying 333 Jewish Israeli T1DM patients with duration 1.6-30 years, found retinopathy only during or after puberty but suggested that pre-pubertal years contribute to DR in the long run, independently of metabolic control. Donaghue et al. [9] found similar prevalences of retinopathy in 38 prepubertal and 140 pubertal patients of the same age group (10-14 years), 27% and 29% respectively, although the former had significantly longer duration of diabetes (7.55 vs 6.1). In a

<table>
<thead>
<tr>
<th>Duration of diabetes</th>
<th>Pre-pubertal N/tot (%)</th>
<th>Post-pubertal N/tot (%)</th>
<th>PRR (95% CI)</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 yr (n = 46)</td>
<td>0/1 (0.0%)</td>
<td>6/45 (13.3%)</td>
<td>—</td>
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</tr>
<tr>
<td>5-9 yr (n = 96)</td>
<td>6/25 (24.0%)</td>
<td>21/71 (29.6%)</td>
<td>1.23 (0.56-2.70)</td>
<td>0.594</td>
</tr>
<tr>
<td>10-14 yr (n = 123)</td>
<td>14/46 (30.4%)</td>
<td>43/77 (55.8%)</td>
<td>1.83 (1.14-2.97)</td>
<td>0.006</td>
</tr>
<tr>
<td>15-19 (n = 121)</td>
<td>27/47 (57.4%)</td>
<td>61/74 (82.4%)</td>
<td>1.43 (1.10-1.88)</td>
<td>0.003</td>
</tr>
<tr>
<td>20-24 (n = 104)</td>
<td>28/33 (84.8%)</td>
<td>57/71 (80.3%)</td>
<td>0.95 (0.79-1.14)</td>
<td>0.575</td>
</tr>
<tr>
<td>25-29 (n = 68)</td>
<td>21/23 (91.3%)</td>
<td>35/45 (77.8%)</td>
<td>0.85 (0.70-1.04)</td>
<td>0.167</td>
</tr>
<tr>
<td>30-34 (n = 51)</td>
<td>15/19 (78.9%)</td>
<td>28/32 (87.5%)</td>
<td>1.11 (0.85-1.45)</td>
<td>0.417</td>
</tr>
<tr>
<td>35-39 (n = 19)</td>
<td>6/6 (100.0%)</td>
<td>13/13 (100.0%)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

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second group of 193 adolescents aged 15-22, also with prepubertal onset but longer duration of diabetes (6-0-13.5 years), they found that the years between onset of diabetes and gonadalarche were an independent predictor of DR. Lobefalo et al. [10] evaluated 246 children and adolescents of age 0.5-26.9 and duration 0.1-19.8 years. Only 2 prepubertal patients had retinopathy but the length of pre-pubertal diabetes correlated significantly with presence and severity of DR, independently of metabolic control. In particular, longer pre-pubertal diabetes was associated with severe non proliferative DR.

Finally, in the EURODIAB Prospective Complications Study, we found that onset of diabetes before age 13 was an independent risk factor for the progression of existing DR to proliferative DR in 157 patients out of a cohort of 1249 T1DM patients with diabetes duration 13 ± 8 years [12]. However, there were too few people with proliferative DR in the present cross-sectional study to support that earlier observation.

Data on metabolic control and exact determination of pubertal age were not available for this study. Metabolic control is an important determinant of the onset and progression of retinopathy, as conclusively demonstrated by the Diabetes Control and Complications Trial [13]. Although some of the above studies had concluded that the effect of pre-pubertal diabetes on DR is independent of metabolic control [5, 8-10, 12], it cannot be ruled out that differences in HbA1c levels might have influenced the course of retinopathy in our patients. However, screening in our Centre is routinely provided as a service to many clinics, using different laboratories, and HbA1c is neither measured routinely nor can be checked reliably from records at the time of eye examination. Even more to the point, retrospective data on metabolic control could not be obtained reliably from our patients. With regard to determination of pubarche, other authors have arbitrarily set ages of puberty at 12 for males and 11 for females [3] or 12 for both sexes in the absence of individual staging data [4], based upon published averages [14].

In conclusion, that DR is infrequent and generally mild during childhood [6, 15] is probably due more to the relatively short duration of diabetes than to a specific “protective” effect of the pre-pubertal state. Puberty, possibly by worsening metabolic control [10, 16] and/or through the influence of Growth Hormone and Insulin-Like Growth Factor-1 [8], may have an accelerating effect on DR. In the long run, pre-pubertal years with diabetes are likely to matter and, according to those authors who studied patients with long enough disease duration and took into account the roles of metabolic control and other risk factors for diabetic retinopathy [10, 12], might even become an independent predictor for the development of eye complications.

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References


