Age at Onset and the Risk of Proliferative Retinopathy in Type 1 Egyptian Diabetic Patients

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Abstract

Background: Growing evidence suggests that the age at onset of diabetes may influence the development of proliferative retinopathy in type 1 diabetic patients.

Aim of Work: This study was designed to evaluate how the age at onset of type 1 diabetes influences the long-term risk of proliferative retinopathy in Egyptian patients with type 1 diabetes.

Subjects and Methods: This study included 115 type 1 Egyptian diabetic patients (64 females, 51 males) attending the outpatient clinics of NIDE and 50 normal controls. Blood pressure, waist circumference, BMI, FBS, HBA1c, lipid profile, urea, creatinine, uric acid and microalbuminurea were measured. Fundus examination, chest X-ray and ECG were performed for all subjects and echocardiography was done when indicated.

Results: 46.1% of patients with type 1 diabetes included in the study had no diabetic retinopathy. Non proliferative diabetic retinopathy was found in 32.2% of patients, while proliferative retinopathy was found in 21.7% of patients. There was a highly significant statistical difference among the studied patients regarding systolic and diastolic blood pressure, fasting plasma glucose, HBA1c, microalbuminurea and duration of diabetes being higher in patients having proliferative retinopathy, than patients having non proliferative retinopathy, being lower in patients with no diabetic retinopathy, when we compared patients included in the study according to the age at onset of type 1 diabetes; there was a high statistical difference among the studied patients being higher in patients with age at onset between 5 and 14 years of age (27.5%) than patients with age at onset >14 years (15.1%), being lower in patients with age at onset between 0 and 4 years (7.7%).

Conclusion: The highest risk was in age at onset 5-14 years, whereas the lowest risk was in age at onset 0-4 years.

Key Words: Type-1 diabetes – Microvascular complications – Proliferative retinopathy.

Introduction

THE incidence of type 1 diabetes, which is one of the most common metabolic disorders in children, is on the rise (Harjutsalo et al., 2008). Diabetic retinopathy is an important microvascular complication in patients with type 1 diabetes. Almost all patients with type 1 diabetes show signs of retinopathy after 20 years of diabetes. When retinopathy worsens, visual loss eventually threatens 5-10% of the patients (Klein, 1987). Proliferative retinopathy is the most severe form of retinopathy, and most of the patients with this complication become blind after 5-10 years if not treated (Deckert et al., 1967). After 15-25 years of diabetes, the prevalence of proliferative retinopathy varies between 13 and 50% in patients with type 1 diabetes (Klein, 1987). There are several risk factors for the development of diabetic retinopathy including; duration of diabetes, glycemic control, male sex and high blood pressure (Rossing et al., 1998). Poor glycemic control increases both the incidence and the progression of retinopathy. Genetic factors are also likely to play a major role (The Diabetes Control and Complications Trial Group, 2000). The age at onset of diabetes may predispose certain patients to diabetic retinopathy (Donaghue et al., 2003).

Aim of work:

Our aim was to evaluate how the age at onset of type 1 diabetes influences the long-term risk of proliferative retinopathy in patients with type 1 diabetes.

Subjects and Methods

The study was conducted on 115 previously diagnosed type 1 diabetic patients (64 females, 51 males) with age ranging from 11-54 years old and and 50 age and sex matched normal healthy con-
trols. All patients were selected from the outpatient clinics of National Institute of Diabetes and Endocrinology. Type-1 DM was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2006). The normal control subjects, with age and sex matching to patients with type 1 diabetes, were clinically free from any recognizable diseases. They were not receiving any medications and represented the control group.

Demographic data was recorded for each subject using self-made questionnaire. Approval had been taken from the research ethics committee of General Organization of Teaching Hospitals and Institutes. An informed consent was obtained from all patients and normal control subjects that described the aim of the study and the procedures that would be required from them. Samples were analyzed at the Department of Clinical Chemistry, National Institute of Diabetes and Endocrinology.

Blood pressure (mmHg) was measured once after 10min rest. Weight (Kg) and height (m) were measured with the subjects wearing light clothes and without shoes. The waist circumference (cm) was measured at the level of the umbilicus. BMI was calculated as weight/ hight $^2$ (Kg/m$^2$) (Garrow and Webster, 1985).

Ophthalmoscopic examinations were carried out in all patients by experienced ophthalmologists searching for pathological changes including; dot and blot haemorrhages, and hard exudates in background retinopathy, cotton wool spots, venous beading, venous loops and intraretinal microvascular abnormalities in pre-proliferative retinopathy, new blood vessel formation, preterinal haemorrhage and vitreous haemorrhage in proliferative retinopathy, retinal fibrosis and traction retinal detachment in advanced cases.

Chest X-ray and ECG were performed for all subjects and echocardiography was done when indicated.

Blood samples were taken on EDTA for qualitative colorimetric determination of HbA1c level using commercial kit (Stanbio Lab, Inc. USA). Hemolysed samples were excluded. Serum fasting glucose concentration was assayed at once by enzymatic method according to Barham and Trinder (1972) using Synchron CX5 Beckman, blood chemistry analyzer, USA. Total cholesterol was determined by the enzymatic method (Roeschelau et al., 1974). Triacylglycerol was assayed by peroxidase-coupled method (McGowan et al., 1983). HDL-c was measured by enzymatic method after precipitation of other lipoproteins with MgCl$_2$ and dextran sulphate (Finley et al., 1978), LDL-c was calculated according to Friedewald et al., (1972). The above lipid profile was measured using Dimension RxL Max autoanalyzer (DADE BEHRING).

Statistical analysis:

Data was expressed as the mean ± S.D. Statistical analysis was performed with Statistical Package for the Social Science for Windows (SPSS, version 10.0, 1999, Chicago, IL, USA). One-way analysis of variance (ANOVA) was used to compare the variables between groups.

Results

The baseline characteristics of subjects included in the study are shown in Table (1):

- The study comprised 115 type 1 diabetics (64 females and 41 males) and 50 normal controls. The mean age of patients studied was 29.33 ± 9.18, the mean duration of diabetes was 22.96 ± 12.15 years and the mean age at onset of type 1 diabetes was 18.2 ± 8.7 years.

- Patients were then divided into three groups according to presence or absence of diabetic retinopathy:
  - Group A: Included 53 type 1 diabetic patients with no diabetic retinopathy (46.1%).
  - Group B: Included 37 patients with non proliferative diabetic retinopathy (32.2%).
  - Group C: Included 25 patients with proliferative diabetic retinopathy (21.7%).

When we compared the three groups regarding other parameters:

As regards systolic blood pressure, there was a highly significant statistical difference among the three studied groups being higher in group C (m=131.5 ± 11.6), than group B (m=128.4 ± 12.1) than group A (m=126.1 ± 10.9) ($p$-value <0.01) as shown in Table (2) and Fig. (2).

Regarding diastolic blood pressure, there was also a highly significant statistical difference among the three studied groups being higher in group C (m=78.3 ± 8.9), than group B (m=76.9 ± 7.5) than group A (m=73.4 ± 5.1) ($p$-value <0.01) as shown in Table (2) and Fig. (2).

As regards fasting plasma glucose, there was a highly significant statistical difference among the three studied groups being higher in group C (m=142.5 ± 38.6), than group B (m=133.4 ± 23.1) than group A (m=116.1 ± 12.9) ($p$-value <0.01) as shown in Table (2) and Fig. (3).
Table (1): The baseline characteristics of patients included in the study (n=115).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11</td>
<td>54</td>
<td>29.33</td>
<td>9.18</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>1</td>
<td>32</td>
<td>22.96</td>
<td>12.15</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>2</td>
<td>35</td>
<td>18.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>63</td>
<td>111</td>
<td>79.5</td>
<td>12.3</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>18.7</td>
<td>41.6</td>
<td>27.25</td>
<td>5.6</td>
</tr>
<tr>
<td>Systolic BP (Sitting) (mmHg)</td>
<td>90</td>
<td>185</td>
<td>128.4</td>
<td>16.4</td>
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<tr>
<td>Diastolic BP (Sitting) (mmHg)</td>
<td>60</td>
<td>110</td>
<td>77</td>
<td>9</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>101</td>
<td>175</td>
<td>131.4</td>
<td>16.6</td>
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<tr>
<td>HbA1c (%)</td>
<td>6.4</td>
<td>13.2</td>
<td>8.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>76</td>
<td>214</td>
<td>177.8</td>
<td>15.6</td>
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<tr>
<td>TG (mg/dl)</td>
<td>80</td>
<td>157</td>
<td>126.9</td>
<td>14.8</td>
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<tr>
<td>HDL-c (mg/dl)</td>
<td>36</td>
<td>55</td>
<td>43.1</td>
<td>4.3</td>
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<tr>
<td>LDL-c (mg/dl)</td>
<td>80</td>
<td>135</td>
<td>103.8</td>
<td>14.1</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>0.7</td>
<td>1.6</td>
<td>1.12</td>
<td>0.56</td>
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<tr>
<td>Uric acid (mg/dl)</td>
<td>4.5</td>
<td>8.3</td>
<td>5.8</td>
<td>3.61</td>
</tr>
<tr>
<td>Microalbuminuria (mg/24 hr)</td>
<td>11</td>
<td>265</td>
<td>110.4</td>
<td>66.2</td>
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</table>

Table (2): Comparison between the three groups included in the study.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A n=53</th>
<th>Group B n=37</th>
<th>Group C n=25</th>
<th>ANOVA</th>
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</thead>
<tbody>
<tr>
<td>Systolic BP (Sitting) (mmHg)</td>
<td>m=126.1±10.9</td>
<td>m=128.4±12.1</td>
<td>m=131.5±36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic BP (Sitting) (mmHg)</td>
<td>m=73.4±5.1</td>
<td>m=76.9±7.5</td>
<td>m=78.3±8.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>m=116.1±12.9</td>
<td>m=133.4±23.1</td>
<td>m=142.5±38.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>m=7.9±0.6</td>
<td>m=8.2±0.9</td>
<td>m=8.5±0.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Microalbuminuria (mg/24 hr)</td>
<td>m=68.9±44.5</td>
<td>m=104.7±80.2</td>
<td>m=134.9±54.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Fig. (1): Distribution of diabetic retinopathy in patients included in the study.
No.D.Ret.: No diabetic retinopathy.
Non Pr.D.Ret.: Non proliferative diabetic retinopathy.

Fig. (2): Comparison between the studied groups regarding systolic and diastolic blood pressure.
Group A: No diabetic retinopathy.
Group B: Non proliferative diabetic retinopathy.
Group C: Proliferative diabetic retinopathy.

Fig. (3): Comparison between the studied groups regarding fasting plasma glucose.
Group A: No diabetic retinopathy.
Group B: Non proliferative diabetic retinopathy.
Group C: Proliferative diabetic retinopathy.
Regarding HBA1c, there was also a highly significant statistical difference among the three studied groups being higher in group C (m=8.5 ± 0.8), than group B (m=8.2 ±0.9) than group A (m 7.9±0.6) (p-value <0.01) as shown in Table (2) and Fig. (4).

As regards microalbuminurea, there was a highly significant statistical difference among the three studied groups being higher in group C (m=134.9 ±54.3), than group B (m=104.7 ±80.2) than group A (m=68.9±44.5) (p-value <0.01) as shown in Table (2) and Fig. (5).

Patients were then divided according the duration of type 1 diabetes into five groups. The first is group A of patients with duration of diabetes 1 <5 years, the second is group B patients with duration of diabetes 5 <10 years, third is group C whose duration of diabetes 10 <15 years, fourth is group D with duration of diabetes 15 <20 years and fifth is group E of patients whose duration of diabetes ≥20 years.

- On comparing the five groups regarding presence or absence of proliferative diabetic retinopathy; there was a high statistical difference among the studied groups being higher in group E (34.7%), than group D (31.8%), than group C (23.1%), than group B (10.3%), than group A (6.7%) as shown in Table (3) and Fig. (6).

Patients were then divided into three groups according to the age at onset of type 1 diabetes:

Group 1: Included 13 patients with age at onset of type 1 diabetes between 0 and 4 years of age (11%).

Group 2: Included 69 patients with age at onset of type 1 diabetes between 5 and 14 years of age (60%).

Group 3: Included 33 patients with age at onset of type 1 diabetes ≥14 years of age (29%).

- On comparing the three groups according to presence or absence of proliferative diabetic retinopathy; there was a high statistical difference
among the studied groups being higher in group 2 (27.5%) than group 3 (15.1%), than group 1 (7.7%) as shown in Table (4) and Fig. (7).

Table (4): Comparison between the studied groups regarding proliferative diabetic retinopathy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative diabetic</td>
<td>7.7%</td>
<td>27.5%</td>
<td>15.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>retinopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. (7): Comparison between the studied groups regarding proliferative diabetic retinopathy and age at onset of diabetes.

Group 1: Patients with age at onset of diabetes <4 years.
Group 2: Patients with age at onset of diabetes 5-14 years.
Group 3: Patients with age at onset of diabetes >14 years.

Discussion

Type 1 diabetes mellitus is one of the most common metabolic disorders in children. The prevalence of type 1 diabetes mellitus increases with age, and the overall incidence of the disease may be increasing [10]. Proliferative retinopathy is a severe microvascular complication in patients with type 1 diabetes and is considered a leading cause of blindness in diabetics [11].

Our study showed that proliferative retinopathy was found in 21.7% of Egyptian type 1 diabetic patients. Non proliferative diabetic retinopathy was found in 32.2% of patients, while 46.1% of patients with type 1 diabetes included in the study had no diabetic retinopathy.

Several epidemiologic studies have evaluated risk factors for development of diabetic retinopathy, such as patient age, duration of diabetes, metabolic control, and control of blood pressure [20].

The results of our study have shown that type 1 diabetic patients with proliferative diabetic retinopathy had higher systolic and diastolic blood pressures, than patients having non proliferative retinopathy, being lower in patients with no diabetic retinopathy. These results are in agreement with those of Klein et al., [13] who found that better blood pressure control was beneficial in reducing the incidence of diabetic proliferative retinopathy.

There was also a highly significant statistical difference between the three groups as regards fasting blood sugar and HBA1c. These results reinforce the arguments of previous studies by others for tight control of hypertension and hyperglycaemia. Several previous reports have suggested that poor metabolic control might be involved in haemodynamic changes of retinal circulation, and thereby lead to maculopathy. It is conceivable that increases in the retinal blood flow could play a part in haemodynamic changes of increased intracapillary retinal pressure and shear stress, thereby leading to diabetic maculopathy [17,9].

In our results, proliferative retinopathy was higher in patients with longer duration of diabetes. These results are in line with the results of Rossing [19].

We also found a highly significant statistical difference among the studied patients regarding microalbuminuria being higher in patients with proliferative retinopathy than those with non proliferative retinopathy than those with no retinopathy. This is in agreement with Klein [11].

Our results also showed that the highest proportion of type 1 diabetic patients with proliferative retinopathy was found in age-at-onset group 5-14 years (27.5%), the second highest in age-at-onset group ≥15 years of (15.1 %), and the lowest in age-at-onset group 0-4 years (7.7%). This observation is in agreement with earlier findings by Kustaa et al., [15] who concluded that age at onset significantly modifies the long-term risk of proliferative retinopathy in type 1 diabetes and the highest risk was found in age-at-onset group 5-15 years, whereas the lowest risk was found in age-at-onset group 15-40 years.

Therefore, the aim of this study was to elucidate how the age at onset of type 1 diabetes influences the long-term risk of proliferative retinopathy in patients with type 1 diabetes.

References


