

# ABNORMALITIES OF ERYTHROCYTE FILTRABILITY IN DIABETIC MICROANGIOPATHY

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## SUMMARY

In 30 ambulatory patients (14 men and 16 women), with diabetes mellitus (7 of type I and 23 of type II) of variable duration and with ages averaging 52.2 years, the degree of retinal microangiopathy was assessed along with the erythrocyte filtration rate (FR) and the percentage of glycosylated hemoglobin (HbA<sub>1c</sub>).

The FR was significantly ( $p < 0.001$ ) lower among the diabetics ( $12.09 \pm 2.71 \mu\text{l sec}^{-1}$ ) than in the controls ( $15.80 \pm 1.75$ ). On the other hand, the level of HbA<sub>1c</sub> was significantly ( $p < 0.001$ ) higher in the diabetics ( $12.26 \pm 3.83$ ) than in the control group ( $7.97 \pm 1.47$ ). The severity of the diabetic retinopathy was estimated as follows: degree I in 10 patients, degree II in 10 patients also, degree III in 4 patients and no abnormalities in 6 individuals.

Among the patients the retinal lesions were significantly correlated ( $r = -0.46$ ,  $p < 0.01$ ) with the value of FR but were not affected by the level of HbA<sub>1c</sub>. No significant correlation was detected between FR and HbA<sub>1c</sub>.

Our results suggest that, as a consequence of the metabolic abnormalities present in the diabetics, the non-enzymatic glycosylation of hemoglobin A is increased.

The rise of erythrocyte rigidity, while hampering blood-flow through already injured microvessels, could contribute to the development of retinal abnormalities irrespective of the HbA<sub>1c</sub> level. Consequently, the abnormalities in the retinal microcirculation could, directly or indirectly, influence red cell filtrability, worsening the rheologic behaviour in the local microvessels.

## INTRODUCTION

Macro- and microvascular abnormalities are frequently reported in association to diabetes.<sup>1,2</sup> The retinopathy is part of the systemic microangiopathy and is frequently observed in long-established diabetes.<sup>2,3</sup> Apparently, the retinal lesions observed in diabetes stand for similar abnormalities in other tissues. Among other important factors, the development of the microangiopathy seems to depend on the date of onset of the disease and the degree of metabolic control.<sup>2</sup>

Several rheologic abnormalities have been detected in diabetes. Former works suggest that these hemorheologic disturbances contribute to the development and/or progress of diabetic vasculopathy.<sup>4-6</sup>

This work was meant to study the relationship between the changes of erythrocyte filtrability and the presence of retinal microangiopathy in a group of adult diabetic patients either insulin-dependent or not.

## MATERIAL AND METHODS

Thirty ambulatory diabetic patients and 34 healthy controls consented to take part in this study. The group of diabetics, made up by 14 men and 16 women with 52.2 years of average age and whose disease already coursed for a variable time had no ketoacidosis or other pathologic complications. The control group included 16 men and 18 women of comparable age (average 54.6 years) without family history of diabetes, retinal vascular pathology or excessive weight.

Besides the physical examination, ECG and routine hematologic and biochemical analysis, in all the individuals (diabetic patients and controls) signs of retinal microangiopathy were searched for.

Based on the separate observations of two ophthalmologists a protocol was worked up including the assessment of all visual functions and eye structures taking particular notice of the ocular fundi (reflection, biomicroscopy, tonometry and funduscopy).

TABLE 1 — Values (mean  $\pm$  standard deviation) of plasma glucose, total glycosylated hemoglobin (HbA<sub>1</sub>) and red cell filtration rate (FR) in 30 diabetics and 34 normal controls.

Groups	Glucose (mmol/l)	HbA <sub>1</sub> (%)	FR $\mu$ l. seg <sup>-1</sup>
Diabetics	11.82 $\pm$ 3.48	12.26 $\pm$ 3.83	12.09 $\pm$ 2.71
<i>p</i> values	< 0.001	< 0.001	< 0.001
Controls	3.88 $\pm$ 0.67	7.97 $\pm$ 1.47	15.80 $\pm$ 1.75

The study was completed with fluorescein angiography (50 ml, 20% sodium fluorescein injected in veins of the forearm) to assess the degree of microvascular involvement of the retina.

The diabetic patients were classified according to the presence and extent of retinal abnormalities; viz: Grade 0 — no retinopathy (total 6); grade I — background retinopathy (total 10); grade II — retinopathy showing signs of ischemia (total 10); grade III — proliferative retinopathy (total 4).

A fasting venous blood sample was collected from each individual in order to assay plasma glucose (by glucose-oxidase method, Kit n.º 510 Sigma), glycosylated hemoglobin (HbA<sub>1</sub>)<sup>7</sup> and red cell filtration rate (FR, corrected by hematocrit).<sup>8</sup>

## RESULTS AND DISCUSSION

The HbA<sub>1</sub> is considered to be a better marker of the metabolic control of diabetes than the glucose blood levels.<sup>9, 10</sup> As opposed to the daily fluctuations of glycemia, the HbA<sub>1</sub> values tend to suffer deep variations after a couple of weeks of therapy or following severe drawback in the clinical course of the disease.<sup>11, 12</sup> However, according to the values obtained for both these parameters (Table I) in the present work, the diabetic patients seemed to be in a rather poor metabolic condition. The very significant rise of HbA<sub>1</sub> was clearly affected ( $r = 0.43$ ,  $p < 0.05$ ) by simultaneous fluctuations of glucose level. None of these parameters was either dependent on age or time of onset of the disease nor did they interfere with the severity of retinal abnormalities (detected in 80% of the patients), which is in accordance with the sluggishness of evolution of diabetic microangiopathy.<sup>3</sup> Retinal lesions have been attributed, among other causes, to the hypoxia associated to metabolic imbalance.<sup>2, 13</sup> Apparently, diabetes affects, by itself, the capacity of tissue oxygenation, which would be related with the overproduction of a hemoglobin fraction with an increased oxygen affinity (HbA<sub>1</sub>).<sup>14</sup>

Tissue oxygenation may, however, be affected by other factors. Besides oxygen affinity of the hemoglobin, local changes of bloodflow may also significantly contribute to the reduction of oxygen delivery to peripheral tissues, favouring the development of microangiopathy of which retinal abnormalities are an outstanding component.<sup>15, 16</sup> The well known microrheologic disorders found in diabetes,<sup>4, 6, 16</sup> particularly the increased red cell rigidity (Table I), would contribute to bloodflow stagnation and, accordingly, to local hypoxia. The development of retinal lesions would be, therefore, partly ascribed to episodes of hypoxia, dependent on the rise of HbA<sub>1</sub> and on the reduction of red cell deformability. As opposed to the lack of correlation between the severity of retinal abnormalities and the percentage of HbA<sub>1</sub>, the parallelism observed with filtration rate values ( $r = -0.46$ ,  $p < 0.01$ ) hints that diabetic microangiopathy is affected by circulating red cells' rigidity.

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