Metabolic factors and the foveal avascular zone of the retina in diabetes mellitus

J Conrath¹,², R Giorgi², B Ridings¹, D Raccah³

SUMMARY

Aim: To study the foveal avascular zone (FAZ) of the central retina in diabetic patients with retinopathy having undergone metabolic evaluation.

Methods: One hundred and ten digital fluorescein angiograms were chosen from our digital image bank after cross matching diabetic patient lists of the ophthalmology and endocrinology departments of our institution. The patients had undergone day visits with systemic, biological and ophthalmologic evaluation, including digital fluorescein angiography.

Results: Sex ratio was M 62/F 48. Average age was 52.4 years (r 13.8) with 44 type 1 diabetics and 66 type 2. Retinopathy was present in all patients (54 background (BDR), 30 pre-proliferative (PPDR), 26 proliferative (PDR)). Age was positively correlated with FAZ grade (47.3 years r 13.2 for normal FAZ, 53.8 years r 13.7 for abnormal FAZ, P = 0.03). Lipid profile showed a protective tendency of the Apo A1 fraction of cholesterol on macular vascularization (1.7 gr./l in normal FAZ patients vs 1.43 gr./l in abnormal FAZ patients, P = 0.004). Body mass index was negatively correlated with macular ischemia (28.11 if FAZ not severely altered, 25.97 if FAZ severely altered, P = 0.03).

Conclusions: We found possible relations between BMI and Apo A1 cholesterol and macular vascularization which may warrant further investigation.

Key-words: Diabetic retinopathy · Foveal avascular zone · Macular ischemia · Body mass index · Apolipoprotein A1.

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RéSUMÉ

Objectifs : Étudier la zone avasculaire centrale (ZAC) de la rétine chez des patients diabétiques avec une rétinopathie ayant eu une évaluation métabolique.

Méthodes : Cent dix angiographies rétiniennes à la fluorescéine, numérées, ont été choisies dans notre banque d’images après avoir croisé les listes des patients suivis par les services d’ophtalmologie et d’endocrinologie de notre hôpital. Les patients avaient bénéficié d’un bilan en hôpital de jour avec réalisation d’un examen clinique, biologique et ophtalmologique avec angiographie rétinienne.

Résultats : Le sex ratio était 62 H/48 F. L’âge moyen était de 52,4 ans (r 13,8). Il y avait 44 diabétiques de type 1 et 66 diabétiques de type 2. Une rétinopathie diabétique (RD) était présente chez tous les patients (54 RD minimes ou modérées, 30 RD non proliférantes sévères et 26 RD proliférantes). L’âge était corrélé positivement au grade de la ZAC (47,3 ans r 13,2 en cas de ZAC normale, 53,8 ans r 13,7 en cas de ZACa normale, P = 0,03). Le profil lipidique montrait un effet protecteur de la fraction ApoA1 sur la vascularisation maculaire (1,7 g/l en cas de ZAC normale, 1,43 g/l en cas de ZAC anormale, P = 0,004). L’indice de masse corporelle (IMC) était corrélé négativement avec l’ischémie maculaire (IMC = 28,11 en cas de ZAC non ou peu altérée, IMC = 25,97 en cas de ZAC très altérée, P = 0,03).

Conclusion : Des relations possibles entre d’une part la vascularisation maculaire et d’autre part l’indice de masse corporelle et le cholestérol ApoA1 pourraient mériter des explorations plus poussées.

Mots-clés : Rétinopathie diabétique · Zone avasculaire centrale · Ischémie maculaire · Indice de masse corporelle · Apolipoprotéine A1.

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Introduction

It is well known that diabetic retinopathy is related to metabolic control, poorer control being related to higher retinopathy stage, more complications and a greater risk of blindness [1, 2]. The first cause of poor vision in diabetics is diabetic maculopathy [3], which may combine both macular edema and ischemia as well. The importance of macular ischemia in diabetic vision loss is difficult to assess. It is due to macular capillary occlusion in the posterior pole of the eye, and more specifically at the level of the capillary net defining the foveal avascular zone.

The foveal avascular zone or FAZ is an area located in the center of the macula which is physiologically avascular. It is this region that provides highest visual acuity, contrast vision and color vision, with a maximum ratio of photoreceptors (cones) to nerve fibers.

Ischemia of the foveal region secondary to diabetes has aroused less research interest than macular oedema, perhaps because to this day, no physical or pharmacological treatment such as laser photocoagulation [4] or corticosteroid injections [5] (both used to treat diabetic macular edema) exists to specifically manage macular ischemia. This paper deals with the study of the metabolic parameters that may be correlated with macular vascularization.

Patients and methods

One hundred and ten high quality digital fluorescein angiograms (1024x1024 pixels) of 110 patients were retrospectively chosen from our digital image bank after cross matching diabetic patient lists of the ophthalmology and endocrinology departments of our institution. The patients had undergone day visits with ophthalmologic, systemic and biological evaluation.

Ophthalmologic evaluation included visual acuity, refraction, slit lamp examination, intra-ocular pressure measurement, dilated fundus examination (with evaluation of retinopathy level) and a digital fluorescein angiogram (5 ml of 10% sodium fluorescein were injected rapidly into the antecubital vein) with early, mid and late phase pictures. Angiograms were chosen on the basis that the FAZ must be sufficiently visible to allow quantitative and qualitative evaluation: the chosen study eye was the eye for which the FAZ was best visible on the digital fluorescein angiogram. Diabetic retinopathy (DR) was classified by fundus examination as background (BDR, ETDRS levels 20 to 47), pre-proliferative (PPDR, ETDRS levels 53) or proliferative (PDR, ETDRS levels 61 and above). The FAZ was evaluated qualitatively and quantitatively as described elsewhere [6]. Briefly, a single layer capillary ring surrounds the center of the fovea. Capillary dropout may be estimated by evaluating the amount of this ring that has been interrupted by capillary closure, with a qualitative grade ranging from 0 to 4 being assigned to each FAZ (Fig. 1). Quantitative FAZ evaluation was performed using the Image J freeware to outline the FAZ (Fig 2) and subsequently determine surface area in mm².

Systemic evaluation included age, date of onset of diabetes, type of diabetes, height, weight, body mass index, presence or absence of arterial hypertension, presence or absence of peripheral neuropathy, nephropathy, and macroangiopathy (assessed by presence or absence of coronary ischemia and/or carotid stenosis).

Biological evaluation included glycated hemoglobin (HbA1c) levels, which had been measured by HPLC on the VARIANT II® machine (Bio-Rad, Hercules, California, USA). ApoA1 and ApoB cholesterol had been dosed by immunonephelemetry (BN II®, Dade-Behring, Liederbach, Germany).

Statistical analysis

Correlations of systemic and biological factors to both retinopathy and macular ischemia were sought out, as well as the relations between retinopathy and macular ischemia, by statistical analyses using the SPSS 10 software package. Non-parametric tests were preferred as the population of subgroups was rarely above 30 (ANOVA requiring a normal distribution in subgroups). Quantitative variables were compared using the U test of Mann-Whitney or...
Kruskal-Wallis test according to the number of groups to compare and qualitative variables were compared using the Fisher’s exact probability test. P-values less than 0.05 (two-side tests) were considered as statistically significant.

Results

Study Population

Sex ratio was 62 males/48 females. Average age was 52.4 years (± 13.78) with 44 type 1 and 66 type 2 diabetics. Retinopathy was present in all the eyes studied (110 eyes of 110 patients): 54 eyes presented BDR, 30 PPDR, and 26 PDR.

FAZ correlations with systemic and biological factors

Table I shows general results for FAZ normal or questionable versus FAZ abnormal. Age was positively correlated with FAZ grade (47.3 years ± 13.2 for normal FAZ, 53.8 years ± 13.7 for abnormal FAZ, P = 0.03). Other systemic factors (type of diabetes, duration of diabetes, BMI, hypertension, neuropathy, nephropathy, macroangiopathy) were not significantly associated with FAZ grade. When considering highly altered FAZs versus normal or slightly altered FAZs, BMI was negatively correlated with macular capillary closure (Tab II). Lipid profile evaluation showed a protective tendency of the ApoA1 fraction of cholesterol on macular vascularization (see Table 1: 1.7 gr/l in normal FAZ patients (grade 0 and 1, n = 9) es 1.43 gr/l in abnormal FAZ patients (grades 2 through 4, n = 30), P = 0.004). Other biological factors (ApoB, HbA1c) were not significantly associated with FAZ grade.

FAZ correlations with diabetic retinopathy

Severity of diabetic retinopathy was correlated with severity of macular capillary occlusion as measured by FAZ surface area: average FAZ surface area in PDR was 0.61 mm², in PPDR, 0.42 mm² and in BDR 0.30 mm² (P < 0.03). Likewise, severity of diabetic retinopathy also correlated with FAZ grade, with a higher proportion of altered FAZs present among eyes with PDR than PPDR or BDR (P = 0.003, Tab III).

All of these analyses were univariate in nature. When two variables (FAZ grade and diabetic retinopathy stage, FAZ grade and type of diabetes) were studied at the same time, population subgroups became quite small, and results were not significant.

Discussion

The anatomic effects of diabetic macular capillary occlusion may be evidenced with histological techniques in the enucleated eye [7], by measurement with non-invasive entoptic techniques [8, 9] or invasive fluorescein angiography [10-14]. Fluorescein angiography shows variable results, with a normal value usually situated between 0.205 mm² [15] and 0.405 mm² [13]. Values for diabetic patients with retinopathy vary from 0.318 mm² (BDR, [10]) to 0.86 (PDR, [13]).

Another technique is the evaluation of the contour of the FAZ using the ETDRS grading level [16]. In a previous paper, we described this technique in the same population.
### Table I
General results for FAZ Normal or questionable versus FAZ definitely Abnormal.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FAZ Normal or questionable</th>
<th>FAZ Abnormal</th>
<th>Significance P level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>47.3 ± 13.2, n = 24</td>
<td>53.8 ± 13.7, n = 86</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes duration (yrs)</td>
<td>13.9 ± 8.1, n = 24</td>
<td>17.5 ± 9.4, n = 82</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes type</td>
<td>Type 1: n = 12</td>
<td>Type 1: n = 32</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>Type 2: n = 12</td>
<td>Type 2: n = 52</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>27.8 ± 5.7, n = 23</td>
<td>27.1 ± 4.6, n = 74</td>
<td>0.81</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Present, n = 16</td>
<td>Present, n = 51</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>Absent, n = 8</td>
<td>Absent, n = 27</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Present, n = 15</td>
<td>Present, n = 55</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>Absent, n = 8</td>
<td>Absent, n = 17</td>
<td></td>
</tr>
<tr>
<td>Nephropathy stage</td>
<td>Stage 0, n = 10</td>
<td>Stage 0, n = 39</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Stage 1, n = 9</td>
<td>Stage 1, n = 16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 2, n = 5</td>
<td>Stage 2, n = 26</td>
<td></td>
</tr>
<tr>
<td>Carotid stenosis and/or myocardial ischemia</td>
<td>Present, n = 16</td>
<td>Present, n = 58</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Absent, n = 8</td>
<td>Absent, n = 18</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.2 ± 1.7, n = 24</td>
<td>8.9 ± 1.7, n = 80</td>
<td>0.40</td>
</tr>
<tr>
<td>Apo A1 (g/l)</td>
<td>1.7 ± 0.28, n = 9</td>
<td>1.4 ± 0.2, n = 30</td>
<td>0.004</td>
</tr>
<tr>
<td>Apo B (g/l)</td>
<td>0.9 ± 0.2, n = 9</td>
<td>1.0 ± 0.3, n = 30</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Notes:
1: in this table, results of both quantitative values (eg: age) and qualitative values (e: diabetes type) are given. For quantitative values, either the U test of Mann-Whitney or Kruskal-Wallis test were used, according to the number of groups to compare; for qualitative values, the Fisher’s exact probability test was used (see Methods section).
2: Totals for each line of data may not add up to 110, as data were not available for all patients.
3: BMI = body mass index, Apo A1 = apolipoprotein A1, Apo B = apolipoprotein B.
4: Nephropathy stages were defined as: Stage 0: no nephropathy, Stage 1: microalbuminuria, Stage 2: gross proteinuria.

### Table II
Body Mass Index (BMI) and grade of foveal avascular zone (FAZ).

<table>
<thead>
<tr>
<th>FAZ grade</th>
<th>Average BMI</th>
<th>SD</th>
<th>median</th>
<th>minimum</th>
<th>maximum</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1/2 destroyed</td>
<td>28,1103</td>
<td>4,81856</td>
<td>27,45</td>
<td>19,6</td>
<td>41,1</td>
<td>58</td>
</tr>
<tr>
<td>&gt;1/2 destroyed</td>
<td>25,9667</td>
<td>4,77545</td>
<td>25</td>
<td>18,2</td>
<td>39,10</td>
<td>39</td>
</tr>
</tbody>
</table>

< ½ destroyed = grades 0, 1, 2; > ½ destroyed = grades 3, 4; P = 0.033. Note: Total is less than 110 because data were not available for BMI calculation for all patients.

### Table III
FAZ correlations with diabetic retinopathy. (Reprinted from Conrath J. et al. [6] with permission from the journal Eye).

<table>
<thead>
<tr>
<th>FAZ contour grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDR</td>
<td>5 (9.3%)</td>
<td>12 (22.2%)</td>
<td>25 (46.3%)</td>
<td>10 (18.5%)</td>
<td>2 (3.7%)</td>
<td>54 (100%)</td>
</tr>
<tr>
<td>PPDR</td>
<td>0 (4.3%)</td>
<td>13 (43.3%)</td>
<td>8 (26.7%)</td>
<td>5 (16.7%)</td>
<td>30 (100%)</td>
<td></td>
</tr>
<tr>
<td>PDR</td>
<td>0 (3.7%)</td>
<td>3 (11.5%)</td>
<td>5 (19.2%)</td>
<td>16 (61.5%)</td>
<td>2 (7.7%)</td>
<td>26 (100%)</td>
</tr>
</tbody>
</table>

P = 0.003.
and found it to correlate to surface measurements [6]. As our subgroup sizes were small, we regrouped patients for further analyses. Other authors have done the same before [17].

In general, body weight is not a parameter that fluctuates very rapidly [18] (aside from wasting or fasting). In our study, BMI was found to be lower in the group with an altered FAZ. This may seem surprising at first, but it has been suggested among type 2 diabetics (60% of our study population), that those who necessitate insulin present a more severe disease [19]. By lack of insulin, they also would have a lower BMI. Patients in whom endogenous insulin secretion is sufficient would tend to be on the overweight side and present a less severe form of the disease. Several authors have already found negative correlations between BMI and diabetic retinopathy [19-21]. In our study, FAZ destruction appears thus to be a severity marker of diabetic retinal disease.

We did not find blood pressure (evaluated by patients presenting or not known arterial hypertension) to influence macular microcirculation, as Arend et al. [22] who did not find it to be an aggravating factor for macular capillary dropout. Perhaps the fact that our patients were largely being treated by antihypertensive drugs could explain this in part. We did find a correlation between age and macular ischemia: capillary dropout related to age has been reported in the literature in non-diabetic populations [23], however in diabetics, other authors have found no effect of age [12, 13]. We realize that this may be a confounding factor when analysing our other results.

Serum lipids have been variably incriminated in diabetic retinopathy. Total cholesterol levels have been found higher in patients with retinopathy [20, 24, 25] as have also triglyceride levels [20, 24, 26]. Other authors have found no link between either of them and diabetic retinopathy [27]. Total cholesterol levels have been found to be linked to macular exudates [28, 29]. A recent paper by Lyons et al. [30] showed a significant correlation between higher ApoB levels and more severe retinopathy in men of the DCCT cohort, and a general trend for lower ApoA1 with more severe retinopathy.

Apolipoprotein A1 is a structural element of HDL cholesterol, which promotes inverse flux of cholesterol from peripheral plasma membranes towards HDL molecules [31]. Apo A1 has been found to be a protector of macroangiopathic events, such as coronary infarction [32]. Finding higher levels in patients with a preserved FAZ incites us to look farther into a possible role it might play in microcirculation. Up until recently however, pathogenic hypotheses of microvascular retinal abnormalities in diabetes have been mainly focused upon pathologic leukocyte adhesion [33], red blood cell anomalies [34], fibrin/platelet anomalies [35] as well as generalized capillary endothelial dysfunction [36].

A drawback of our study is the single dosage of blood lipids: daily intrapatient variability may be high, from 3.5% for HDL to 6.5% for Apo A1 and B, to 29.5% for triglycerides [37]. We also recognize that this work presents a major weakness as only a fraction of our patients underwent Apo A1 dosage, and it is difficult to extrapolate results to the entire population. However, the significance level we found was quite high.

In a group of patients with either no retinopathy, or else BDR, Sander [15] found a significant correlation between perifoveal capillary loss (a marker of vessel closure situated around the FAZ) and glycated hemoglobin levels, but did not find such a relation concerning FAZ size itself. Doft [17] found a positive correlation between macular capillary closure as measured by estimating FAZ size in papillary surfaces (a rough estimate at best) and HbA1c levels in case of abnormal capillary perfusion. We found no significant correlations between FAZ indexes (surface, grade) and HbA1c. As with lipids, single dosage is less reliable than the average of a series of measures of course, but this was difficult to overcome given the retrospective nature of our study.

In conclusion, in our study population, we find possible relations between BMI and Apo A1 cholesterol and the morphology of the foveal avascular zone that may warrant further investigation. A controlled, prospective study with a larger population might help to answer these questions as well as ones concerning evolution of the FAZ, as there remains no known therapy for macular ischemia to this day.

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