Foveal sensitivity after focal photocoagulation in eyes with diabetic macular edema

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Abstract

Background: Clinically significant macular edema (CSME) is a common cause of visual loss in diabetic patients and can reduce macular sensitivity, regardless of visual acuity and retinal thickness. Photocoagulation reduces the risk of visual loss but may affect the sensitivity at the site of treatment. The effect could improve global macular sensitivity. The purpose of the study was to identify the change of foveal sensitivity in CSME after focal photocoagulation.

Methods: A nonexperimental, analytical, longitudinal, prospective study was conducted in diabetic patients with CSME treated with photocoagulation. Anatomic, foveal sensitivity and visual acuity changes after treatment were compared between eyes with central point thickness (group 1) and without (group 2) and with visual acuity ≥0.5 (group A) and <0.5 (B, Mann-Whitney U). Topical treatment after photocoagulation was evaluated as a secondary outcome.

Results: There were 37 eyes included with a mean patient age of 59.4 years. Twelve eyes were assigned to group 1 and 25 to group 2. Ten eyes were allocated to group A and 17 to group B. 10 eyes received ketorolac, one was treated with nepafenac and 26 with artificial tears. Anatomic, visual acuity and foveal sensitivity variables did not change either in the sample or between groups. Foveal sensitivity decreased in eyes treated with artificial tears and increased in eyes treated with ketorolac. These outcomes caused a difference of mean sensitivity change (–1.96 vs. 1.7 dB, p = 0.026).

Conclusion: Foveal sensitivity decreased significantly after treatment. The change, which was unnoticed in the sample, could be inflammation mediated. The outcome in eyes treated with ketorolac needs additional evaluation.

Key words: Clinically significant macular edema, diabetic retinopathy, foveal sensitivity, photocoagulation.

Introduction

Clinically significant macular edema (CSME) is a major cause of visual loss in patients with diabetic retinopathy. Its prevalence among diabetic patients in the Mexican population is 5.8%. The diagnosis is done clinically, but the evaluation is complemented with tools such as retinal angiography, which identifies sites of capillary leak and optical coherence tomography, which quantitatively measures macular thickening.

Functional evaluation of the macula has fallen on the best corrected visual acuity (BCVA), an outcome variable used in the Early Treatment Diabetic Retinopathy Study (ET-DRS) to determine the effectiveness of photocoagulation. However, the BCVA does not fully characterize macular function because scotomas or neural dysfunction (measured by foveal sensitivity, contrast sensitivity and color vision) can appear before the appearance of retinal thickening or visual loss.

Decreased foveal sensitivity in diabetic patients has already been reported. Vujosevic et al. identified this in eyes with CSME when compared in eyes without edema or without CSME (p <0.001). Okada et al. found this in eyes with diabetic macular edema (cystoid) when compared with healthy eyes (p <0.001). Verma et al. found it in diabetic eyes without retinopathy when compared with eyes of patients without diabetes (p = 0.003). Hatef et al. described it in eyes with retinal thickness >280 µm when they compared it with eyes with thickness <200 µm.

Treatment of CSME with focal angiographic filtration is done by means of photocoagulation, which interrupts the leakage into the extravascular space and allows for the ex-
travasating fluid to be removed from the retina in 3 to 6 weeks. The purpose of photocoagulation is to stabilize vision and reduce the risk of visual loss; it has been reported that visual improvement is uncommon.

Among the adverse events associated with focal treatment of CSME are paracentral scotomas (due to damage to the photoreceptors at the site of the burn) and increased edema and transient reduced vision (due to treatment-induced inflammation), among others. A Swedish study showed that the proportion of eyes with any of these complications was 20.6%.

In eyes with CSME, an increase in the central point thickness has been reported 3 weeks after photocoagulation and is significant when central point thickness is normal before the procedure. The thickness caused by photocoagulation is made even if the macular volume decreases significantly, a characteristic with which the efficacy of the treatment is evaluated.

It has been reported that after photocoagulation, foveal sensitivity can decrease, although not significantly (p > 0.05). When there are exudates, the decrease is more marked although the BCVA improves and central visual function may deteriorate even when sensitivity remains stable or may even improve.

Rohrschneider et al. identified improvement of 3 dB in 50% of eyes treated with photocoagulation, even when they described that the procedure destroys afferent cells; however, in this study the improvement of the foveal sensitivity had no significant correlation with the BCVA.

After photocoagulation, a high incidence of visual improvement in diabetic patients with CSME has been reported. This rate of visual improvement may be associated with an increase of foveal sensitivity. A study was carried out to identify the change of the foveal sensitivity in eyes with CSME treated with focal photocoagulation.

Subjects and Methods

We performed an observational, analytical, longitudinal, prospective, open study in patients with type 2 diabetes in Mexico City and the metropolitan area. The accessible population was comprised of type 2 diabetic patients treated at the ophthalmology service of a general hospital in Mexico City from January 1, 2012 to May 31, 2013. The study adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the hospital where it was developed. Type 2 diabetic patients with CSME of focal angiographic type were included. Patients were of either gender, ages 25 to 80 years, with any degree of retinopathy and central fixation and who had obtaining an optical coherence tomography of adequate quality. We excluded eyes with diseases of the optic nerve, the visual pathway or any other condition that decreased BCVA.

Degree of retinopathy was defined according to the International Clinical Severity of Diabetic Retinopathy Scale. A retina specialist diagnosed the CSME using a contact lens and slit lamp under mydriasis of at least 6 mm according to the criteria of the ETDRS: retinal thickness up to 500 µm from the center of the fovea, exudates up to 500 µm from the foveal center if accompanied by thickening of the adjacent retina or one zone or zones of thickness greater than a disk area, localized at least 1 disk diameter from the foveal center.

BCVA was measured under subjective refraction in decimal equivalent; retinal thickness was measured with a Stratus optical coherence tomography, v.4.0.1 (Zeiss). The 6-mm macular fast mapping test was used (Figure 1). To standardize measurements the spherical equivalent and the antero-posterior axis were included and the z-axis and polarization were optimized. Photos were taken with a flash between 9:00 and 11:00 o’clock with a mode of acquisition for eyes with dark irises. A single investigator, independent of the one who clinically assessed the patients, obtained the maps. Any deviation from the line of recording of the optical coherence tomography with respect to the actual margin of the retina was considered to be a measurement error.

A macular perimeter of 10° was obtained in all patients with a Humphrey campimeter model 750i (software v. 4.1); the 16 points evaluated were arbitrarily identified as shown in Figure 2. Retinal thickness within the 3 mm around the foveal center was measured in nine fields according to the fast macular map.

Study variables were foveal sensitivity, central point thickness, central field thickness, macular volume and BCVA in decimal equivalents; the first was operationally defined as

![Figure 1. Distribution of the fields of the optical coherence tomography](image-url)
Negative result corresponded to a reduction.

To calculate variables generated by the fast macular map.

The sample was divided into groups: group 1 with central disorder (central field thickness >212 µm, higher than the average reported in diabetic patients without retinopathy in the reference population) and group 2 without central disorder. Changes were also compared according to the visual function prior to treatment: group A were assigned eyes with BCVA ≥0.5 and group B eyes with BCVA <0.5. Topical treatment used after photocoagulation (ketorolac, nepafenac or ocular lubricant) was considered as a secondary variable.

In each group the averages of the sensitivities were compared at each point of the perimetry, retinal thickness in the nine fields of the rapid macular map, central point thickness, central field thickness, macular volume and BCVA before and 3 weeks after photocoagulation (paired t-test). A value of p <0.05 was considered to be statistically significant.

The averages in changes of foveal sensitivity were compared, from the central point thickness, central field thickness, macular volume and BCVA between groups 1 and 2, between groups A and B, and between eyes with different topical treatments after photocoagulation (ketorolac or ocular lubricant). These comparisons were carried out with Mann-Whitney U test. Data were stored and analyzed with SPSS v.20 by the same investigator.

The mean change in BCVA in the sample was from -0.015 ± 0.16, thickness of the central field 5.89 ± 13.17 µm, central point thickness 6.54 ± 22.37 µm, macular volume 0.039 ± 0.22 mm³ and foveal sensitivity of -0.81 ± 4.47 dB. Twelve eyes had thickening of the central field (32.5%) and were evaluated in group 1, the remaining 25 (67.5%) were evaluated in group 2; 20 eyes had BCVA ≥0.50 (54.1%) and were evaluated in group A, the remaining 17 (45.9%) were evaluated in group B. Baseline variables and distribution of the location of the edema did not differ between groups 1 and 2, between groups A and B, and between eyes with different topical treatments after photocoagulation (ketorolac or ocular lubricant). These comparisons were carried out with Mann-Whitney U test. Data were stored and analyzed with SPSS v.20 by the same investigator.

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There were 37 eyes evaluated of 25 patients aged 26 to 76 years (mean 59.4 ±11.23 years); 14 patients were males (56%). Time of evolution of diabetes was from 2 to 30 years (mean 14.68 ±7.07 years); 17 eyes corresponded to patients treated with oral hypoglycemics (68%) and nine to patients treated with insulin (36%). Mean fasting blood sugar was 156.57 mg/dL (±51.64), glycated hemoglobin 8.96% (±1.69), total cholesterol 218.15 mg/dL (±69.84) and triglycerides 237.15 mg/dL (±135.76).

Seventeen patients had hypertension (68%), 16 of whom were treated with angiotensin converting enzyme (ACE) inhibitors (64%). Seven patients had hypertriglyceridemia and hypercholesterolemia (28%) and seven had nephropathy (28%); one received dialysis treatment (4%).

BCVA before photocoagulation ranged from 0.13 to 1.00 (mean 0.57 ± 0.28); one eye had rubeosis (2.7%) and 18 had lens opacity (48.6%). Degree of nonproliferative diabetic retinopathy was mild in seven eyes (18.9%), moderate in 21 (56.8%), severe in one (2.7%) and proliferative in eight (21.6%). Edema type was monofocal in 24 eyes (64.9%) and multifocal in 13 (35.1%).

The retinal thickening location was superonasal in ten eyes (18.5%, 95% CI 8.2–28.9), superior in ten (18.5%, 95% CI 8.2–28.9), superotemporal in nine (16.7%, 95% CI 6.7–26.6) inferotemporal in six (11.1%, 95% CI 2.7–19.5), temporal in five patients (9.2%, 95% CI 1.5–16.9), inferior in five patients (9.2%, 95% CI 1.5–16.9), inferonasal in five (9.2%, 95% CI 1.5–16.9), and nasal in four (7.4%, 95% CI 0.4–14.4).

Photocoagulation therapy was used during 5 to 30 shots (mean 15.86 ± 7.62) with a mean power of 158.92 ± 34.78 mW, diameter spot of 100 µm and shot duration of 200 msec. After photocoagulation, ten eyes were treated with topical ketorolac and 27 were not (one received nepafenac and the remaining 26 received lubricant).

BCVA after treatment ranged from 0.1 to 1.00 (mean 0.55 ± 0.27, p = 0.58). Mean retinal thickness only changed significantly in field 1 (Table 1). The mean retinal sensitivity changed statistically in points 4, 10, 11, 13 (corresponding to quadrant 4) and 16 (Table 2).

The mean change in BCVA in the sample was from -0.015 ± 0.16, thickness of the central field 5.89 ± 13.17 µm, central point thickness 6.54 ± 22.37 µm, macular volume 0.039 ± 0.22 mm³ and foveal sensitivity of -0.81 ± 4.47 dB. Twelve eyes had thickening of the central field (32.5%) and were evaluated in group 1, the remaining 25 (67.5%) were evaluated in group 2; 20 eyes had BCVA ≥0.50 (54.1%) and were evaluated in group A, the remaining 17 (45.9%) were evaluated in group B. Baseline variables and distribution of the location of the edema did not differ between groups 1 and 2, between groups A and B, and between eyes with different topical treatments after photocoagulation (ketorolac or ocular lubricant). These comparisons were carried out with Mann-Whitney U test. Data were stored and analyzed with SPSS v.20 by the same investigator.

The averages in changes of foveal sensitivity were compared, from the central point thickness, central field thickness, macular volume and BCVA between groups 1 and 2, between groups A and B, and between eyes with different topical treatments after photocoagulation (ketorolac or ocular lubricant). These comparisons were carried out with Mann-Whitney U test. Data were stored and analyzed with SPSS v.20 by the same investigator.

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Table 1. Distribution of the retinal thickness by fields of the OCT before and after treatment

<table>
<thead>
<tr>
<th>OCT</th>
<th>Initial Average ± SD</th>
<th>3 weeks Average ± SD</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field 1</td>
<td>207.32 ± 30.5</td>
<td>213.22 ± 34.67</td>
<td>0.01</td>
</tr>
<tr>
<td>Field 2</td>
<td>284.11 ± 24.92</td>
<td>286.35 ± 23.83</td>
<td>0.45</td>
</tr>
<tr>
<td>Field 3</td>
<td>275.05 ± 28.01</td>
<td>273.62 ± 31.42</td>
<td>0.71</td>
</tr>
<tr>
<td>Field 4</td>
<td>276.59 ± 20.85</td>
<td>277.78 ± 22.72</td>
<td>0.49</td>
</tr>
<tr>
<td>Field 5</td>
<td>273.54 ± 23.35</td>
<td>278.73 ± 22.13</td>
<td>0.16</td>
</tr>
<tr>
<td>Field 6</td>
<td>269.92 ± 26.83</td>
<td>271.59 ± 24.86</td>
<td>0.59</td>
</tr>
<tr>
<td>Field 7</td>
<td>260.86 ± 37.15</td>
<td>257.70 ± 30.86</td>
<td>0.21</td>
</tr>
<tr>
<td>Field 8</td>
<td>249.92 ± 22.88</td>
<td>252.05 ± 22.25</td>
<td>0.18</td>
</tr>
<tr>
<td>Field 9</td>
<td>271.92 ± 20.67</td>
<td>276.7 ± 23.06</td>
<td>0.04</td>
</tr>
<tr>
<td>CPT</td>
<td>178.3 ± 32.54</td>
<td>184.84 ± 45.78</td>
<td>0.08</td>
</tr>
<tr>
<td>Macular volume</td>
<td>7.51 ± 0.52</td>
<td>7.54 ± 0.52</td>
<td>0.29</td>
</tr>
</tbody>
</table>

*Paired t-test.

OCT, optical coherence tomography; SD, standard deviation; CPT, central point thickness.

Table 2. Distribution of the perimetry points before and after photocoagulation

<table>
<thead>
<tr>
<th>Campimetry</th>
<th>Initial Average ± SD</th>
<th>3 weeks Average ± SD</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point 1</td>
<td>27.22 ± 6.93</td>
<td>27.32 ± 5.56</td>
<td>0.90</td>
</tr>
<tr>
<td>Point 2</td>
<td>27.32 ± 6.32</td>
<td>26.86 ± 7.85</td>
<td>0.60</td>
</tr>
<tr>
<td>Point 3</td>
<td>27.84 ± 5.41</td>
<td>27.32 ± 8.12</td>
<td>0.56</td>
</tr>
<tr>
<td>Point 4</td>
<td>28 ± 4.67</td>
<td>25.68 ± 7.96</td>
<td>0.03</td>
</tr>
<tr>
<td>Point 5</td>
<td>26.86 ± 7.13</td>
<td>26.32 ± 8.08</td>
<td>0.63</td>
</tr>
<tr>
<td>Point 6</td>
<td>24.11 ± 9.53</td>
<td>23.41 ± 9.73</td>
<td>0.53</td>
</tr>
<tr>
<td>Point 7</td>
<td>25.59 ± 8.89</td>
<td>25.78 ± 8.54</td>
<td>0.84</td>
</tr>
<tr>
<td>Point 8</td>
<td>25.68 ± 8.84</td>
<td>24.73 ± 9.09</td>
<td>0.42</td>
</tr>
<tr>
<td>Point 9</td>
<td>25.81 ± 8.28</td>
<td>24.57 ± 8.41</td>
<td>0.30</td>
</tr>
<tr>
<td>Point 10</td>
<td>28.14 ± 5.48</td>
<td>25.86 ± 7.68</td>
<td>0.03</td>
</tr>
<tr>
<td>Point 11</td>
<td>28.27 ± 4.39</td>
<td>26.46 ± 6.15</td>
<td>0.02</td>
</tr>
<tr>
<td>Point 12</td>
<td>27.43 ± 6.48</td>
<td>25.46 ± 8.56</td>
<td>0.055</td>
</tr>
<tr>
<td>Point 13</td>
<td>28.95 ± 5.08</td>
<td>26.62 ± 7.67</td>
<td>0.02</td>
</tr>
<tr>
<td>Point 14</td>
<td>28.14 ± 4.97</td>
<td>26.78 ± 6.72</td>
<td>0.21</td>
</tr>
<tr>
<td>Point 15</td>
<td>26.16 ± 5.92</td>
<td>25.3 ± 8.42</td>
<td>0.43</td>
</tr>
<tr>
<td>Point 16</td>
<td>28.59 ± 5.37</td>
<td>26.08 ± 7.74</td>
<td>0.01</td>
</tr>
<tr>
<td>Quadrant 1</td>
<td>103.73 ± 28.29</td>
<td>103.76 ± 26.91</td>
<td>0.99</td>
</tr>
<tr>
<td>Quadrant 2</td>
<td>106.76 ± 26.41</td>
<td>101.08 ± 28.68</td>
<td>0.11</td>
</tr>
<tr>
<td>Quadrant 3</td>
<td>111.51 ± 18.04</td>
<td>105.95 ± 23.67</td>
<td>0.05</td>
</tr>
<tr>
<td>Quadrant 4</td>
<td>113.22 ± 16.63</td>
<td>104.3 ± 25.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Foveal sensitivity</td>
<td>29.84 ± 4.48</td>
<td>29.03 ± 6.74</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Paired t-test.

SD, standard deviation.

In the eyes treated with ketorolac, confidence intervals of the mean change in sensitivity corresponded to an increase, whereas in eyes treated with placebo, the mean change of sensitivity was consistently reduced (Figure 4); confidence intervals of both means were exclusive.

Discussion

Retinal thickness and visual function of patients with CSME may change after photocoagulation, although DRCR.net has reported that there may be paradoxical responses in which the increased retinal thickness is accompanied by visual improvement. Cases have also been reported in which reduction of retinal thickening is associated with a decrease in BCVA.25
The change in retinal sensitivity may be associated with the variability of the visual outcome of photocoagulation in eyes with CSME, although it has been reported that eyes at a higher risk of visual loss are those with thickening of the center of the macula. Retinal sensitivity did not differ between those with and those without it. This lack of difference could explain the lack of response in some eyes with significant reduction in retinal thickness after photocoagulation and requires further evaluation.

Foveal sensitivity did not change significantly in the sample after photocoagulation, although there was a significant decrease in points 4, 10, 11 and 13 (corresponding to quadrant 4), which represents the superior temporal macula. This localized reduction was not sufficient to affect the foveal sensitivity. Lack of modification did not change when comparing eyes with and without central field thickness or when comparing eyes with and without BCVA ≥0.5.

These results differ globally from those reported by Hudson et al. and Striph et al. who reported that grid photocoagulation reduced foveal sensitivity, although patients in the sample received focal photocoagulation. Sims et al. also reported a reduction in sensitivity after this procedure. Ludwig et al. reported a lack of modification of the sensitivity after grid photocoagulation.

Bengtsson et al. reported that, in eyes with CSME, foveal sensitivity may decrease 2.6 dB for each mm² of the extension of the avascular foveal zone and the intercapillary perifoveal region increases (p = 0.007). This reduction in sensitivity was not associated with BCVA or with the degree of diabetic retinopathy. In this study, only eyes with clinically significant focal angiographic macular edema and spongiform retinal thickening were evaluated. Patients with ischemia on angiography were not included so that the reduction in foveal sensitivity in the sample would not be attributed to this feature.

Photocoagulation induces retinal inflammation during the first week after its application. In the ETDRS this inflammation caused a greater proportion of moderate visual loss during the first 6 weeks in eyes treated with photocoagulation than in untreated eyes. Although it had already been identified that photocoagulation reduced retinal sensitivity, it had not been associated with inflammation.

Originally it was not planned to separately evaluate eyes receiving anti-inflammatories and those that did not. In the eyes that received only lubricant there was a significant reduction in foveal sensitivity, consistent with what was reported by Hudson et al. and Striph et al. after grid photocoagulation, and by Sims et al. after focal photocoagulation. This reduction in foveal sensitivity was not evident in the sample due to the increased sensitivity in eyes treated with ketorolac.

The increased sensitivity found in eyes treated with ketorolac was not significant, but contrasted with the significant reduction in eyes receiving a lubricant. It is noteworthy that the standard error of the mean rate of sensitivity was the same in both treatment groups (0.90), generating confidence intervals of the same amplitude but exclusive. These characteristics make it necessary to investigate this difference through a study specifically designed for it.

In our environment it is more common to find eyes with CSME without ischemia than patients with it. In accordance with the results of this study, retinal dysfunction identified in the macular campimetry does not require capillary closure and increases with the inflammation induced by...
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photocoagulation. To improve the results after focal photocoagulation it is necessary to evaluate the correlation between BCVA and foveal sensitivity before the procedure, as well as the impact in its changes to treat the induced inflammation.

In conclusion, focal photocoagulation in patients with diabetic macular edema significantly reduced foveal sensitivity. This outcome could be mediated by inflammation.

References