Long-Term Follow Up of Oral Administration of Flavonoids, *Centella asiatica*, and *Melilotus* for Diabetic Cystoid Macular Edema Without Macular Thickening*

Raimondo Forte, Gilda Cennamo, Paola Bonavolonta, Arduino Pascotto, Giuseppe de Crecchio, and Giovanni Cennamo

Abstract

**Purpose:** To evaluate long-term follow up of the orally administered combination of flavonoids with *Centella asiatica* and *Melilotus* for treatment of diabetic cystoid macular edema (CME) without macular thickening.

**Methods:** Seventy consecutive patients with type 2 diabetes and CME without macular thickening at optical coherence tomography (OCT) were prospectively and randomly enrolled in two groups of 35 subjects each (treatment and control groups). Patients in the treatment group were treated with an oral combination of diosmin (300 mg/day), with *C. asiatica* (15 mg/day) and *Melilotus* (160 mg/day). All patients underwent a complete ophthalmologic examination, OCT (Spectralis HRA-OCT), and central microperimetry (SD-SLO/OCT) at baseline, month 3, month 6, month 12, month 24, and month 36.

**Results:** No differences in HbAc1 percentage, blood pressure, microalbuminuria, visual acuity, mean central retinal thickness, and stability of fixation were present between the two groups during follow up (*p* > 0.05). Retinal sensitivity reduced in the control group only from month 6 until month 36 (*p* < 0.001). In the treatment group, a greater retinal sensitivity was present at month 12, at month 24, and at month 36 (*p* = 0.001). No side effects of treatment were observed.

**Conclusion:** Oral administration of flavonoids, *C. asiatica*, and *Melilotus* in patients with CME without macular thickening provided preservation of retinal sensitivity during 36 months of follow up when compared with untreated patients.

Introduction

**Diabetic maculopathy** is the main reason for visual loss in patients with diabetic retinopathy, besides proliferative diabetic retinopathy.1-3 Cystoid macular edema (CME) may be present in diabetic patients even in the absence of macular thickening at optical coherence tomography (OCT) examination.4,5 Flavonoids are polyphenolic compounds with potent anti-inflammatory and antioxidant properties, and they are shown to reduce expression of VEGF in experimental models.6 *Melilotus officinalis* has anti-inflammatory effects due to the activation of circulating phagocytes and lowering of citrulline production.7 *Centella asiatica* decreases endothelial permeability and capillary filtration.8 The beneficial effect of flavonoids with *C. asiatica* and *Melilotus* administered during 14 months has been suggested for diabetic CME without retinal thickening.9

Methods

Seventy consecutive patients with type 2 diabetes and CME without macular thickening at OCT were prospectively and randomly enrolled in two groups of 35 subjects each (treatment and control groups). The study was approved by the ethics committee of the University Federico II of Naples and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Criteria for inclusion were absence of clinically significant macular edema at clinical examination, presence of non-ischemic CME, normal central retinal thickness (CRT) and normal foveal contour at OCT examination, and absence of any previous treatment for diabetic retinopathy in the 6 months preceding the first examination. Patients with coexisting ocular pathologies and significant media opacities that precluded fundus examination were excluded.
Patients in the treatment group were treated with an oral combination of diosmin (300 mg/day), C. asiatica (15 mg/day), and Melilotus (160 mg/day). An oral pill (VENO-PLANT 20; Aesculapius Farmaceutici Srl Italia) containing the combination described earlier was given once daily during follow up. At each follow-up visit, patients were asked to report onset of other treatments and to confirm adherence to protocol.

Data at baseline, month 3, month 6, month 12, month 24, and month 36 are presented.

At baseline and at each follow-up visit, all patients underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA) after refraction using the Early Treatment Diabetic Retinopathy Study (ETDRS) letters scale, slit-lamp examination, funduscopy and fundus photography, OCT, and central microperimetry. At baseline, fluorescein angiography was performed to exclude ischemic macular edema. At baseline and at each visit, mean value of glycosylated hemoglobin (HbA1c) and blood pressure were monitored. Normal range of HbA1c was considered between 4% and 6%. Blood hypertension was classified in normal tension (<120/80), pre-hypertension (120–139/80–89), stage 1 (140–159 systolic or 90–99 diastolic), and stage 2 (≥160 systolic or ≥100 diastolic).10

To assess CRT, a spectral domain OCT device (Spectralis HRA-OCT, Heidelberg Engineering) was used. Active eye tracking of Spectralis OCT enables the system to have a precise automatic rescan function that places follow-up scans in precisely the same location as previous scans. CRT was considered the thickness in the central 1-mm disc, representing the foveal area. An upper limit of 270 μm for normal CRT was chosen according to the previously reported normal retinal thickness values as measured with Spectralis OCT.11 Normal foveal contour was determined by funduscopy and fundus photography, OCT, and central microperimetry. At baseline, fluorescein angiography was performed to exclude ischemic macular edema. At baseline and at each visit, mean value of glycosylated hemoglobin (HbA1c) and blood pressure were monitored. Normal range of HbA1c was considered between 4% and 6%. Blood hypertension was classified in normal tension (<120/80), pre-hypertension (120–139/80–89), stage 1 (140–159 systolic or 90–99 diastolic), and stage 2 (≥160 systolic or ≥100 diastolic).10

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Table 1. Characteristics of 70 Patients Presenting with Cystoid Macular Edema Without Macular Thickening at Baseline and Randomized in Two Groups (Control Group and Group Treated with Flavonoids, Centella asiatica, and Melilotus)

<table>
<thead>
<tr>
<th></th>
<th>Treatment group</th>
<th>Control group</th>
<th>Statistical difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (eyes)</td>
<td>35 (35)</td>
<td>35 (35)</td>
<td>–</td>
</tr>
<tr>
<td>Female/male</td>
<td>19/16</td>
<td>21/14</td>
<td>P=0.1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.8±3.6</td>
<td>65.1±3.1</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Duration of diabetes (mean±SD), years</td>
<td>6.9±5.2</td>
<td>6.6±4.1</td>
<td>P=0.1</td>
</tr>
<tr>
<td>%HbA1c (mean±SD, range)</td>
<td>7.1±1.4 (5.0–12.0)</td>
<td>7.3±1.2 (5.3–11)</td>
<td>P=0.2</td>
</tr>
<tr>
<td>% HbA1c of the last 5 years (mean±SD)</td>
<td>7.0±2.4</td>
<td>6.5±1.2</td>
<td>P=0.1</td>
</tr>
<tr>
<td>Hypertension stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 No. (%)</td>
<td>16 (45.7)</td>
<td>15 (42.9)</td>
<td>P=0.1</td>
</tr>
<tr>
<td>Stage 2 No. (%)</td>
<td>11 (31.4)</td>
<td>10 (28.5)</td>
<td>–</td>
</tr>
<tr>
<td>Prehypertension No. (%)</td>
<td>8 (22.9)</td>
<td>10 (28.5)</td>
<td>–</td>
</tr>
<tr>
<td>Microalbuminuria (mean±SD), mg/L</td>
<td>4.12±2.7</td>
<td>4.10±4.1</td>
<td>P=0.1</td>
</tr>
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</table>

SD, standard deviation; HbA1c, glycosylated hemoglobin.

Statistical analysis was performed using the Statistical Package for Social Sciences (version 17.0; SPSS Inc.). Repeated-measures ANOVA with Dunnett correction for multiple comparisons was used to compare intragroup and intergroup differences. Fisher exact test was used to compare the retinal sensitivity between eyes that showed an anatomical improvement and the control group at each follow-up visit. Results were considered significantly different if the p-value was <0.05.

Results

In the treatment group, the 35 patients (19 women, 16 men, 35 eyes) had a mean age of 64.8±3.6 years. In the control group, the 35 patients (21 women, 14 men, 35 eyes) had a mean age of 65.1±3.1 years. Characteristics of the 70 patients in the two groups at baseline are resumed in Table 1. No differences were present at baseline between the two groups with regard to sex, age, mean duration of diabetes, actual HbA1c percentage and HbA1c percentage in the last 5 years, microalbuminuria, and blood pressure.

No patient was lost to follow up. No statistically significant differences were found during follow up between the two groups with regard to HbA1c percentage, blood pressure, and microalbuminuria (Table 2). Side effects of treatment during follow up were not observed.

In the treated group, a reduction of mean retinal sensitivity was found during follow up, although it was not significant (p>0.05 at month 3, month 6, month 12, month 24, and month 36). On the other hand, BCVA slightly increased at month-12 and at month-24 visit (p>0.05), and returned to baseline values at month-36 visit. Intraretinal cysts were always localized in the central 3 mm ETDRS ring, in the inner nuclear layer in 31 cases (88.6%), and in the outer nuclear layer in 4 cases (11.4%). Disappearance of the retinal cysts was noticed in 7 out of 35 eyes (20%) after a mean period of 3.1±0.4 months, and persisted during follow up. When compared with control group, these 7 eyes showed no statistically different mean BCVA (75.50±3.7 ETDRS letters at baseline, p=0.8; 75.09±3.5 ETDRS letters at month 3, p=0.8; 75.61±3.1 ETDRS letters at month 6, p=0.6; 75.51±4.5 ETDRS letters at month 12, p=0.6; 75.38±4.1 ETDRS letters at month 24, p=0.5; 75.10±3.1 ETDRS letters at month 36, p=0.6) and a greater mean retinal sensitivity (16.12±0.25 dB at baseline, p=0.8; 16.41±0.32 dB at month 3, p=0.02;
# Table 2. Intragroup and Intergroup Differences at Baseline and During 36 Months

<table>
<thead>
<tr>
<th></th>
<th>Baseline treatment group</th>
<th>Baseline control group</th>
<th>Month-12 treatment group</th>
<th>Month-12 control group</th>
<th>Month-24 treatment group</th>
<th>Month-24 control group</th>
<th>Month-36 treatment group</th>
<th>Month-36 control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA, ETDRS letters (mean ± SD)</td>
<td>77.21 ± 5.2</td>
<td>76.82 ± 3.7</td>
<td>77.32 ± 4.1</td>
<td>76.43 ± 3.2</td>
<td>77.35 ± 4.2</td>
<td>77.22 ± 5.1</td>
<td>77.21 ± 3.3</td>
<td>76.10 ± 4.4</td>
</tr>
<tr>
<td>CRT, µm (mean ± SD)</td>
<td>220.0 ± 41.1</td>
<td>226.18 ± 22.8</td>
<td>224.21 ± 32.1</td>
<td>227.2 ± 27.3</td>
<td>231.13 ± 26.4</td>
<td>223.81 ± 22.4</td>
<td>231.41 ± 23.3</td>
<td>230.26 ± 24.1</td>
</tr>
<tr>
<td>MP retinal sensitivity, dB (mean ± SD)</td>
<td>16.12 ± 0.55</td>
<td>16.21 ± 0.27</td>
<td>15.82 ± 0.37</td>
<td>15.45 ± 0.39</td>
<td>15.71 ± 0.27</td>
<td>15.22 ± 0.18</td>
<td>15.71 ± 0.42</td>
<td>15.22 ± 0.39</td>
</tr>
<tr>
<td>MP fixation stability, n (mean ± SD)</td>
<td>Stable 35</td>
<td>Stable 35</td>
<td>Stable 35</td>
<td>Stable 35</td>
<td>Stable 35</td>
<td>Stable 35</td>
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<tr>
<td>%HbA1c (mean ± SD)</td>
<td>7.5 ± 1.6</td>
<td>7.7 ± 1.1</td>
<td>7.4 ± 2.7</td>
<td>7.3 ± 3.0</td>
<td>7.3 ± 1.6</td>
<td>7.0 ± 2.1</td>
<td>7.0 ± 1.4</td>
<td>6.9 ± 1.5</td>
</tr>
<tr>
<td>Hypertension stage</td>
<td>Stage 1, 16 patients</td>
<td>Stage 1, 15 patients</td>
<td>Stage 1, 15 patients</td>
<td>Stage 1, 18 patients</td>
<td>Stage 1, 16 patients</td>
<td>Stage 1, 18 patients</td>
<td>Stage 1, 13 patients</td>
<td>Stage 1, 15 patients</td>
</tr>
<tr>
<td>Microalbuminuria, mg/L (mean ± SD)</td>
<td>4.10 ± 2.9</td>
<td>4.21 ± 2.6</td>
<td>4.07 ± 3.0</td>
<td>4.19 ± 4.2</td>
<td>4.15 ± 4.1</td>
<td>4.15 ± 3.6</td>
<td>4.12 ± 3.8</td>
<td>4.10 ± 4.1</td>
</tr>
</tbody>
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**Discussion**

Administration of flavonoids, C. sinensis, and antioxidants to diabetic macular edema has been previously suggested to improve macular edema, visual acuity, retinal circulation times, and macular edema.

No significant differences were observed between the two groups with regard to changes in HbA1c percentage. According to these data, we may speculate that the functional preservation of the retina in diabetic retinopathy due to their effects on endothelial cell function, and on release of retinal vein occlusion.[4,13] Fibrinolitic agents, and blood pressure during follow-up. Administration of flavonoids, C. sinensis, and antioxidants to diabetic macular edema has been previously suggested to improve macular edema, visual acuity, retinal circulation times, and macular edema.

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In this study, a Spectralis OCT device was used. Active eye tracking of Spectralis OCT enables the system to have a precise automatic rescan function that places follow-up scans in precisely the same location as previous scans. By this method, an exact evaluation of changes in intraretinal cysts was possible. In 7 out of 35 treated eyes (20%), disappearance of intraretinal cysts was noticed during follow-up, while such an improvement was not observed in the control group. As previously suggested, the beneficial effects on retinal sensitivity and the disappearance of intraretinal cysts could be related to the combination of anti-inflammatory effect and the reduction of endothelial cell permeability.9

Despite worsening of retinal sensitivity in the untreated group, BCVA and retinal fixation were stable in both groups. BCVA and fixation depend on the foveal area, while microperimetry tests sensitivity in a larger area surrounding the fovea. Therefore, focal macular changes could likely affect macular sensitivity, leaving BCVA and fixation unchanged in the long term. Diabetic macular edema without retinal thickening is characterized by focal alterations in an

![FIG. 1. Diabetic macular edema without retinal thickening. (a) Color fundus image, (b) microperimetry, and (c) longitudinal B scan showing a well-circumscribed hyporeflective intraretinal cystoid space (arrow) at baseline. Retinal sensitivity is reduced in the 7x7 central macula. (d) Color fundus image, (e) microperimetry, and (f) longitudinal B scan passing for the same point after 12 months of treatment with diosmin, Centella asiatica, and Melilotus. An improvement of retinal sensitivity and disappearance of the intraretinal cyst were present and lasted until month-36 visit.](image-url)
otherwise normal macular area. Focal alterations may
determine a reduction of light sensitivity more than diffuse
edema, as they block the light from photoreceptors even
before establishment of a structural damage to the retina.
Microperimetry of eyes with CME without macular thick-
ening could, therefore, be considered a reliable method to
assess functional changes during follow up.

A limitation of this study is the relatively small sample size
in the two groups, mainly due to the prospective design.
On the other hand, major strengths are the prospective na-
ture, standardization of data collection, length of follow up,
and high rate of follow-up visits.

In conclusion, oral administration of flavonoids, C. asiatica,
and Melilotus in patients with CME without macular thick-
ening provided preservation of retinal sensitivity during 36
months of follow up when compared with untreated patients.
Such a combination could be considered a valid therapeu-
tical option to stabilize retinal function in these cases.

Author Disclosure Statement

No competing financial interests exist.

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