Author's response to reviews

Title: Central macular thickness in with type 2 diabetes mellitus without clinical retinopathy

Authors:

Mehmet Demir (dramehmetfe@hotmail.com)
Ersin Oba (ersinoba@yahoo.com)
Burcu Dirim (burcu_dirim@hotmail.com)
Erhan Ozdal (eozdal2002@gmail.com)
Efe Can (efecan06@hotmail.com)

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Central macular thickness in patients with type 2 diabetes mellitus without clinical retinopathy

Abstract

Objective: To examine the central macular thickness in patients with type 2 diabetes without clinical retinopathy.

Material and Methods: Optical coherence tomography (OCT) measurements were performed in 124 eyes of 62 subjects with diabetes mellitus without clinically retinopathy (study group: 39 female, 23 male, mean age: 55.06 ±9.77 years) and in 120 eyes of 60 healthy subjects (control group: 35 female, 25 male, mean age: 55.78 ± 10.34 years). Blood biochemistry parameters were analyzed in all cases. The data for central macular thickness (at 1 mm) and the levels of the fasting plasma glucose and glycosylated hemoglobin (HbA1c) were compared in both groups.

Results: The mean central macular thickness was 232.12±24.41 µm in the study group and 227.19± 29.94 µm in the control group.

The mean HbA1c level was 8.92 ± 2.58% in the study group and 5.07 ± 0.70% in the control group (p=0.001). No statistically significant relationship was found between CMT, HbA1c, and fasting plasma glucose level in either group (p=0.05).

Conclusions: Central macular thickness was thicker in patients with type 2 diabetes without clinical retinopathy than in healthy subjects.

Key words: diabetes mellitus, central macular thickness, glycosylated hemoglobin, fasting plasma glucose level.
Introduction

Diabetic retinopathy is the leading cause of blindness in working aged adults in westernized countries. Diabetic macular edema (DME) has been reported at rates of 10% and occurs more frequently in type 2 diabetes mellitus than in type 1. Diabetic patients also have multiple risk factors for retinopathy, such as hyperglycemia and hypertension.\textsuperscript{1} Their visual acuity is often dependent the central foveal involvement, perifoveal capillary blood flow velocity, severity of perifoveal capillary occlusion, and retinal thickness at the central fovea.\textsuperscript{2,3} The clinical findings of diabetic retinopathy are microaneurysms, soft exudates, accumulation of hard exudates, and neovascularisation.

Macular edema can develop at any stage of diabetic retinopathy. In the past, macular edema was diagnosed with slit-lamp view. Fundus fluorescein angiography provides guidance for treatment of macular edema. Optical coherence tomography (OCT) has been used for detection of macular edema secondary to different pathologies, such as diabetes mellitus, central or branched retinal vein occlusion, uveitis, and age related macular degeneration.\textsuperscript{4-11}

Material and Methods

The central macular thickness (CMT) was measured in both groups by OCT (Optovue Inc. Co., RTVue 100 model, Fremont, CA). The CMT was measured after providing pupil dilation with tropicamide drops 2 times, 10 minutes before measurement (Tropicamide 1%, Alcon Lab. Inc, USA). Three measurements were taken from each patient after pupillary dilatation. Blood biochemical tests for glycosylated hemoglobin (HbA1c) and fasting plasma glucose levels were run on all
patients. Each subject gave written informed consent to participate in the study. Ethic Committee approval was obtained from local committee.

The study group included 62 patients (124 eyes; 39 female, 23 male, mean age: 55.06 ±9.77 years) who had type 2 diabetes mellitus without clinical retinopathy and a control group of 60 patients (120 eyes; 35 female, 25 male, mean age: 55.78 ± 10.34 years) (table 1). Inclusion criteria for the study group included: no visible findings of diabetic retinopathy (hard-soft exudates, microaneurysms) on retina at slit-lamp fundus examination with a +78 D lens, type 2 diabetes mellitus, no other problems (such as hypertension, uveitis), and no history of ophthalmologic trauma, intravitreal injection, high refractive errors (spherical equivalent; between: +1.00 D to -1.00 D) or use of drugs(s) for retinal problems. Inclusion criteria for the control group patients included: no ophthalmologic or systemic problems, no history of intraocular surgery or treatment of the retina, and no high refractive errors (spherical equivalent: between -1.0 D to +1.0 D).

All cases underwent ophthalmological examinations including best corrected visual acuity (BCVA), anterior and posterior segment examinations under slit-lamp, intraocular pressure (IOP) (applanation tonometer model AT 900; Haag-Streit, Switzerland), and central macular thickness measured by OCT Visual acuity was measured with an Early Treatment Diabetic Retinopathy Study chart at 4 meters.

Exclusion criteria for both groups were visible retinopathy or uveitis, hypertension, or previous ophthalmologic surgery. In the study group, the duration of diabetes mellitus ranged from 0 – 20 years and the average was 7.19 ± 4.87 years. Five patients were newly diagnosed, 19 patients had been diagnosed for 1–5 years, 23 patients had been diagnosed for 6–10 years, 9 patients had been diagnosed for 11–15 years, and
6 patients had been diagnosed for more than 15 years. In the study group; five patients were newly diagnosed, 48 patients were undergoing insulin treatment, and 9 patients were taking oral antidiabetic drugs (table 2). Both groups were compared based on mean age, central macular thickness, fasting plasma glucose, and HbA1c levels.

The NCSS (Number Cruncher Statistical System) 2007 and the PASS 2008 Statistical Software (Utah, USA) programs were used to evaluate the results of the study.

Descriptive statistical methods (mean, standard deviation) and Student's t-test were used together to compare the data from the two groups and the parameters that showed normal distribution. The Mann Whitney U test was used to compare parameters of the two groups that did not show normal distribution. A Chi-square test was used to compare the quality of the data. Pearson correlation analyses were conducted to evaluate the relationship between the parameters showing normal distribution and Spearman's rho correlation analyses have been used to evaluate correlation between the parameters not showing normal distribution. A value of $p<0.05$ was considered significant.

**Results**

Best corrected vision (BCVA) was log MAR 0.00) in both groups. No significant differences were found for the mean age, IOP, or gender distribution (Table1).

The mean HbA1c level was $8.92 \pm 2.58\%$ in the study group, and $5.07 \pm 0.70\%$ in the control group. The mean level of HbA1c was statistically higher in the study group
than in the control group (Table 1, p=0.001). Fasting plasma glucose level was statistically higher in the study group than in the control group (Table 1, p=0.01). The duration of diabetes mellitus was 7.19±4.8 (range: 0-20) years. The mean of CMT was 232.12±24.41 µm in the study group and 227.19±29.94 µm in the control group (Table 1). The CMT was thicker in the study group than in the control group but this difference was not statistically significant.

No relationship was found between CMT and fasting plasma glucose level in the study (p=0.483) and control (p=0.399) groups. No relationship was found between CMT and HbA1c level in the study (p=0.550), and control (p=0.997; table 3).

**Discussion**

We found no studies in the literature which reviewed CMT, fasting plasma glucose level, and level of HbA1c less than HbA1c 8%.

Several previous studies \(^{12-17}\) determined that optical coherence tomography can help in the evaluation of macular edema in diabetic or non-diabetic patients, and also help in the follow-up of the patients during treatment to establish quantitative or qualitative responses to therapy.

We reviewed the relationship between central macular thickness, HbA1c, and fasting plasma glucose levels in patients with type 2 diabetes without clinical diabetic retinopathy. Optical Coherence Tomography (OCT) was used for objective measurement and monitoring of central macular thickness. Browning and Hee, et al. \(^{18,19}\) described that a change in the OCT measurements greater than 10% of the baseline thickness is likely to represent a true change in macular thickness.
Glycosylated hemoglobin is a parameter that can be used to follow up hyperglycemia over the long term. Moon, at al.\textsuperscript{20} suggested that a high baseline HbA1c and a large reduction in HbA1c were risk factors for increase in macular thickness. Yeung, et al.,\textsuperscript{21} showed that HbA1c level positively correlated with macular thickness in patients with type1 and 2 diabetes of 10 or more years’ duration without diabetic macular edema. Chou, Moreira at al.\textsuperscript{22} showed that a HbA1c level of 8% or above was associated with an increase in macular thickness in diabetic patients with diabetic retinopathy. Yeung, at al.\textsuperscript{21-23} concluded that meticulous diabetes control may slow the progression of early diabetic retinopathy and may play an important role in preventing macular dysfunction. In type 1 and 2 diabetes patients, strict follow-up of plasma glucose level could reduce the progression and development of diabetic retinopathy.

The purpose of this study was to examine central macular thickness in patients with type 2 diabetes mellitus without retinopathy. This study showed the following four results: 1) The mean central macular thickness is thicker in diabetic patients without diabetic retinopathy than in healthy subjects, but this difference was not statistically significant; 2) No positive relationship was found between fasting plasma glucose level and the central macular thickness in patients with diabetes mellitus without retinopathy; 3) Central macular thickness was not increased by mild or high levels of HbA1c (8.92±2.59%); and 4) Central macular thickness was not affected by the duration of diabetes mellitus in patients with diabetes type 2 without retinopathy.

Our opinion is that the truly effective parameter on macular thickness is vascular permeability in patients with diabetes mellitus. In this study, glycosylated HbA1c and fasting plasma glucose levels were significantly higher in diabetic patients without
retinopathy than in the control group, although there was no difference in central macular thickness between the two groups.

There are limitations to our study. One of these is the small sample size in both groups and another is that no patients had diabetes mellitus for longer than 20 years.
References


21. Yeung L, Sun CC, Ku WC, Chuang LH, Chen CH, Huang BY, et al. Associations between chronic glycosylated haemoglobin (HbA1c) level and macular volume in


Tables:

CENTRAL MACULAR THICKNESS IN PATIENTS WITH TYPE II DIABETES MELLITUS WITHOUT CLINICAL RETINOPATHY

Table 1. Demographic Characteristics, Values for Central Macular Thickness (CMT), and Biochemical Analysis in Patients with Type 2 Diabetes without Clinical Retinopathy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study group (n=62)</th>
<th>Control group(n=60)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>BCVA</td>
<td>1.0 log MAR</td>
<td>1.0 logMAR</td>
<td>NS</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>------------</td>
<td>----</td>
</tr>
<tr>
<td>IOP mmHg</td>
<td>17.8 ±2.3 mmHg</td>
<td>18.1 ±2.1 mmHg</td>
<td>NS</td>
</tr>
<tr>
<td>Age(year)</td>
<td>55.06±9.77</td>
<td>55.78±10.34</td>
<td>NS</td>
</tr>
<tr>
<td>Male/Female Gender</td>
<td>23/39</td>
<td>25/35</td>
<td>NS</td>
</tr>
<tr>
<td>CMTµm(±SD)</td>
<td>232.12±24.41</td>
<td>227.19±29.94</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c ( mean±SD)</td>
<td>8.92±2.58</td>
<td>5.07±0.70</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting blood glucose Average ±SD</td>
<td>202.14±104.78 (median:178)</td>
<td>92.17±7.75 (median:92)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

BCVA: Best corrected visual acuity, IOP: Intraocular pressure, CMT: Central macular thickness, µm:micrometer, SD: standard deviation, logMAR: minimum angle of resolution, NS: Non significant; Study group: Patients with type 2 diabetes without clinical retinopathy; Control group: healthy controls.

Table 2: Duration and Treatment of Diabetes mellitus in Patients with Type 2 Diabetes without Clinical Retinopathy

<table>
<thead>
<tr>
<th>Duration of DM</th>
<th>n(=62)</th>
<th>%</th>
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<tbody>
<tr>
<td>New diagnosis</td>
<td>5</td>
<td>8.1</td>
</tr>
<tr>
<td>1-5 years</td>
<td>19</td>
<td>30.6</td>
</tr>
<tr>
<td>6-10 years</td>
<td>23</td>
<td>37.1</td>
</tr>
<tr>
<td>11-15 years</td>
<td>9</td>
<td>14.5</td>
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</tbody>
</table>
DM: Diabetes mellitus, n: number of patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study group</th>
<th>Study group</th>
<th>Control group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>CMT-HbA1c</td>
<td>-0.077</td>
<td>0.550</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>CMT-Fasting glucose level</td>
<td>-0.091</td>
<td>0.483</td>
<td>0.0111</td>
<td>NS</td>
</tr>
</tbody>
</table>

CMT: Central macular thickness, HbA1c: glycosylated hemoglobin, NS: Non significant;
Study group: Patients with type 2 diabetes without clinical retinopathy; Control group: healthy controls.

Table 3. Relationship between Central Macular Thickness (CMT), Glycosylated Hemoglobin (HbA1c), and Fasting Blood Glucose levels in Patients with Type 2 Diabetes without Clinical Retinopathy