Research Article

Variables Associated with Diabetic Maculopathy: A Cross Sectional Study from Basrah -

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ABSTRACT

Background: Diabetic Maculopathy (DME) does not compulsorily fit the usual course of diabetic retinopathy advancement. This work aimed to study the variables associated with DME in a cohort of patients with type 2 diabetes mellitus from Basrah (Southern Iraq).

Patients and Methods: This was a cross-sectional study from Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC) done over the period of January - April 2014. The study enrolled 197 patients with type 2 diabetes mellitus with at least 10 years duration and aged >30 years.

Results: No significant differences between those with DME and no maculopathy regarding age, gender, BMI, family history of diabetes, duration of diabetes, hypertension, systolic or diastolic blood pressure, current smoking, HbA1c, lipid profile, laser treatment, cataract surgery or drug treatment.

Comparison between maculopathy 1 and 2 was showed that all the studied variables were not significantly different except for Total Cholesterol (TC), which was higher in the maculopathy 2 (P value = 0.026) and High-Density Lipoprotein Cholesterol (HDL-C) higher among maculopathy 1 (p = 0.003). Furthermore, comparing more severe maculopathy (M2) with no maculopathy only the TC remain significantly higher (p values = 0.032) among those with severe maculopathy (M2).

Only Duration of diabetes ≥ 13 years (odds ratio [OD], 0.53; 95% confidence interval [CI], 0.303 to 0.951; p = 0.032), TC ≥ 200 mg/dL (OD, 0.25; 95% CI, 0.13 to 0.47; p = 0.0001), low-density lipoprotein cholesterol (LDL-C) ≥ 100 mg/dL (OD, 0.15; 95% CI, 0.08 to 0.31; p < 0.0001) were statistically associated with DME.

On logistic regression analysis, the TC ≥ 200 mg/dL (B = -0.734, Wald = 3.900, Exp (B) = 0.480, 95% CI = 0.232 to 0.994; p = 0.048) and LDL-C ≥ 100 mg/dL (B = -1.403, Wald = 12.664, Exp (B) = 0.246, 95% CI = 0.114 to 0.533; p < 0.0001) remains significantly associated with DME.

Conclusion: Only TC and LDL-C correlated with the presence of DME. No significant associated seen with age, gender, smoking state, duration of diabetes, hypertension, BMI, high density lipoprotein cholesterol (HDL-C), HbA1c, previous laser treatment, cataract surgery or treatment for diabetes.

Keywords: Diabetic Maculopathy; Type 2 diabetes; Dyslipidemia

INTRODUCTION

Diabetic Maculopathy or Called Macular Edema (DME) is the major cause of visual loss in the working age in developed countries. According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the prevalence of DME after 15 years of known diabetes was approximately 25% in patients with type 2 who were on insulin, and 14% of patients with type 2 diabetes who were not on insulin [1,2].

Despite the fact that DME is a common complication of diabetic retinopathy and shows a clear association with the systemic metabolic diversifications of diabetes, it does not compulsorily fit the usual course of diabetic retinopathy advancement. It may occur at any stage of diabetic retinopathy, whether non-proliferative, or proliferative, or even at the most advanced stages of the retinopathy [3].

DME is characterized by increased vascular permeability and the deposition of hard exudate in the central retina. This hard exudate is thought to be the result of lipoproteins leaking from retinal capillaries into the extra-cellular space of the retina with cystic retinal thickening or lipid deposition [4].

In the retina, there is a specialized structure, blood-retinal barrier (BRB) that regulates fluid movements into and out of the retinal tissue. Breakdown of the BRB is the cause of a leak, and it’s mediated by ischemic oxygen free radicals and inflammatory mediators [5].

Retinal edema occurs when there is an increase of water in the retinal tissue, resulting in an increase in its thickness. This increase in water content of the retinal tissue may be initially intracellular (cytotoxic edema) or extra-cellular (vasogenic edema) [6].

In DME, extracellular edema resulting from the breakdown of the BRB is present [7]. All of these pathological changes were typical in diabetes, hypertension, and dyslipidemia.

DME is associated with dyslipidemia in diabetes mellitus, but the treatment of lipid disorder may not reduce these complications [8].

In the view of the increasing incidence of diabetes mellitus worldwide, DME is still representing a widespread cause of visual loss, and because of the difficulty of its treatment, it is important to identify the risk factors involved, to prevent it or get the right treatment options. The understanding of the main pathophysiologic mechanisms of this disease is demanding in the useful treatment option [9].

AIM

This work aimed to study the variables associated with DME in a cohort of patients with type 2 diabetes mellitus from Basrah (Southern Iraq).

PATIENTS AND METHODS

Study design

This was a cross-sectional study from Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC) done over the period of January – April 2015.

Participants

The total enrolled patients were 197 of them 104 (52.8%) females. All patients informed about the study and permission was taken.

Inclusion criteria

- Type 2 diabetes.
- 10 years or more of diabetes duration.
- Adult’s ≥30 years of age.

Exclusion criteria

- Type 1 diabetes.
Pregnant women.  
Those with no lipid profile or retinal examination.  
Patient’s refusal.  
Patients on statin before lipid estimation.  
Diabetes less than 10 years.  
Amputation.

We enrolled the first 2-3 patients seen in the center in the morning daily for four months (the study period) if they are fulfilled the inclusion criteria.

Patients with inclusion criteria were assessed by a single doctor for full history and examination. Including measurement of height, weight and blood pressure, which was measured in the right arm after 5 minutes rest.

Variables: age, gender, duration of diabetes, Oral Antidiabetic Drugs (OAD), insulin alone, and insulin with OAD.

Blood pressure systolic and diastolic, weight, height, family history of diabetes, previous LASER, cataract surgery.

Hypertension was defined as a doctor’s diagnosis with a drug used in the past or an average of two readings of blood pressure measurement of 140/90 or more for new cases.

Eye examination

The full Ophthalmological examination was done in the form of; best corrected visual acuity (BCVA), slit-lamp examination and intraocular pressure measurement, fundus examination using indirect slit-lamp biomicroscopy to determine the presence or absence of maculopathy, and optical coherence tomography (OCT) was done when indicated.

Maculopathy (M) was divided according to grading scheme of the Scottish Diabetic Retinopathy Screening Collaboration [10].

M1 (observable):
- Lesions within a radius of >1 but < − 2 disc diameters of the center of the fovea
- Any hard exudates

M2 (referable):
- Lesions within a radius of < − 1 disc diameter of the center of the fovea
- Any blot hemorrhages
- Any hard exudates

For all patients fasting lipid profile was done at 8:00 a.m. advising the patient to omit statin therapy two weeks before the day of the test for those taking statin.

Biochemical testing

HbA1c was done using Biolyzer 300 chemistry analyzer and D-10 hemoglobin testing system by Bio-Rad Laboratories, Inc., Hercules, CA 94547 respectively.

Serum lipid profile was measured in the early morning after at least 10 hours fasting using 5 ml of venous blood and, the measurement was done using Fully Automated Clinical Chemistry Analyzer Biolyzer’ 300. Lipid profile abnormalities were classified according to National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [11].

STATISTICAL ANALYSIS

All data were entered into SPSS-15. Continuous variables expressed as mean ± SD categorical variables as number and percent accordingly. Chi squared (χ²) test, and Student t-test was used to studying the difference between variables. All continuous variables were put into categorical variables to be used for univariate analysis. Variables significantly associated with maculopathy on univariate analysis were entered into a logistic regression analysis to see which variable remains statistically significantly associated with maculopathy. A P values less than 0.05 were reported as statistically significant.

RESULTS

Table 1 show basic characteristics. The mean age was 56.8 ± 7.7 years, ranged between 36 and 82 years. Of them, 52.8% were men with a mean duration of diabetes was 14.3 ± 5.2 years, ranged between 10 and 45 years. The Family history of diabetes was positive in 63.5% ,and 45.2% were hypertensive. The mean of BMI (Kg/m²) was 29.9 ± 4.8. We have 66 patients (33.5%) with varying degree of DME. There were 41 patients (62.1%) exhibited grade 1 maculopathy (M1), and 25 patients (37.9%) had grade 2 maculopathy (M2).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD or number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.8 ± 7.7</td>
</tr>
<tr>
<td>Male gender</td>
<td>104 (52.8)</td>
</tr>
<tr>
<td>Female gender</td>
<td>93(47.2)</td>
</tr>
<tr>
<td>Duration of DM (years)</td>
<td>14.3 ± 5.2</td>
</tr>
<tr>
<td>Current smoker</td>
<td>51 (25.9)</td>
</tr>
<tr>
<td>Family history of diabetes mellitus</td>
<td>125 (63.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89(45.2)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>137.7 ± 18.9</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>81.0 ± 9.6</td>
</tr>
<tr>
<td>Body mass index (BMI) - kg/m²</td>
<td>29.9 ± 4.8</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>10.4 ± 2.0</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (HDL-C) mg/ dl</td>
<td>46.6 ± 16.9</td>
</tr>
<tr>
<td>Triglycerides (TG) mg/dL</td>
<td>197.2 ± 139.7</td>
</tr>
<tr>
<td>Very-low-density lipoprotein cholesterol (VLDL-C) mg/dL</td>
<td>39.0 ± 27.9</td>
</tr>
<tr>
<td>No maculopathy</td>
<td>131.0 (66.5)</td>
</tr>
<tr>
<td>Maculopathy (any)</td>
<td>66(33.5)</td>
</tr>
<tr>
<td>Maculopathy 1</td>
<td>41 (62.1)</td>
</tr>
<tr>
<td>Maculopathy 2</td>
<td>25 (37.9)</td>
</tr>
<tr>
<td>Laser Treatment</td>
<td>9(4.6)</td>
</tr>
<tr>
<td>Cataract Surgery</td>
<td>18 (9.1)</td>
</tr>
<tr>
<td>Oral Antidiabetic Drugs (OAD)</td>
<td>58 (29.4)</td>
</tr>
<tr>
<td>Insulin alone</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>OAD+ insulin</td>
<td>135 (68.5)</td>
</tr>
</tbody>
</table>

Table 1: Demographic characteristics of 197 patients with type 2 diabetes mellitus.
Differences between 197 patients with maculopathy and no maculopathy are present in Table 2. No significant differences between the two groups regarding age, gender, BMI, family history of diabetes, duration of diabetes, hypertension, systolic or diastolic blood pressure, current smoking, HbA1c, lipid profile, laser treatment, cataract surgery or drug treatment.

Comparison between maculopathy 1 and 2 was made in Table 3. Again, all the studied variables were not significantly different except for Total Cholesterol (TC), which was higher in the maculopathy 2 (P value = 0.032) and high-density lipoprotein cholesterol (HDL-C) higher among maculopathy 1 (p = 0.003).

When we compared more severe Maculopathy (M2) with no maculopathy only the TC remain significantly higher (p values = 0.032) among those with severe maculopathy (M2) in table 4.

All variables changed to categorical variables to study the association with maculopathy using univariate analysis (Table 5). Only duration of diabetes≥13 years (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.303 to 0.951; p = 0.032), TC ≥200mg/dL (OR, 0.15; 95% CI, 0.08 to 0.31; p <0.0001) were statistically associated with DME.

DISCUSSION

The prevalence of maculopathy has varied widely depending on the methodology and populations. In this study, the overall prevalence of diabetic maculopathy was 33.5%, which is comparable to Raman et al., study [12] and Al-Till et al., [13], was 31.76%, 30.8% respectively. Several studies show a lower prevalence of maculopathy; like Zander et al., Study [14], which reported the prevalence of
maculopathy in the type 2 diabetic cohort was 23%, whereas Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found a DME prevalence of 28% among 1121 people whose age at diagnosis was 30 years or older whose duration of diabetes was 20 or more years. In Salem et al. study the prevalence of maculopathy was (17%) [15] and the prevalence was 6.3% by Khanekar et al. [16]. This variation may reflect the poor glycemic control of Iraqis in addition to socioeconomic and racial factor with food habits. In this study, there is no significant association between DME and age. The similar finding also reported by others [17,18].

Gender is not identified as a risk factor in our study, which was also seen in previous studies [12,17,18].

BMI showed no significant association with maculopathy; a similar finding reported before [20,21]. On the other hand, cross sectional study done by Van Leiden et al., [22] and Laila H.M. El-Shaly et al., [23] both reported association of macular edema and increased BMI. However, Looker et al., [24] found that lower BMI was associated with increased severity of retinopathy.

The relationship between smoking and DME is not well understood. Smoking in this study was not associated with maculopathy that, a similar finding to others [17,25,26]. An analysis of data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy found that smoking status was not related to the incidence and progression of DR over 4 years. [27] Similarly, a more recent analysis of 25-year data from the same Wisconsin study found a univariate relationship of a higher incidence of macular edema in diabetic persons who smoked more than 15 pack-years after diabetes diagnosis; however, this relationship was not significant in multivariate analyzes. [28]. The reasons for not finding a relation are not known. Regardless, smoking should be avoided due to its relation to increased risk of death and other systemic complications.

Because of the cross sectional design in our study, the relation between maculopathy and hyperglycemia (as measured by HbA1C), was not seen like that was seen in prospective studies [29]. Yet, there was an association between maculopathy and the duration of DM (as demonstrated by univariate analysis) and hence with exposure to hyperglycemia. Zander et al. Study [14] found the same results.

Table 5: Univariate analysis, among those with maculopathy and those without among 197 patients with type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No maculopathy</th>
<th>Maculopathy</th>
<th>OR Maculopathy vs. no maculopathy (95% Confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥60 years</td>
<td>45(40.5)</td>
<td>37(43.0)</td>
<td>0.903(0.510, 0.598 )</td>
<td>0.726</td>
</tr>
<tr>
<td>Male gender</td>
<td>55(49.5)</td>
<td>49(57.0)</td>
<td>0.742(0.421, 1.306)</td>
<td>0.300</td>
</tr>
<tr>
<td>Current smoker</td>
<td>25 (22.5)</td>
<td>26 (30.2)</td>
<td>0.671(0.354,1.273)</td>
<td>0.220</td>
</tr>
<tr>
<td>Family history of diabetes mellitus</td>
<td>69(62.2)</td>
<td>56 (65.1)</td>
<td>0.880(0.490,1.582)</td>
<td>0.669</td>
</tr>
<tr>
<td>Duration of diabetes≥13 years</td>
<td>47 (42.7)</td>
<td>50 (58.1)</td>
<td>0.537(0.303,0.951)</td>
<td>0.032</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (44.1)</td>
<td>40 (46.5)</td>
<td>0.909 (0.516,1.600)</td>
<td>0.741</td>
</tr>
<tr>
<td>Systolic BP (mmHg) ≥ 140</td>
<td>61 (55.0)</td>
<td>39(45.3)</td>
<td>1.470 (0.835,2.589)</td>
<td>0.181</td>
</tr>
<tr>
<td>Diastolic BP (mmHg) ≥ 90</td>
<td>24 (21.6)</td>
<td>19 (22.1)</td>
<td>0.973(0.492, 1.922)</td>
<td>0.937</td>
</tr>
<tr>
<td>Body mass index (BMI) - kg/m² ≥ 25</td>
<td>95(85.6)</td>
<td>76 (88.4)</td>
<td>0.781(0.335,1.820)</td>
<td>0.567</td>
</tr>
<tr>
<td>HbA1c % ≥10</td>
<td>61 (55.0)</td>
<td>58 (67.4)</td>
<td>0.589 (0.326,1.058)</td>
<td>0.076</td>
</tr>
<tr>
<td>Total cholesterol (TC) mg/ dL ≥ 200</td>
<td>49 (44.1)</td>
<td>65 (75.6)</td>
<td>0.255 (0.138,0.474)                                     &lt;.00001</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (LDL-C) mg/ dL ≥100</td>
<td>50(45.0)</td>
<td>72 (83.7)</td>
<td>0.159 (0.080,0.316)                                     &lt;.00001</td>
<td></td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (HDL-C) mg/ dL &lt;40</td>
<td>47 (42.3)</td>
<td>33 (38.4)</td>
<td>1.179 (0.664, 2.096)</td>
<td>0.574</td>
</tr>
<tr>
<td>Triglycerides (TG) mg/ dL ≥ 150</td>
<td>62 (55.9)</td>
<td>51 (59.3)</td>
<td>0.886 (0.491, 1.536)</td>
<td>0.628</td>
</tr>
<tr>
<td>Very-low-density lipoprotein cholesterol (VLDL-C) mg/dL &gt;30</td>
<td>61 (55.0)</td>
<td>50 (58.1)</td>
<td>0.878 (0.497, 1.551)</td>
<td>0.655</td>
</tr>
<tr>
<td>Laser treatment</td>
<td>5 (4.5)</td>
<td>4 (4.7)</td>
<td>0.967 (0.252, 3.715)</td>
<td>0.961</td>
</tr>
<tr>
<td>Cataract surgery</td>
<td>8 (7.2)</td>
<td>10 (11.6)</td>
<td>0.590 (0.222, 1.566)</td>
<td>0.286</td>
</tr>
<tr>
<td>OAD+ insulin</td>
<td>72 (53.7)</td>
<td>62 (46.3)</td>
<td>0.715 (0.388,1.317)</td>
<td>0.356</td>
</tr>
</tbody>
</table>

Table 6: logistic regression analysis for variables significantly associated with maculopathy on univariate analysis.

<table>
<thead>
<tr>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>P value</th>
<th>Exp (B)</th>
<th>95% Confidence interval for EXP (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes≥13 years</td>
<td>-0.532</td>
<td>-0.532</td>
<td>2.757</td>
<td>1</td>
<td>0.097</td>
<td>0.587, 0.313, 1.101</td>
</tr>
<tr>
<td>Total cholesterol (TC) mg/dL ≥200 mg/dL</td>
<td>-0.734</td>
<td>0.372</td>
<td>3.900</td>
<td>1</td>
<td>0.048</td>
<td>0.480, 0.232, 0.994</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (LDL-C) mg/dL ≥100 mg/dL</td>
<td>-1.403</td>
<td>0.394</td>
<td>12.664</td>
<td>1</td>
<td>&lt;0.0001</td>
<td>0.246, 0.114, 0.533</td>
</tr>
</tbody>
</table>
Regarding the duration of diabetes, it was found to be significantly higher in patients with maculopathy on univariate analysis, but the relationship was no longer significant in a multivariate logistic regression analysis in this study. Few previous studies showed the duration of diabetes as a risk factor for diabetic macular edema [14,30,31]. Wisconsin Epidemiologic Study of Retinopathy also exhibited the importance of the diabetic duration, which showed an increased prevalence of diabetic maculopathy of 28% of patients whose age at the time of diagnosis was 30 years or older and whose diabetes duration was 20 years or longer [32]. This discrepancy could be explained as the macular edema may occur at any stage of diabetic retinopathy even in the absence of severe retinopathy and sometimes can present as early diabetic sign. Our finding correlates with the study reported by Sasaki et al., [18].

Previous studies have found that serum lipids were associated with macular hard exude and DME [12,33-38].

The Early Treatment Diabetic Retinopathy Study (ETDRS) reported an association of total cholesterol and LDL-C levels in the presence of hard exudates in the macula in patients with DR [35]. Idiculla et al., [36] reported that cholesterol levels were associated with hard exudates in the center of the macula, and LDL cholesterol levels were associated with CSME in patients with type 2 diabetes. The Chennai Urban Rural Epidemiology Study (CURES) Eye Study also found a correlation between LDL-C level and CSME and DME [39].

The Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study13 reported that total cholesterol related to severe maculopathy and that LDL cholesterol related to DME [12].

The WESDR also reported an association between serum cholesterol and severity of hard exudates [29]. Our results are consistent with findings from these studies. Our study observed the association of serum lipids with maculopathy. Concerning the no maculopathy versus maculopathy group, increasing proportions with elevated levels was noted for serum total cholesterol and serum LDL cholesterol in univariate analysis. Even, after adjusting the confounding variables, the multivariate analysis identified two variables associated with maculopathy; serum total cholesterol and LDL-C. As mentioned above, the ETDRS was reported that higher baseline total and LDL-C levels increased the risk of retinal exudation by two-fold [35].

CONCLUSION

Only TC and LDL-C correlated with the presence of DME. No significant associated seen with age, gender, smoking state, duration of diabetes, hypertension, BMI, HDL-C HbA1c level, previous laser treatment, cataract surgery, or treatment for diabetes. However, larger studies may give more information.

REFERENCES

25. Looker HC, Knowler WC, Hanson RC. Changes in BMI and weight before...


