Association between diabetic macular edema and ischemic Heart diseases in type 2 Diabetes Mellitus

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Abstract:

Introduction: Diabetic macular edema is the most important cause of visual loss in diabetic patients.

Aim of study: To evaluate the association between Ischemic heart diseases and diabetic macular edema in type two diabetes mellitus patients by assessing the severity of visual impairment, assessment of central macular thickness and macular cystoid changes by ocular coherence tomography when both diseases coexist.

Patients and methods: In this study, total of (128) patients studied and classified into two groups , (64) patients were in the first group whom have Ischemic heart diseases and type 2 diabetes mellitus, those compared with a second group of another (64) patients whom have type 2 diabetes mellitus without Ischemic heart event. Visual acuity, cystoid macular edema by ocular coherence tomography, central macular thickness by ocular coherence tomography compared between two groups.

Results: In this study, we noticed that 77.4 % of studied eyes with visual acuity of 6/60 or worse were in first group with a significant association. Regarding ocular coherence tomography results, 80.8 % of studied patients with bilateral cystoid macular edema also were in first group with a significant association.

Regarding central macular thickness, the mean was higher in first group (330.96±133.79) as compared with second group (284.03±93.26) with a significant association (p=0.001).

Conclusion: Comparison between two groups revealed significant association between ischemic heart diseases and severity of visual acuity impairment with more sever ocular coherence tomography findings in the first group.

Key words: ischemic heart disease, visual acuity, type 2 diabetes

1. Introduction:

1.1. Overview

Diabetic maculopathy (DM) is one of the major causes of vision impairment in patients with diabetes mellitus. The traditional approach to DM includes fundus ophthalmoscopy and fluorescein angiography. Despite very useful clinically, these methods do not contribute much to the evaluation of retinal morphology and its thickness profile. That is why a technique called optical coherence tomography (OCT) was utilized to perform cross-sectional imaging of the retina, which facilitates measuring the macular thickening, quantification of diabetic macular edema and detecting vitreoretinal traction (1).

Diabetic macular edema (DME) may occur at any stage of diabetic retinopathy and is the leading cause of moderate vision loss in adults of working age (2). Cardiovascular events, such as myocardial infarctions (MI) are known macrovascular complications of diabetes mellitus. Furthermore, microvascular complications, like DME, are associated with progressive or uncontrolled diabetes (3).

1.2. Anatomy of macula

The macula is an oval-shaped pigmented area near the center of the retina of the human eyes. The macula in humans has a diameter of around 5.5 mm and is subdivided into the umbo, foveola, foveal avascular zone, fovea, parafovea, and perifovea areas. The anatomical macula at 5.5 mm is much larger than the clinical macula which, at 1.5 mm corresponds to the anatomical fovea (4).

1.3. Definition of diabetic maculopathy

Diabetic maculopathy, resulting from diabetic retinopathy, is defined as the presence of retinal thickening within one-disc diameter or two of the macula. Macular edema results from the accumulation of fluid at the posterior pole of the retina and visual acuity is threatened if the retina in the center of the macula is thickened. Factors associated with the development of maculopathy are mostly unknown. Since diabetic maculopathy is characterized by increased capillary leakage in the main retinal vessels and by alterations in the microcirculation of the macula, several previous reports have suggested that poor metabolic control might be involved in haemodynamic changes of retinal circulation, and thereby lead to maculopathy (5).

1.4. Cystoid diabetic macular edema

The American Academy of Ophthalmology Preferred Practice Patterns defines Cystoid Macular Edema (CME) as retinal thickening of the macula due to a disruption of the normal blood-retinal barrier; this causes leakage from the perifoveal retinal capillaries and accumulation of fluid within the intracellular spaces of the retina, primarily in the outer plexiform layer. Visual loss occurs from retinal thickening and fluid collection that distorts the

architecture of the photoreceptors. CME is a leading cause of central vision loss in the developed world (6).

1.5. Pathophysiology

Chronic hyperglycemia, hypercholesterolemia, free oxygen radicals, advanced glycation end-products, and protein kinase C are involved in the pathologic process of DME (7). The common characteristic is the increase in levels of vascular endothelial growth factor (VEGF), which is responsible for the disruption of the inner blood–retinal barrier (BRB) (8).

1.6. Investigations: Optical coherence tomography (OCT)

The current use of OCT as a method of exploring the macular area has changed the way of diagnosing macular edema. OCT is an effective method of diagnosis of DME and in turn has become an essential technique for classifying the edema and observing the effect of its treatment. In the near future, OCT is likely to become the gold standard method of diagnosis and monitoring of patients with macular edema (9).

1.7. Vascular changes in diabetes and Ischemic heart diseases

Reducing atherosclerotic cardiovascular disease burden in diabetes mellitus is a major clinical imperative that should be prioritized to improve quality of life, and lessen individual and economic burdens of associated morbidities, decreased work productivity, and high cost of medical care (10). Diabetes is a major risk factor for the development of ischemic heart disease (IHD) with a higher incidence of MI in patients with DM than those without. Although the exact pathophysiology of IHD progression in patients with DM has not yet been determined, It is thought that the higher incidence of myocardial infarction in patients with DM is attributable to increased coagulability. Many studies have found that diabetics have increased expression of glycoprotein IIB/IIIA receptors and von-Willebrand factor (VWF), which are responsible for platelet activation. Patients with DM also have increased plasminogen activator inhibitor type I which could decrease fibrinolysis, increase thrombus formation and accelerate plaque formation. Finally, diabetic patients also tend to have decreased circulating anti-coagulants such as protein c and antithrombin III due in a large part to the proteinuria. Collectively, these factors place patients with DM in a prothrombotic and procoagulant state, which may account for the higher rates of IHD seen in diabetic patients (11).

Some clinical (e.g. hypertension, nephropathy) and biological parameters (e.g. high glycated hemoglobin) are established risk factors for DME and cardiovascular events (12).

A recent retrospective study comparing incidence rates of myocardial infarction and cerebrovascular accident requiring hospitalization in DME patients and in diabetic patients without retinal involvement, found significantly more cardiovascular events, such as myocardial infarction and cerebrovascular events, in patients with DME (13). One possible hypothesis explaining these associations is that retinal microvascular abnormalities may reflect early subclinical disease in the coronary or cerebral microvasculature, predisposing people to develop clinical cardiovascular events (14).

2. Patients and Methods:

2.1. Study design

In this retrospective cohort study, (128) patients were enrolled and classified into two groups, each group comprised (64) patients with (128) eyes studied, first group were patients with history of Ischemic heart diseases and onset of type 2 DM (NIDDM) between 5-15 years, second group were patients with type 2 (NIDDM) for 5-15 years without history of Ischemic heart diseases.

This study done in medical city complex-Ghazi Al-Hariri Teaching Hospital in coordination with diabetic disease center in Baghdad Teaching Hospital, between November 2018 and April 2019.

Each patient asked about type of DM, duration of type 2 DM, clinically proved Ischemic heart disease which either necessitate CCU admission or proved cardiologist senior visits with medical reports, previous ECG findings of Ischemic heart disease , number of Ischemic attacks, and also ophthalmic history for any ocular surgeries or intravitreal Anti-VEGF injections evaluated.

Each patient examined for best-corrected visual acuity by Snellen s chart, slit lamp biomicroscopic examination for media opacity and then underwent macular OCT for cystoid changes detection and central thickness measurement.

2.2. Inclusion Criteria

Type 2 DM (NIDDM) for 5-15 years, Type 2 DM (NIDDM) for 5-15 years with one or more clinically proved Ischemic heart disease attacks, and age more than 50 years for both groups.

2.3. Exclusion criteria

Type 1 DM (IDDM), type 2 DM (NIDDM) less than 5 years or more than 15 years or with uncertain duration from history, age less than 50 years for both groups, hospital admitted severely ill diabetic patients (those with Diabetic foot, Diabetic Nephropathy),

 eyes with media opacity that affect OCT interpretation or affect VA, patients with history of ocular surgery or Anti-VEGV injections, and patients with other non-diabetic retinopathies.

2.4. Optical coherence tomography screening:

All patients examined in Ophthalmology department in Ghazi Al-Hariri Hospital, by the same OCT device (Optovue, software version 6, 8, 0, 27), time domain OCT (TD-OCT) imaging of the maculae of both groups performed by the same experienced optometrist team.

Pupillary dilatation was performed for those with small pupil diameters that affect OCT imaging, all patients learned how to perform the test to avoid artifacts or unwanted eye movements during test performance.

In this study, we considered central macular thickness (CMT) of (275 μm) by OCT as the upper normal limit, as the normal central macular thickness never exceed (253 μm) (15),

Browning et al. and Hee et al. 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 (16), cystoid macular edema (CME) considered by the presence of cystic cavities in the macular region by OCT.

2.5. Severity of visual acuity impairment:

In this study, visual acuity (VA) assessed by Snellen s chart for each patient and we considered VA of 6/6 as normal. VA of (6/9 up to 6/18) as mild visual impairment, VA of (6/24 up to 6/60) as moderate visual impairment, and VA of 6/60 or worse as sever visual impairment (17), (18).

2.6. Statistical Analysis:

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges, Chi square test used to assess the association between categorical variables, a level of P – value less than 0.05 considered significant.

2.7. Ethical Issues:

The study design and data collection done after getting approval of Iraqi committee for medical specialization. All patients informed about methodology and purpose of study and verbal consents obtained.

3. Results:

The total number of patients in this study was 128 with 256 eyes. All of them diagnosed with type 2 diabetes mellitus. They divided into two groups, first group included 64 patients and 128 eyes with history of ischemic heart disease, and second group included the other 64 patients and 128 eyes with no history of ischemic heart disease.

3.1. Age and Gender

Study patient's age was ranging from 50 to 81 years with a mean of 58.17 years and standard deviation (SD) of ± 7.6 years. The highest proportion of study patients was aged < 60 years (64.8%), regarding gender, proportion of males was higher than females (54.7% versus 45.3%) with a male to female ratio of 1.2:1.

In our study, regarding first group mean age was (59.23) years with standard deviation (SD) of ± (7.99) years, and regarding second group mean age was (56.99) years with standard deviation (SD) of ± (6.94) years.

Regarding male gender total number were (70) patients from total of (128) patients studied, (31) male patients were in first group and (39) male patients were in second group, from total male gender with mean of (54.7), first group mean male gender was (48.4) and second group mean male gender was (60.9).

Regarding female gender total number were (58) patients from total of (128) patients studied, (33) female patients were in first group and (25) female patients were in second group, from total female gender with mean of (45.3), first group mean female gender was (51.6) and second group mean female gender was (39.1).

In comparison between study group and age and gender, we noticed that there were no significant differences (P ≥ 0.05) in age and gender between study groups as shown in table (3.1) and (3.2).

Table 3.1: Comparison between study groups in age.

| Age (Years) | Study Group | | P - Value |
	First Group Mean ± SD	Second Group Mean ± SD	
	59.23 ± 7.99	56.99 ± 6.94	0.093

Table 3.2: Comparison between study groups in gender.

| Gender | Study Group | | Total (%) n= 128 | P- Value |
	First Group n= 64	Second Group n= 64		
Male	31 (48.4)	39 (60.9)	70 (54.7)	0.155
Female	33 (51.6)	25 (39.1)	58 (45.3)	

3.2. Clinical parameters

3.2.1. Distribution of study patients by Visual acuity:

In our study, total number of eyes with normal visual acuity were (46) with mean of (18.0) from total (256) studied eyes, (16) eyes with normal VA were in the first group with mean of (12.5) and (30) eyes with normal VA were in the second group with mean of (23.4).

Total number of eyes with mild visual impairment were (133) with mean of (52.0) from total studied eyes, (63) eyes with mild visual impairment were in the first group with mean of (49.2) and (70) eyes were in the second group with mean of (54.7).

Total number of eyes with moderate visual impairment were (46) with mean of (18.0) from total studied eyes, (25) eyes with moderate visual impairment were in the first group with mean of (19.5) and (21) eyes were in the second group with mean of (16.4).

Total number of eyes with severely impaired vision were (31) with mean of (12.0) from total studied eyes, (24) eyes with sever impairment were in the first group with mean of (18.8) and (7) eyes were in the second group with mean of (5.5).

3.2.2. Distribution of study patients by central macular thickness:

In this study, from 256 studied eyes in both study groups, CMT was less than 275 μm in (143) eyes with mean of (55.9), in the first group (66) eyes and in the second group (77) eyes. While CMT was ≥ 275 μm in (113) eyes with mean of (44.1), in the first group (62) eyes and in the second group (51) eyes.

Table 3.3: Distribution of study patients' eyes by clinical information

Clinical Parameters	Study Group (number of eyes)		Total (%) n= 256
	First Group n= 128	Second Group n= 128	
Visual Acuity			
Normal vision	16 (12.5)	30 (23.4)	46 (18.0)
Mild impairment	63 (49.2)	70 (54.7)	133 (52.0)
Moderate impairment	25 (19.5)	21 (16.4)	46 (18.0)
Severe impairment	24 (18.8)	7 (5.5)	31 (12.0)
Central Macular Thickness (μm)			
< 275	66 (51.6)	77 (60.2)	143 (55.9)
≥ 275	62 (48.4)	51 (39.8)	113 (44.1)

3.2.3. Distribution of study patients by OCT findings:

In this study, from total of (128) studied patients (70) patients have normal OCT findings with mean of (54.7), (26) patients in the first group and (44) patients in the second group, unilateral CME found in (32) studied patients with mean of (25.0), among them (17) patients were in the first group and (15) in the second group. While bilateral CME found in (26) patients with mean of (20.3), among them (21) patients were in the first group and only (5) patients were in the second group.

Table 3.4: Distribution of study patients by clinical information

Clinical Parameters	Study Group (number of patients)		Total (%) n= 128
	First Group n= 64	Second Group n= 64	
Optical Coherence Tomography			
Unilateral Cystoid Macular Edema	17 (26.6)	15 (23.4)	32 (25.0)
Bilateral Cystoid Macular Edema	21 (32.8)	5 (7.8)	26 (20.3)
Normal	26 (40.6)	44 (68.8)	70 (54.7)
Number of ischemic attacks			
One	33 (51.6)	0 (0)	33 (51.6)
Frequent	31 (48.4)	0 (0)	31 (48.4)

3.3. Association between Ischemic heart disease and clinical data:

Tables 3.5 and 3.6 show the association between IHD and both of visual acuity and optical coherence tomography results.

majority of eyes (77.4 %) with severe visual impairment had previous ischemic attacks, and only (22.6 %) of eyes with severe visual impairment had no previous ischemic attacks, and majority of eyes (65.2 %) with normal vision had no IHD as compared with (34.8 %) eyes with normal vision and previous IHD

Table 3.5: Association between IHD and visual acuity

Variable	Study Group (no. of eyes)		Total (%) n= 256	P- Value
	First Group n= 128	Second Group n= 128		
Visual Acuity				
Normal vision	16 (34.8)	30 (65.2)	46 (18.0)	
Mild impairment	63 (47.4)	70 (52.6)	133 (52.0)	0.003
Moderate impairment	25 (54.3)	21 (45.7)	46 (18.0)	
Severe impairment	24 (77.4)	7 (22.6)	31 (12.0)	

majority of patients (80.8 %) with bilateral CME had previous ischemic attacks as compared with (19.2 %) with bilateral CME had no previous IHD, and larger proportion of patients (62.9 %) with normal OCT had no previous IHD as compared with (37.1 %) of patients with normal OCT had previous IHD

Table 3.6: Association between IHD and optical coherence tomography results

Variable	Study Group (no. of patients)		Total (%) n= 128	P- Value
	First Group n= 64	Second Group n= 64		
Optical Coherence Tomography Results				
Unilateral CME	17 (53.1)	15 (46.9)	32 (25.0)	
Bilateral CME	21 (80.8)	5 (19.2)	26 (20.3)	0.001
Normal	26 (37.1)	44 (62.9)	70 (54.7)	

In comparison between study groups by central macular thickness, mean of CMT was significantly higher in the first group than that in the second group (330.96 versus 284.03 μm) as shown in table (3.7).

Table 3.7: Comparison between study groups by CMT.

Central Macular Thickness (μm)	Study Group		P- Value
	First Group Mean ± SD	Second Group Mean ± SD	
	330.96 ± 133.79	284.03 ± 93.26	0.001

3.4. OCT in the first group:

Table 3.8 shows the association between Optical Coherence Tomography Results and no. of previous ischemic attacks in the first group.

From (64) patients in the first group (33) patients have one ischemic attack and (31) patients have frequent attacks, total patients in this group with normal OCT were (26) from those (12) patients have one attack and (14) patients have frequent attacks, also we have (17) patients with unilateral CME in this group from those (8) have one ischemic attack and (9) have frequent attacks, and from (21) patients in this group with bilateral CME (13) have one attack and (8) have frequent attacks.

From (64) patients in this group (31) were male patients and (33) were female patients, (11) male as compared with (15) female patients have normal OCT findings, (7) male as compared with (10) female patients have unilateral CME, and (13) male patients as compared with (8) female patients have bilateral CME.

Table 3.8: Association between OCT and no. of previous ischemic attacks

Variable	Optical Coherence Tomography Results			Total (%) n= 64	P- Value
	Bilateral CME n= 21	Unilateral CME n= 17	Normal n= 26		
No. of ischemic attacks					
One	13 (39.4)	8 (24.2)	12 (36.4)	33 (51.6)	0.511
Frequent	8 (25.8)	9 (29.0)	14 (45.2)	31 (48.4)	
Gender					
Male	13 (41.9)	7 (22.6)	11 (35.5)	31 (48.4)	0.32
Female	8 (24.2)	10 (30.3)	15 (45.5)	33 (51.6)	

4. Discussion:

4.1. Comparison between study groups by age and gender:

In this study, we noticed that there is no significant difference between two groups in age and gender with ($p \geq 0.05$) as shown in table 3.1and 3.2.

4.2. Comparison between study groups by visual acuity:

The visual acuity of the majority of eyes in both groups were mildly impaired (49.2% and 54.7% respectively), but majority of eyes with normal VA were in the second group as compared with the first group. while majority of eyes with severe visual acuity impairment were in the first group as shown in table 3.3, also we noticed that 77.4% of eyes with severe impairment had previous ischemic attacks with a significant association between study groups and visual acuity (P= 0.003) as shown in table 3.5. our study results are compatible with St

Vincent et al which demonstrated that a reduction In visual acuity by 30 % can occur in patients with both Diabetes type 2 and Ischemic heart diseases caused by high serum triglyceride levels(19) (20).

4.3. Comparison between study groups by CMT:

In our study, as mentioned in chapter three and shown in table (3.7) mean central macular thickness was significantly higher in the first group with (p=0.001). This result is comparable with a study, which demonstrated that, the presence of ischemic coronary heart disease correlated with a slight increase of both retinal thickness and foveal volume (21).

4.4. Comparison between study groups by CME:

We noticed that majority of patients have normal OCT with higher proportion in the second group, and majority of patients with bilateral CME were in the first group as compared with the second group (32.8 % and 7.8 % respectively), and no significant difference by OCT with unilateral CME between two groups as shown in table (3.4). However, 80.8% of patients with bilateral CME had previous ischemic attacks with significant association between study group and OCT results (P= 0.001).

These results are compatible with studies that revealed the association between exudative type diabetic maculopathy and Ischemic heart diseases caused by abnormal lipid profile (22) (23).

 Comparison of a small group of diabetic patients with severe exudative maculopathy to a group with non-exudative retinopathy demonstrated a significantly higher level of serum triglyceride and consequent IHD in the former group, although serum cholesterol was not significantly different(22), an elevation in cholesterol has been shown in studies of exudative maculopathy in type 1 diabetes not type 2 DM (23)(24).

Further studies have linked LDL cholesterol with maculopathy, although numbers of patients in these studies were small (25) (26), a direct toxic effect of LDL on retinal capillary pericytes has also been demonstrated, and this toxic effect can be enhanced by LDL glycation or oxidation. In other small cross-sectional studies, lipoprotein (a) has been suggested as a risk factor for maculopathy (27) (28). however, this is against an old study by Ossama et al, which after adjustment for risk factors, the relationship between IHD and maculopathy was no longer significant (29).

4.5. Others:

there is no significant association between OCT findings and number of ischemic attacks with (p=0. 511) as shown in table 3.8. and no significant association between OCT finings and gender with (p=0.32) as shown in table 3.8.

5. Conclusion:

5.1. Conclusion:

According to our aim and in comparison between two groups, the majority of studied eyes with visual acuity of 6/60 or worse were in the first group.

The central macular thickness was significantly higher in the first group.

Regarding OCT findings, the majority of patients with bilateral cystoid macular edema were in the first group with no significant difference in unilateral cases between two groups.

The number of previous ischemic heart attacks has no significant effect on cystoid maculopathy detected by OCT among patients with type 2 DM.

This is consistent with previous reports of an association of proliferative retinopathy with ischemic coronary heart disease in people with type 2 DM (30) (31).

5.2. Limitations of study:

1. Lack of comparable data, most resources not included all our parameters in one study.

2. Our study strongly depended on history taken from patients particularly about onset of two diseases compared in the study, whether DM started first or Ischemic attack preceded.

3. Duration of DM was difficult to be addressed accurately.

4. Limited age group included in the study.

5. Conflicts in patient referral from diabetic center to do OCT in not so close ophthalmology department of another hospital.

6. Our study strongly depended on other specialists decision to consider patients whom known to have ischemic heart diseases.

7. Many patients in both groups received antihypertensive medications for episodes of elevated blood pressure but not clearly diagnosed hypertension.

5.3. Recommendations:

1. All age groups should included.

2. Further studies required about effect of ischemic heart diseases as risk for ischemic maculopathy by fluorescein angiography that may poorly respond to Anti-VEGF.

3. Type 1 DM patients needed to be included.

4. Hypertension should addressed in further studies and added as variable

   to our study variables because of common coexistence of hypertension

   with ischemic heart diseases and diabetes mellitus.

5. **Further studies required to reveal that diabetic macular edema is a risk factor for development of Ischemic heart diseases in diabetic patients so that necessitate closer cardiovascular follow up.**

6. **Further understanding of the relation of atherosclerosis with retinopathy will require long-term cohort studies begun at or before the onset of diabetes.**

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