Original Article
Turk J Endocrinol Metab. 2020;24:198-205

Association of Types of Diabetic Macular Edema with Different Anti-Diabetic Therapies

Farklı Antidiyabetik Tedavilerle Diyabetik Makuler Ödem Tiplerinin İlişkisi

Luxmi SINGH, Yadav SWATI, Karoli RITU*, Priyanka RAJ

Era's Lucknow Medical College and Hospital, Department of Ophthalmology, Uttar Pradesh, INDIA
*Era's Lucknow Medical College and Hospital, Department of Medicine, Uttar Pradesh, INDIA

Abstract

Objective: To evaluate and assess the association of diabetic macular edema with different anti-diabetic therapy regimens. **Material and Methods:** We recruited 340 patients with prediagnosed Type 2 diabetes mellitus attending the ophthalmology and medicine outpatient department. Patients were older than 30 years with Type 2 diabetes mellitus and on a specific anti-diabetic regimen (monotherapy/combination therapy) for ≥6 months, and who underwent macular edema assessment by using spectral domain optical coherence tomography. The patterns of macular edema per retinal morphology were grouped as diffuse retinal thickening, cystoid macular edema, and serous retinal detachment. **Results:** No significant association was found between edema pattern and dual therapy regimen (metformin+1 other oral hypoglycemic agent) (p=0.685) in the 680 eyes of the 340 patients. In patients on all the other triple therapy regimens (metformin+2 other oral hypoglycemic agents), diffuse retinal thickening was the most common type, except in patients on thiazolidinediones and insulin in conjunction with metformin in which cystoid macular edema was the most common. However, the difference between different triple therapy regimens was statistically significant (p=0.053). **Conclusion:** The most common form of macular edema was diffuse retinal thickening irrespective of the type and regimen of anti-diabetic therapy. Increased incidence of cystoid macular edema was observed in patients on triple therapy, including insulin. Because of the difference in the patterns, it is imperative to evaluate patients for different types of edema due to ongoing anti-diabetic treatment.

Keywords: Diabetes mellitus; diabetic retinopathy; macular edema; anti-diabetic therapy

Özet

Amaç: Diyabetik makuler ödemin farklı antidiyabetik tedavi rejimleriyle ilişkisinin değerlendirilmesi. **Gereç ve Yöntemler:** Oftalmoloji ve medikal oftalmoloji polikliniğine başvuran, önceden tanı almış Tip 2 diabetes mellituslu 340 hasta çalışmaya alındı. Otuz yaşından büyük, Tip 2 diabetes mellituslu ve ≥6 aydır spesifik bir antidiyabetik rejim (monoterapi/kombinasyon terapisi) alan hastalar, spektral alan optik koherens tomografisi kullanılarak makuler ödem değerlendirmesine tabi tutulmuşlardır. Her bir retina morfolojisi için makuler ödem paternleri; diffüz retina kalınlaşması, sistoid makuler ödem ve seröz retina dekolmanı olarak gruplandırıldı. **Bulgular:** Toplam 340 hastadaki 680 gözde ödem paterni ve ikili tedavi rejimleri (metformin+diğer 1 oral hipoglisemik ajan) (p=0,685) arasında anlamlı bir ilişki bulunmadı. Diğer tüm üçlü tedavi rejimlerindeki (metformin+diğer 2 oral hipoglisemik ajan) hastalarda, kistoid makuler ödemin en yaygın olduğu tiazolidindionlar ve metformin ile birlikte insülin kullanan hastalar hariç, diffüz retinal kalınlaşma en yaygın tipti. Bununla birlikte, farklı üçlü tedavi rejimleri arasındaki fark istatistiksel olarak anlamlıydı (p=0,053). **Sonuç:** Makuler ödemin en yaygın formu, antidiyabetik tedavinin tipi ve rejimine bakılmaksızın diffüz retinal kalınlaşma idi. İnsülin de dâhil olmak üzere üçlü tedavi gören hastalarda artmış kistoid makuler ödem insidansı gözlenmiştir. Paternlerdeki farklılık nedeni ile devam eden antidiyabetik tedaviye bağlı olarak hastaları farklı ödem tipleri açısından değerlendirmek zorunludur.

Anahtar kelimeler: Diabetes mellitus; diyabetik retinopati; makuler ödem; antidiyabetik tedavi

Address for Correspondence: Priyanka RAJ, Era's Lucknow Medical College and Hospital, Department of Ophthalmology, Uttar Pradesh, INDIA
Phone: 7238091536 **E-mail:** drpriyankarajy@gmail.com

Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 03 Feb 2020 **Received in revised form:** 30 May 2020 **Accepted:** 26 Jun 2020 **Available online:** 31 Aug 2020

DOI: 10.25179/tjem.2020-74091

Introduction

Diabetes mellitus is a group of disorders characterized by hyperglycemia and glucose intolerance due to insulin deficiency, impaired effectiveness of insulin action, or both (1). Retinopathy is probably the most common microvascular complication of diabetes. Diabetic macular edema (DME) results in severe vision loss in Type 2 diabetes because of fluid leakage due to increased vascular permeability, owing to anatomical and biochemical changes. Increased vascular permeability of retinal blood vessels and subsequent edema and hard exudates are the key features of DME. The Wisconsin Epidemiological Study of Diabetic Retinopathy (2) reported the prevalence to be 29% in younger-onset diabetic patients and 28% in older-onset diabetic patients, after 20 years. As there is no definitive cure for diabetes, glycemic control using oral hypoglycemic agents (OHAs) and insulin remains the current mainstay of treatment, which has side effects. DME is the warning sign associated with the development and progression of diabetic retinopathy (DR). However, some specific classes of OHAs alone or in combination with insulin are associated with fluid retention and peripheral edema (3-5). The treatment of diabetes with insulin may result in increased retinal vascular permeability, and then induce DR progression and visual impairment (4,6,7). Therefore, there is a need to review the treatment strategies for diabetes mellitus in this perspective. Various studies have recently assessed the association of DME with anti-diabetic treatments; however, data regarding the severity and morphology of DME are scarce.

Hence, we conducted this study to find an association between the different types of macular edema and different anti-diabetic treatment regimens.

Material and Methods

This is a hospital-based cross-sectional study conducted at a tertiary care center in North India. We recruited 340 patients with prediagnosed Type 2 diabetes mellitus attending the ophthalmology and medicine outpatient department of our facility. We obtained their informed and written consent after adhering to the tenets of the Declaration of Helsinki after approval of our institutional ethics committee (Institutional Ethics Committee, Era's Lucknow Medical College and Hospital; Approval No. ELMC/R_Cell/EC/2017/71; Dated: 14/02/2017). Patients older than 30 years with Type 2 diabetes mellitus and who were on a specific anti-diabetic regimen (monotherapy/combination therapy) for ≥6 months were included.

Patients with any other ocular disease altering macular thickness, hazy ocular media obscuring fundus examination and imaging, patients on other medications alongside anti-diabetic treatment, those with a history of recent (<3 months) intraocular surgeries or laser treatment, chronic renal disease, uncontrolled use of hypertensives, dyslipidemia, chronic smokers, and patients not willing to participate in the study were excluded.

Detailed history regarding the demographic profile of the patients and that of diabetes and anti-diabetic medications and symptoms indicative of macular pathology were obtained. Afterward, patients underwent a best-corrected visual acuity assessment by Snellen's Chart, anterior segment assessment using a slit lamp, and a fundus examination using indirect ophthalmoscopy and +90D lens. Fundus photography and fluorescein angiography were performed using Carl Zeiss Visucam724 (Carl Zeiss Meditech Inc.). Patients then underwent optical coherence tomography (macula) using Carl Zeiss cirrus HD-Optical Coherence Tomography (OCT), and 512x128 macular cube axial scans covering an area of 6 mmx6 mm were obtained. Center-involving DME was considered to be present based on the incidence of foveal intraretinal fluid SD-OCT in association with the clinical diagnosis of DR and concurrent appropriate fluorescein angiographic findings. The patterns of macular edema per retinal morphology were grouped as diffuse retinal thickening, cystoid macular edema, and serous retinal detachment.

Statistical analysis was performed using SPSS Version 21.0 0 statistical Analysis Software. The values are represented in number (%) and mean±SD. $p<0.05$ was considered significant, and $p<0.001$ as very highly significant.

Results

We aimed to find the correlation of different patterns of DME with the different types of anti-diabetic regimens for which we included 680 eyes of 340 subjects.

The mean age of patients was 52.0±9.67 years. Most of the patients (55.3%) were women. The duration of diabetes ranged from 1 to 15 years. HbA_{1C} values ranged from 6% to 14% (8.3%±1.2%). Mean fasting and postprandial blood glucose levels were 109.9±36.24 mg/dL and 174.1±45.6 mg/dL, respectively. Out of the 680 eyes of 340 patients, there were 598 (87.9%) with normal vision, 71 (10.4%) with low vision, and 11 (1.6%) with social blindness (vision 3/60 or diminution of the field of vision to 10°). No patients had economic blindness (inability of a person to count fingers from a distance of 6 m or 20 feet). Fifty-eight eyes (8.5%) showed DR. OCT measurements could not be performed in 6 eyes because of poor scan. The central subfield thickness of macula on OCT ranged from 106 µm to 468 µm (mean=238.81±39.94 µm). The mean cube average thickness was 263.41±27.34 µm. Seventy-two eyes (10.7%) showed macular thickening followed by cystoid macular edema (n=20; 3%) and serous retinal detachment (n=6; 0.9%). Twelve eyes (1.8%) had clinically significant macular edema (Table 1).

The majority of patients were on dual therapy taking metformin in combination with one other anti-diabetic medication (58.25%), followed by those on metformin alone (monotherapy) (26.2%) and triple therapy (metformin+2 other anti-diabetic medications) (17.1%).

Among patients receiving dual therapy, most (n=59) were receiving the combination Metformin+Sulfonylureas (M+S), followed by Metformin+DPP4 inhibitors (M+D) (n=53), Metformin+Thiazolidinediones (M+T) (n=38), Metformin+Insulin (M+I) (n=28), and Metformin+Alpha glucosidase inhibitor (M+A) (n=20). Thus, overall, five combinations were used.

Among patients receiving triple therapy, most (n=21) were receiving Metformin+Thiazolidinediones+Insulin (M+T+I), followed by Metformin+Suplhonylurea+Alpha glu-

Table 1. Demographic profile and characteristics of the study population (n=340).

SN	Characteristic	Statistic
1.	Mean age±SD (range) in years	52.00±9.67 (35-76)
2.	Gender Gender (n=340)	
	Male	154 (44.9%)
	Female	186 (55.3%)
3.	Diabetic retinopathy (n=680)	
	Present	58 (8.5%)
	NPDR	54
	PDR	04
	Absent	622
4.	Visual acuity (n=680)	
	≥6/6-6/18	598 (87.9%)
	<6/18-6/60	71 (10.4%)
	<6/60-NPL	0
	<3/60-Pl denied	11 (1.6%)
5	Macular edema (n=674)	72 (10.7%)
	Serous retinal detachment	6 (0.9%)
	Diffuse macular thickening	46 (6.8%)
	Cystoid macular edema	20 (3%)
6.	Clinically significant macular edema (n=674)	12 (1.8%)

SN: Serial number; SD: Standard deviation; NPDR: Non proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy.

cosidase inhibitor (M+S+A) (n=11), Metformin+Sulfonylurea+Insulin (M+S+I) (n=9), Metformin+Alpha glucosidase inhibitor+DPP4 inhibitor (M+A+D) (n=7), Metformin+Sulfonylurea+Dipeptidyl Peptidase 4 (DPP4) inhibitor (M+S+D) (n=5), Metformin+Sulfonylurea+Thiazolidinediones (M+S+T) (n=4), and Metformin+Thiazolidinediones+Alpha glycosidase inhibitor (M+T+A) (n=1). Thus, overall, 7 combinations were used (Table 2).

Irrespective of therapy, diffuse retinal thickening was the dominant type. Although the proportion of cystoid macular edema was higher in mono and triple therapy groups than in the dual therapy group, this difference was not statistically significant (p=0.110) (Table 3).

Irrespective of dual therapy regimen, diffuse retinal thickening was most common. Statistically, there was no significant association between the pattern of edema and dual therapy regimen (p=0.685). Except for M+T+I and M+T+A, diffuse retinal thickening was the most common type for all the other triple therapy regimens. For M+T+I, cystoid macular edema was most common, whereas the lone edematous case of M+T+A was of serous type; however, the difference among different triple therapy regimens was not statistically significant (p=0.053) (Table 4).

Discussion

Diabetes mellitus is a metabolic disorder of multiple etiologies. The long term effects of diabetes mellitus, besides systemic effects, include the progressive development of

Table 2. Distribution of anti-diabetic treatment regimens (n=340).

SN	Treatment modality	Number	%
1.	Monotherapy (metformin)	84	24.7
2.	Dual therapy	198	58.2
	M+T (Metformin+Thiazolidinediones)	38	11.2
	M+A (Metformin+Alpha glucosidase inhibitor)	20	5.9
	M+D (Metformin+DPP4-inhibitors)	53	15.6
	M+I (Metformin+Insulin)	28	8.2
	M+S (Metformin+Suliphonylureas)	59	17.4
3.	Triple therapy	58	17.1
	M+S+T (Metformin+Sulfonylurea+Thiazolidinediones)	4	1.2
	M+A+D (Metformin+Alpha glucosidase inhibitor+DPP4 inhibitor)	7	2.1
	M+S+A (Metformin+Suplhonylurea+Alpha glucosidase inhibitor)	11	3.2
	M+S+I (Metformin+Sulfonylurea+Insulin)	9	2.6
	M+T+I (Metformin+Thiazolidinediones+Insulin)	21	6.2
	M+S+D (Metformin+Sulponylurea+DPP4 inhibitor)	5	1.5
	M+T+A (Metformin+Thiazolidinediones+Alpha glycosidase inhibitor)	1	0. 3

Table 3. Association between the pattern of macular edema and therapy (n=72).

	Monotherapy (n=19)		Dual therapy (n=29)		Triple therapy (n=24)		Total (n=72)	
Pattern	No.	%	No.	%	No.	%	No.	%
Serous retinal detachment	0	0	4	13.8	2	8.3	6	8.3
Diffuse retinal thickening	13	68.4	21	72.4	12	50.0	46	63.9
Cystoid macular edema	6	31.6	4	13.8	10	41.7	20	27.8

x^2=7.54 (df=4); p=0.110 (percentages have been calculated column wise).

Table 4. Pattern of edema by different multi therapies.

	Pattern							
Therapy	**Serous (n=4)**		**Diffuse (n=21)**		**Cystoid (n=4)**		**Total (n=29)**	
Dual therapy	**No.**	**%**	**No.**	**%**	**No.**	**%**		**Statistics**
M+T	3	20.0	11	73.3	1	6.7	15	x^2=5.66 (df=8); p=0.685
M+A	0	0.0	1	50.0	1	50.0	2	
M+D	0	0.0	1	100	0	0.0	1	
M+I	1	12.5	5	62.5	2	25.0	8	
M+S	0	0.0	3	100	0	0.0	3	
	Serous (n=2)		**Diffuse (n=12)**		**Cystoid (n=10)**			
Triple therapy	**No.**	**%**	**No.**	**%**	**No.**	**%**	**Total (n=24)**	
M+S+T	0	0.0	3	100	0	0.0	3	x^2=18.1 (df=10); p=0.053
M+A+D	0	0.0	2	66.7	1	33.3	3	
M+S+A	0	0.0	2	66.7	1	33.3	3	
M+S+I	0	0.0	1	100	0	0.0	1	
M+T+I	1	7.7	4	30.8	8	61.5	13	
M+T+A	1	100	0	0.0	0	0.0	1	

M: Metformin; T: Thiazolidinediones; A: Alpha glucosidase inhibitor; D: DPP4; I: Insulin; S: Sulfonylurea.

retinopathy with potential blindness (8). The total number of people with diabetes is expected to rise to an estimated 300 million by 2025, with the most significant increases occurring in developing countries, probably attributed to population growth, ageing, obesity, and sedentary lifestyles. DME is a vision-threatening complication of diabetic microangiopathy, which demands urgent treatment. The SN-DREAMS (9) study found that the chances of DME increase at the fifth and sixth decades of life and taper thereafter. OCT is a noninvasive, reproducible, and reliable method to evaluate macular thickness (10,11). Several authors have studied the possibility of OCT for the early diagnosis of ME and have suggested criteria to detect so-called subclinical macular edema. Among anti-diabetic medications, thiazolidineiones (12-14) and insulin (3,4,5,15) have been implicated in the rise of macular thickness, which may be due to the side effect of drugs or due to its role progression of retinopathy. However, the evidence obtained is not conclusive. Other anti-diabetic medications like DPP4 inhibitors (vildagliptin) (16-18) and glibenclamide and glicazide (19) have shown to possess a potential role against DR in obese diabetic rats; however, human studies using these medications have not been conducted as yet.

Various studies have speculated the role of anti-diabetic medications in the development of macular edema, but, to the best of our knowledge, there is no available literature regarding the association of type of macular edema with the use of anti-diabetic medications.

In our study, most of the patients were women (55.3%). The diabetic profile of patients revealed that the duration of diabetes was <1 year (59.10%), showing that a fairly large amount of patients had been recently diagnosed, irrespective of their awareness of disease status. The mean HbA_{1c} was 8.3%±1.2% (6%-14%), representing a fair glycemic control in the study population.

Intensive glycemic control was associated with 46% reduction in the incidence of DME at the end of trial, and a 58% reduction in four years later compared with the conventional group. Diabetes Control and Complications Trial (DCCT) reported incentive glycemic control progression of existing DR (65^{th} year treatment). Aggressive glycemic control (<6.5%) did not reduce DR risk and ME. Intensive glycemic control has a meta-

bolic memory, whereby there is low risk of DR/DME progression after 10 years of anti-diabetic therapy (DCCT), but our study did not have many patients with a duration of diabetes mellitus>10 years, but they had fairly controlled HbAlc levels. However, the duration of treatment was not known.

In our study, most of the patients were on dual therapy: metformin+OHA (58.2%), followed by monotherapy (metformin) and triple therapy (metformin+OHA1+OHA2) (6.2%), depicting a study population containing many patients who were not achieving glycemic target even after lifestyle modification and metformin monotherapy for a duration of 3 months (American Diabetes Association), or had a fairly disturbed blood sugar profile on the first diagnosis. Next in the majority were those patients who were fairly controlled on metformin alone and had been taking the drug for ≥6 months, irrespective of previous treatment. In addition, these patients were free of contraindications for metformin therapy. The number of patients on a triple drug regimen to achieve glycemic targets was very small. In our study, out of the 680 eyes of 340 patients, 594 eyes (92.5%) had no DR. The low prevalence of DR could be attributed to the fact that the study population was largely metabolically stable with a duration of diabetes <5 years in many patients with a fair glycemic control. Out of 340 patients, 72 patients had macular edema and 46 patients (63.9%) of them showed diffuse retinal thickening regardless of their anti-diabetic regimen. Jingi et al. evaluated the presence of macular edema in patients on various anti-diabetic medications and found that irrespective of staging, the frequency of DME was significantly higher in the insulin group than in the OHA group (43.5% vs. 19.8%; OR=3.1; 95% CI=1.2 to 8; p=0.019).

We evaluated the association between the pattern of macular edema and the type of anti-diabetic therapy taken by the patients having DME. Irrespective of the type of therapy, diffuse retinal thickening was most common in all anti-diabetic therapy groups. Overall, diffuse retinal thickening was observed in 19 patients on monotherapy (68.4%), 21 (72.4%) on dual therapy, and 12 (50%) on triple therapy. However, cystoid macular edema was common in monotherapy and triple therapy groups than in the dual therapy group, but the difference was not statistically significant. Among dual therapy subgroups, out of 29 eyes, diffuse retinal thickening was most common and most eyes were of patients on M+S (100%) and M+D (100%), followed by M+T (73.33%) and M+I (62.5%), but the difference was not statistically significant. Among triple therapy subgroups, the M+T+I subgroup had cystoid macular edema and the M+T+A subgroup had serous retinal detachment as the most common patterns of macular edema, but the difference was not statistically significant. Previous studies have shown that insulin treatment is a risk factor for DME. Aroca et al. (20) observed that insulin use was a risk factor for focal and diffuse DME in a 4-year prospective study, including 93 Type 2 diabetes mellitus patients.

Within the subgroups of 3 anti-diabetic therapy groups, no statistically significant pattern was associated with the type of anti-diabetic therapy. However, those on the triple combination showed more cystoid and serous retinal detachment (SRD) patterns, hinting at the presence of moderate to severe macular edema; however, the exact duration of treatment was not known. Jingi et al. (21) reported that out of the patients who had developed macular edema, majority of them were on insulin therapy (43.5%) compared with those on OHAs (19.8%). On comparing the severity of macular edema with the type of anti-diabetic regimen, the authors found that in all the subgroups, the number of patients on insulin therapy outnumbered the patients on OHA, where 8.7% of the patients on insulin developed severe macular edema compared with only 2.7% of the patients on OHAs.

Various studies have assessed the effect of anti-diabetic medications on the development of macular edema. Ryan et al. (14) reported the incidence of worsening of macular edema to be 1.5%-2.6%, detected using FFA alone. About 63% of their patients had DME in at least one eye. Among OHAs, Liazos et al., Oshitari et al., Fong et al., Tatti et al., and Agarwal et al. reported a positive association of macular edema with glitazones, but none of these authors studied the type of macular edema in relation to the anti-diabetic regimen. However, regardless

of the anti-diabetic regimen, diffuse retinal thickening was the most common pattern of DME in the previous studies (22-24).

The diffuse thickening pattern of macular edema represents the initial stage of macular edema formation, which may slowly progress to severe visual impairment eventually giving rise to other patterns of macular edema. Thus, this pattern of macular edema, which was present in the majority of our study population, represented the early stage of macular edema formation.

Although various studies have examined the role of oral hypoglycemics and insulin in the development of macular edema, to the best of our knowledge, no study has examined the correlation of various anti-diabetic regimens and different types of DME.

Conclusion

We conclude that the most common form of macular edema is diffuse retinal thickening, irrespective of the type and regimen of anti-diabetic therapy. An increase in the cystoid macular edema was observed among patients on triple therapy, including insulin. With a difference in the pattern of macular edema, the treatment modalities for the pattern might vary; hence, we must evaluate patients for the different types of edema due to ongoing anti-diabetic treatments. Changes are required in the currently available treatment options for diabetes to avoid the vicious cycle set up by certain anti-diabetic medications. Further studies regarding this concern involving a larger population size need to be conducted for in-depth understanding of this association.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

References

1. Toldo S, Boccellino M, Rinaldi B, Seropian IM, Mezzaroma E, Severino A, Quagliuolo L, Van Tassell BW, Marfella R, Paolisso G, Rossi F, Natarajan R, Voelkel N, Abbate A, Crea F, Baldi A. Altered oxido-reductive state in the diabetic heart: loss of cardioprotection due to protein disulfide isomerase. Mol Med. 2011;17:1012-1021. [Crossref] [PubMed] [PMC]
2. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The wisconsin epidemiology study of diabetic retinopathy: XVII. The 14 years incidence and progression of diabetic retinopathy and associated risk factors in type l diabetes. Ophthalmology. 1998;105:1801-1815. [Crossref] [PubMed]
3. Niemeyer NV, Janney LM. Thiazolidinedione-induced edema. Pharmacotherapy. 2002;22:924-929. [Crossref] [PubMed]
4. Mudaliar S, Chang AR, Henry RR. Thiazolidinediones, peripheral edema, and type 2 diabetes: incidence, pathophysiology, and clinical implications. Endocr Pract. 2003;9:406-416. [Crossref] [PubMed]
5. Patel C, Wyne KL, McGuire DK. Thiazolidinediones, peripheral oedema and congestive heart failure: what is the evidence? Diabet Vasc Dis Res. 2005;2:61-66. [Crossref] [PubMed]
6. Henricsson M, Bemtorp K, Femlund P, Sundkvist G. Progression of retinopathy in insulin-treated type 2 diabetic patients. Diabetes Care. 2002;25:381-385. [Crossref] [PubMed]
7. Poulaki V, Qin W, Joussen AM, Hurlbut P, Wiegand SJ, Rudge J, Yancopoulos GD, Adamis P. Acute intensive insulin therapy exacerbates diabetic blood-retinal barrier breakdown via hypoxia-inducible factor-1alpha and VEGF. J Clin Invest. 2002;109:805-815. [Crossref] [PubMed]
8. Huang J, Liu X, Wu Z, Xiao H, Dustin L, Sadda S. Macular thickness measurements in normal eyes with time-domain and Fourier-domain optical coherence tomography. Retina. 2009;29:980-987. [Crossref] [PubMed] [PMC]
9. Munjal YP. Epidemiology and basic considerations of diabetes. In: Ramachandran A, Snehalatha C, eds. API Textbook of Medicine (9th ed). New Delhi: Jaypee; 2012;331-324.
10. Podoleanu AGh. Optical coherence tomography. Br J Radiology. 2005;78:976-988. [Crossref] [PubMed]
11. Paunescu LA, Schuman JS, Price LL, Stark PC, Beaton S, Ishikawa H, Wollstein G, Fujimoto JG. Reproducibility of nerve fiber thickness, macular thickness, and optic nerve head measurements using stratusOCT. Invest Opthalmol Vis Sci. 2004;45:1716-1724. [Crossref] [PubMed] [PMC]

12. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med. 2012;172:1005-1011. [Crossref] [PubMed]
13. Tarbett AK VanRoekel RC, Howard RS, Vigersky RA. The use of optical coherence tomography to determine the effectt of thiazolidinediones on retinal thickness in patients with type 2 diabetes. J Diabetes Sci Technol. 2011;5:945-951. [Crossref] [PubMed] [PMC]
14. Ryan Jr EH, Han DP, Ramsay RC, Cantrill HL, Bennett SR, Dev S, Williams DF. Diabetic Macular Edema Associated With Glitazone Use. Retina. 2006;26:562-570. [Crossref] [PubMed]
15. Hee MR, Puliafito CA, Wong C, Duker JS, Reichel E, Rutledge B, Schuman JS, Swanson EA, Fujimoto JG. Quantitative assessment of macular edema with optical coherence tomography. Arch Ophthalmol. 1995;113:1019-1029. [PubMed]
16. Antcliff R, Marshall J. The pathogenesis of edema in diabetic maculopathy. Semin Ophthalmol. 1999;14:223-232. [Crossref] [PubMed]
17. Raman R, Bhende M. Diabetic macular edema. Sci J Med & Vis Res Foun. 2015;XXXIII:50-56.
18. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103:1796. [Crossref] [PubMed]
19. Zander E, Herfurth S, Bohl B, Heinke P, Herrmann U, Kohnert KD, Kerner W. Maculopathy in patients with diabetes mellitus type 1 and type 2: associations with risk factors. Br J Ophthalmol. 2000;84:871-876. [Crossref] [PubMed] [PMC]
20. Aroca PR, Salvat M, Fernández J, Méndez I. Risk factors for diffuse and focal macular edema. J Diabetes Complications. 2004;18:211-215. [Crossref] [PubMed]
21. Jingi AM, Noubiap JJN, Essouma M, Bigna JJR, Nansseu JRN, Ellong A, Mvogo CE. Association of insulin treatment versus oral hypoglycaemic agents with diabetic retinopathy and its severity in type 2 diabetes patients in Cameroon, sub-Saharan Africa. Ann Transl Med. 2016;4:395. [Crossref] [PubMed] [PMC]
22. Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. Am J Ophthalmol. 1999;127:688-693. [Crossref] [PubMed]
23. Catier A, Tadayoni R, Paques M, Erginay A, Haouchine B, Gaudric A, Massin P. Characterization of macular edema from various etiologies by optical coherence tomography. Am J Ophthalmol. 2005;140:200-206. [Crossref] [PubMed]
24. Kim BY, Smith SD, Kaiser PK. Optical coherence tomographic patterns of diabetic macular edema. Am J Ophthalmol. 2006;142:405-412. [Crossref] [PubMed]