

4. BÖLÜM

DİYABETİK MAKÜLER ÖDEM

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1. GİRİŞ

Diyabetik maküler ödem (DMÖ), diyabet hastalarında görülen görme kaybının ana nedenidir. Makülada kan-retina bariyerinin yıkılması ile beraber plazma ve lipid sızıntısı meydana gelir. Aslında, diyabetik makülopati, maküler ödeme ilaveten daha geniş bir kavramdır ve çoğunlukla kötü прогнозu olan maküler iskemi ile birliktedir.

Wisconsin Epidemiyolojik Diyabetik Retinopati (DR) çalışmasında (WESDR), 25 yilda tip 1 diyabet hastalarında % 29'luk bir DMÖ insidansı bildirilmiştir. Diyabet Kontrol ve Komplikasyonlar çalışmasında (DCCT) ise, diyabet başlangıcından sonraki 9 yıl içinde tip 1 diyabetiklerin % 27'sinde DMÖ geliştiği gözlenmiştir. Başka bir WESDR çalışmasında, tip 2 diyabet hastalarında maküler ödem insidansı, insüline ihtiyaç duyanlarda % 25.4 ve insüline ihtiyaç duymayanlarda % 13.9 olarak kaydedilmiştir. Proliferatif diyabetik retinopati (PDR), 15 yıllık diyabetten sonra tip 1 diyabet hastalarında sadece % 50'sinde ve tip 2 diyabet hastalarının % 10'unda görülmüştür.

2. KLINİK ÖZELLİKLER

DMÖ, DR'nin herhangi bir evresinde gelişebilir. Maküler ödem foveayı etkiliyorsa veya foveayı da tehdit ettiğinde hastalarda metamorfopsi ve görme kaybı gibi semptomlar ortaya çıkar. DMÖ'nün klinik değerlendirilmesinde maküler stereoskopik biyomikroskopi veya stereoskopik fundus görüntüsü önem arz etmektedir.

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KAYNAKLAR

1. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XV: the long-term incidence of macular edema. *Ophthalmology*. 1995;102:7–16.
2. White NH, Sun W, Cleary PA, et al; DCCT-EDIC Research Group. Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents. *Diabetes*. 2010;59:1244–53.
3. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of diabetic macular edema. *Ophthalmology*. 1995;102:7–16.
4. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. ETDRS Report No. 1. *Arch Ophthalmol*. 1985;10:1796–806.
5. Wilkinson CP, Ferris FL 3rd, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity of scales. *Ophthalmology*. 2003;110: 1677–82.
6. Browning DJ, Glassman AR, Aiello LP, et al. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. *Ophthalmology*. 2007;115:525–36.
7. Varma R, Bressler NM, Doan QV, et al. Prevalence and risk factors for diabetic macular edema in the United States. *JAMA Ophthalmol*. 2014;132:1334–40.
8. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol*. 1984;102:520–6.
9. Keenan HA, Costacou T, Sun JK, et al. Clinical factors associated with resistance to microvascular complications in diabetic patients of extreme disease duration: the 50-year medalist study. *Diabetes Care*. 2007;30:1995–7.
10. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329: 977–86.
11. White NH, Sun W, Cleary PA, et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. *Arch Ophthalmol*. 2008;126:1707–15.
12. Frank RN. Diabetic retinopathy. *N Engl J Med*. 2004;350: 48–58.
13. Miao F, Chen Z, Genuth S, et al. Evaluating the role of epigenetic histone modifications in the metabolic memory of type diabetes. *Diabetes* 2014;63:1748–62.
14. The ACCORD Study Group, ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med*. 2010;363:233–44.
15. King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for Type 2 diabetes. *Br J Clin Pharmacol*. 1999;48:643–8.
16. Beulens JW, Patel A, Vingerling JR, et al. Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomised controlled trial. *Diabetologia*. 2009;52:2027–36.
17. Benarous R, Sasongko MB, Qureshi S, et al. Differential association of serum lipids with diabetic retinopathy and diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2011;52: 7464–9.
18. Chew EY, Klein ML, Ferris FL 3rd, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. *Arch Ophthalmol*. 1996;114: 1079–84.
19. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet*. 2007;370:1687–97.

20. The Diabetes Control and Complications Trial research Group. Clustering of long-term complications in families with diabetes in the diabetes control and complications trial. *Diabetes*. 1997;46:1829–39.
21. Tong Z, Yang Z, Patel S, et al. Promoter polymorphism in severe diabetic eye and kidney complications. *Proc Natl Acad Sci U S A*. 2008;105:6998–7003.
22. Kuo JZ, Wong TY, Rotter JI. Challenges in elucidating the genetics of diabetic retinopathy. *JAMA Ophthalmol*. 2014;132:96–107.
23. Tiruppathi C, Malik AB, Del Vecchio PJ, et al. Electrical method for detection of endothelial cell shape change in real time: assessment of endothelial barrier function. *Proc Natl Acad Sci U S A*. 1992;89:7919–23.
24. Tang L, Lee CA, Yunpeng D, et al. My D88 pathways in leukocytes affect the retina in diabetes. *PLoS One*. 2013;8: e68871.
25. Gao BB, Clermont A, Rook, et al. Extracellular carbonic anhydrase mediates hemorrhagic retinal and cerebral vascular permeability through prekallikrein activation. *Nat Med*. 2007;13:181–8.
26. Robinson R, Barathi VA, Chaurasia SS. Update on animal models of diabetic retinopathy: from molecular approaches to mice and higher mammals. *Dis Model Mech*. 2012;5:444–56.
27. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005;54:1615–25.
28. Adamis AP, Berman AJ. Immunological mechanisms in the pathogenesis of diabetic retinopathy. *Semin Immunopathol*. 2008;30:65–84.
29. Miyamoto K, Khosrof S, Bursell SE, et al. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. *Proc Natl Acad Sci U S A*. 1999;96:10836–41.
30. McLeod DS, Lefer DJ, Merges C, et al. Enhanced expression of intracellular adhesion molecule-1 and P-selectin in the diabetic human retina and choroid. *Am J Pathol*. 1995;147:642–53.
31. Kim SY, Kim SY, Johnson MA, et al. Neutrophils are associated with capillary closure in spontaneously diabetic monkey retinas. *Diabetes*. 2005;54:1534–42.
32. Mizutani M, Gerhardinger C, Lorenzi M. Muller cell changes in human diabetic retinopathy. *Diabetes*. 1998;47:445–9.
33. Jackson GR, Scott IU, Quillen DA, et al. Inner retinal visual dysfunction is a sensitive marker of nonproliferative diabetic retinopathy. *Br J Ophthalmol*. 2012;96:699–703.
34. Frank RN. Systemic therapies for diabetic retinopathy: the ACCORD Eye Study (editorial). *Ophthalmology*. 2014;121: 2295–6.
35. Chew E, Davis MD, Danis R, et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. *Ophthalmology* 2014;121:2443–51.
36. Ryan EH Jr, Han DP, Ramsay RC, et al. Diabetic macular edema associated with glitazone use. *Retina*. 2006;26:562–70.
37. Miura Y, Treumer F, Klettner A, et al. VEGF and PEDF secretions over time following various laser irradiations on an RPE organ culture. *Invest Ophthalmol Vis Sci*. 2010;51:469.
38. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117:1064–77.
39. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol*. 1984;102:527–32.

40. Figueira J, Khan J, Nunes S, et al. Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular edema. *Br J Ophthalmol.* 2009;93:1341–4.
41. Diabetic Retinopathy Clinical Research Network. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. *Ophthalmology.* 2010;117:1087–93.
42. PKC-DMES Study Group. Effect of ruboxistaurin in patients with diabetic macular edema: thirty month results of the PKC-DMES clinical trial. *Arch Ophthalmol.* 2007;125: 318–24.
43. Ozaki H, Hayashi H, Vinores SA, et al. Intravitreal sustained release of VEGF causes retinal neovascularization in rabbits and breakdown of the blood-retinal barrier in rabbits and primates. *Exp Eye Res.* 1997;64:505–17.
44. Funatsu H, Noma H, Mimura T, et al. Association of vitreous inflammatory markers in diabetic macular edema. *Ophthalmology.* 2009;116:73–9.
45. Sultan MB, Zhou D, Loftus J, et al; Macugen 1013 Study Group. A Phase 2/3, multicenter, randomized, double-masked, 2 year trial of pegaptanib sodium for the treatment of diabetic macular edema. *Ophthalmology.* 2011;118:1107–18.
46. Brown DM, Nguyen QD, Marcus DM, et al; RIDE and RISE Research Group. Long-term outcome of ranibizumab therapy for diabetic macular edema: 36 month results from two Phase III trials: RISE and RIDE. *Ophthalmology.* 2013;120:2013–22.
47. Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three year randomized trial results. *Ophthalmology.* 2012;119:2312–8.
48. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective, randomized, controlled trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema: 24-month data: Report 3. *Arch Ophthalmol.* 2012;130:972–9.
49. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal afibercept for diabetic macular edema. *Ophthalmology.* 2014;121:2247–54.
50. Jampol L, Bressler NB, Glassman AR. Revolution to a new standard treatment of diabetic macular edema. *JAMA.* 2014;311:2269–70.
51. Rangasamy S, McGuire PG, Das A. Diabetic retinopathy and inflammation: novel therapeutic targets. *Middle East Afr J Ophthalmol* 2012;19:52–9.
52. Boyer DS, Yoon YH, Belfort R, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology.* 2014;121:1904–14.
53. Campochiaro P, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology.* 2011;118:626–35.
54. Thakur A, Kadam R, Kompella UB. Trabecular meshwork and lens partitioning of corticosteroids: implications for elevated intraocular pressure and cataracts. *Arch Ophthalmol.* 2011;129:914–20.
55. Joussen AM, Poulaki V, Mitsiades N, et al. Nonsteroidal anti-inflammatory drugs prevent early diabetic retinopathy via TNF-alpha suppression. *FASEB J.* 2002;16:438–40.
56. Powell ED, Field RA. Diabetic retinopathy and rheumatoid arthritis. *Lancet.* 1964;4:17–8.
57. DAMAD Study Group. Effect of aspirin alone and aspirin plus dipyridamole in early diabetic retinopathy. A multi-center randomized controlled clinical trial. *Diabetes.* 1989;38: 491–8.
58. ETDRS Group. Effects of aspirin treatment on diabetic retinopathy. ETDRS report no. 8. Early Treatment Diabetic Retinopathy Study research group. *Ophthalmology.* 1991;98(5Suppl):757–65.

59. Kern TS, Miller CM, Du T, et al. Topical administration of nepafenac inhibits diabetes-induced retinal microvascular disease and underlying abnormalities of retinal metabolism and physiology. *Diabetes*. 2007;56:373–9.
60. Friedman SM, Almukhtar TH, Baker CW, et al. Topical nepafenac in eyes with noncentral diabetic macular edema. *Retina*. 2015;35:944–56.
61. Rubio R. Phase I Clinical Trial Using a Refillable, Non-biodegradable Long-term Drug Delivery Implant of Ranibizumab. Tokyo, Japan: World Congress of Ophthalmology. 2014.
62. Campochiaro PA, Channa R, Berger BB, et al. Treatment of diabetic macular edema with a designed ankyrin repeat pro-tein that binds vascular endothelial growth factor: a phase I/II study. *Am J Ophthalmol*. 2013;155:697–704.
63. Dugel PU, Blumenkranz MS, Haller JA, et al. A randomized dose-escalation study of subconjunctival and intravitreal injections of sirolimus in patients with diabetic macular edema. *Ophthalmology*. 2012;119:124–31.
64. Scheppke L, Aguilar E, Gariano R, et al. Retinal vascular permeability suppression by topical application of a novel VEGFR2/Src kinase inhibitor in mice and rabbits. *J Clin Invest*. 2008;118:2337–46.
65. Nguyen QD, Schaschar RA, Nduaka CL et al. Dose-ranging evaluation of intravitreal siRNA PF-04523655 for diabetic macular edema (the DEGAS study) *Invest Ophthalmol Vis Sci*. 2012;53:7666e74. iCo Therapeutics Announces Top-Line Primary Endpoint Data from iCo-007 Phase 2 iDEAL Study in Diabetic Macular Edema. http://icotherapeutics.com/newsroom/index.php?&content_id=211. Accessed November 3, 2014.
66. Sfikakis PP, Grigoropoulos V, Emfietzoglou I, et al. Inflix- imab for diabetic macular edema refractory to laser photocoagulation: a randomized, double-blind, placebo-controlled, cross-over, 32 week study. *Diabetes Care*. 2010;33:1523–8.
67. Rangasamy S, Srinivasan R, Maestas J, et al. A potential role of angiopoietin-2 in the regulation of the blood-retinal barrier in diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2011;52: 3784–91.
68. Joussen AM, Poulaki V, Tsujikawa A, et al. Suppression of diabetic retinopathy with angiopoietin-1. *Am J Pathol*. 2002;160:1683–93.
69. Shen J, Frye M, Lee BL, et al. Targeting VE-PTP activates Tie-2 and stabilizes the ocular vasculature. *J Clin Invest*. 2014;124:4564–76.
70. Rao VR, Prescott E, Shelke NB, et al. Delivery of SAR 1118 to the retina via ophthalmic drops and its effectiveness in a rat streptozotocin (STZ) model of diabetic retinopathy (DR). *Invest Ophthalmol Vis Sci*. 2010;51:5198–204.
71. Tanito M, Hara K, Takai Y, et al. Topical dexamethasone- cyclodextrin microparticle eye drops for diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2011;52:7944–8.
72. Cukras CA, Petrou P, Chew EY, et al. Oral minocycline for the treatment of diabetic macular edema (DME): results of a Phase I/II clinical study. *Invest Ophthalmol Vis Sci*. 2012;53: 3865–74.
73. Liu J, Feener EP. Plasma kallikrein-kinin system and diabetic retinopathy. *Biol Chem*. 2013;394:319–28.
74. Navaratna D, McGuire PG, Menicucci G, et al. Proteolytic degradation of VE-cadherin alters the blood-retinal barrier in diabetic retinopathy. *Diabetes*. 2007;56:2380–7.
75. Schmidt M, Tisdale A, Lowden P, et al. Optimized IL-6 Blockade for the Treatment of Diabetic Macular Edema. *Invest. Ophthalmol. Vis. Sci.* 2014;55(13):1062.
76. Inoue T, Morita M, Tojo T, et al. Novel 1H-imidazol-2-amine derivatives as potent and orally active vascular adhesion protein-1 (VAP-1) inhibitors for diabetic macular edema treatment. *Bioorg Med Chem*. 2013;21:3873–81.

77. Campochiaro PA, Shah SM, Hafiz G, et al. Topical meca- mylamine for diabetic macular edema. Am J Ophthalmol. 2010;149:839–51.
78. Hernaez-Ortega MC, Soto-Pedre E, Piniés JA. Lanreotide Autogel for persistent diabetic macular edema. Diabetes Res Clin Pract. 2008;80:e8–10.
79. Sarao V, Veritti D, Lanzetta P. Regression of diabetic macular edema after subcutaneous exenatide. Acta Diabetol. 2014;51:505–8.
80. Friedman EA, Brown CD, Berman DH. Erythropoietin in diabetic macular edema and renal insufficiency. Am J Kidney Dis 1995;26:202–8.
81. Li W, Sinclair SH, Xu GT. Effects of intravitreal erythropoietin therapy for patients with chronic and progressive diabetic macular edema. Ophthalmic Surg Lasers Imaging 2010;41:18–25.
82. Shaw LC, Neu MB, Grant MB. Cell-based therapies for diabetic retinopathy. Curr Diab Rep 2011;11:265–74.