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RETINA TODAY

DME: Focus On Multiple Targets

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The Diabetic Proinflammatory State

Inflammation plays a prominent role in the etiology of diabetes and its complications.

BY DAVID S. BOYER, MD

More than 29 million people in the United States have diabetes, and more than 7 million of these people do not know they have the disease.[1] The Centers for Disease Control and Prevention estimates that one of every three people will develop type 2 diabetes in his or her lifetime.[2]

People with diabetes are at risk for a wide range of complications, both microvascular and macrovascular, and as many as half them have some complications, even at the time of diagnosis.[3,4] As a result, patients have frequent medical appointments and often require multiple therapies.[5] A diagnosis of diabetic macular edema, for example, increases physician visits exponentially, from an average of 15 per year to almost 26 per year.[5]

About 95% of people with diabetes have type 2, in which the body does not use insulin properly or does not produce insulin.[1] Risk factors associated with type 2 diabetes include obesity, physical inactivity, advancing age, family history of diabetes, history of gestational diabetes, and certain ethnicities; comorbidities associated with type 2 diabetes include obesity, hypertension, dyslipidemia, heart failure, depression, anxiety, and arthritis.[6,7]

Type 1 diabetes is a consequence of an autoimmune attack on the beta cells of the pancreas, which leads to cessation of insulin production and secretion.[2] Patients with type 1 diabetes require insulin from the time of diagnosis. Generally, these patients lack the comorbidities associated with type 2 diabetes, such as obesity.[2,6]

GLUCOSE BY THE NUMBERS

Whether patients have type 1 or type 2 diabetes, the one characteristic they have in common is elevated levels of glucose. Therefore, diabetes is diagnosed based on plasma glucose levels. A fasting plasma glucose level ≥126 mg/dL (7.0 mmol/L) indicates diabetes. Importantly, a hemoglobin A1c level ≥6.5% also signals diabetes, even if a patient has a normal fasting plasma glucose level. In addition, a patient who has a 2-hour postprandial plasma glucose level ≥200 mg/dL is also considered diabetic.[6]

As a general guideline, the American Diabetes Association recommends a target A1c level of <7% for adults with diabetes; however, this target may vary, depending on several factors, such as disease duration, life expectancy, and comorbidities.[8]

In my experience, fewer than half of my patients know their current A1c. This is troubling, because A1c is the best indicator of how well patients are controlling their diabetes, and it helps me decide how frequently I should see them. If a patient reports an A1c of 10 or 11, for example, I worry that the disease will progress rapidly, and I schedule more frequent visits. Whereas, if a patient's A1c is 6.6% or 6.5% and stable, we may be able to increase the time between visits.

ROLE OF INFLAMMATION

Inflammation is emerging as an important mechanism in the pathogenesis and progression of diabetes, as well as in its systemic effects.[9-11] In type 1 diabetes, inflammatory processes are thought to be involved with the onset of disease during the destruction of the pancreatic islets. Inflammation may also play a substantial role in long-term disease progression.[9,11] In type 2 diabetes, inflammation and inflammatory factors may contribute to insulin resistance.[9,11]

Inflammation is normally a protective response to tissue stress, infection, or injury and will eventually return to homeostasis once these stressors resolve.[12] In diabetes, however, inflammation cannot resolve the problem, and tissue stress is further exacerbated by the inflammatory action.[12] In addition, hyperglycemia can introduce epigenetic changes that promote the persistent expression of inflammatory-related genes in susceptible tissues, such as endothelial, retinal, and renal cells.[13] These effects can lead to dysregulation of inflammation and, ultimately, chronic inflammation.[12,13]

Markers of inflammation, such as total leukocyte count, have been shown to correlate with worsening of insulin sensitivity.[9] Elevations in inflammatory markers, such as C-reactive protein and interleukin-6 (IL-6), have been reported to increase the risk for diabetes.[11] In addition, diabetes itself is associated with elevated levels of other inflammatory biomarkers, including adhesion molecules, such as vascular cell adhesion molecule-1, cytokines, such as IL-1, and growth factors, such as vascular endothelial growth factor.[14]

Abnormal levels of metabolites, such as lipids, fatty acids, and various cytokines from adipose tissue, may activate monocytes and increase the secretion of inflammatory cytokines, thereby increasing insulin resistance.[11]

Figure 1 illustrates how these various processes correlate. Chronic hyperglycemia mediates multiple cellular pathways, including protein kinase C activation, free-radical production, polyol accumulation, and advanced glycation end-product generation.[11] These changes cause the upregulation of proinflammatory cytokines, chemokines, and adhesion molecules.[10] All of these factors affect vascular permeability and leukocyte infiltration, contributing to the macrovascular and microvascular effects of diabetes.[14]

These effects result in damage to endothelial cells in the blood vessels and additional inflammation, which cause injury to multiple organ systems. Hyperglycemia is believed to be the main initiator of the inflammation underlying diabetic retinopathy and the development of diabetic cardiovascular disease. Therefore, inflammation can be reduced by mediating hyperglycemia.

I will briefly discuss some of the microvascular complications of diabetes.

NEPHROPATHY

Inflammation plays a fundamental role in the development and progression of diabetic nephropathy through the release of inflammatory cytokines and the accumulation of macrophages and T lymphocytes. These result in damage to the nephrons and blood vessels in the kidneys, causing decreased kidney function and eventually leading to kidney failure.[10,15,16]

Figure 2 illustrates the role of inflammation in diabetic nephropathy. Chronic hyperglycemia causes activation of several inflammatory signaling pathways, releasing cytokines and adhesion molecules that recruit inflammatory cells, maintaining the inflammatory state of the kidneys, eventually leading to kidney damage.[15,16] The inflammatory response is actually a loop. Once it starts, it is self-perpetuating, unless the cycle is broken.

NEUROPATHY

Chronic hyperglycemia along with increased inflammatory cytokines can also lead to structural and functional damage to the vasculature and nerves, causing diabetic neuropathy.[10] I believe diabetic neuropathy is quite common, as I often see it as one of the earliest signs of diabetes.

The effects of chronic hyperglycemia on the nerves are twofold. The blood supply decreases secondary to microvascular complications, while oxidative stress leads to damage to the neurons and increased apoptosis.[3,14]

Diabetic neuropathy is characterized by deterioration of neuronal microvasculature and nerve fibers, leading to decreased capillary blood flow to nerve fibers, decreased nerve perfusion, and endoneural hypoxia.[3] Hyperglycemia has been shown to directly induce oxidative stress and apoptosis in neuronal cells.[17]

An increase in inflammatory mediators in diabetic neuropathy has been documented and includes tumor necrosis factor alpha and other inflammatory cytokines that are elevated in patients with diabetes. Researchers are just beginning to explore their potential role, including effects on nerve conduction velocity and epidermal innervation deficits.[18,19] Together, these effects lead to demyelination and neuronal degeneration.[3]

RETINOPATHY

As with other complications associated with diabetes, the prevalence of diabetic retinopathy increases as the duration of diabetes increases.[3] Poor glycemic control has been shown to be the most significant factor in the development and progression of diabetic retinopathy. Chronic hyperglycemia leads to impaired retinal blood flow, resulting in hypoxia and retinal damage.[3]

This direct damage to retinal blood vessels, along with increased inflammatory response, including increases in proinflammatory mediators in the eye, occurs along with

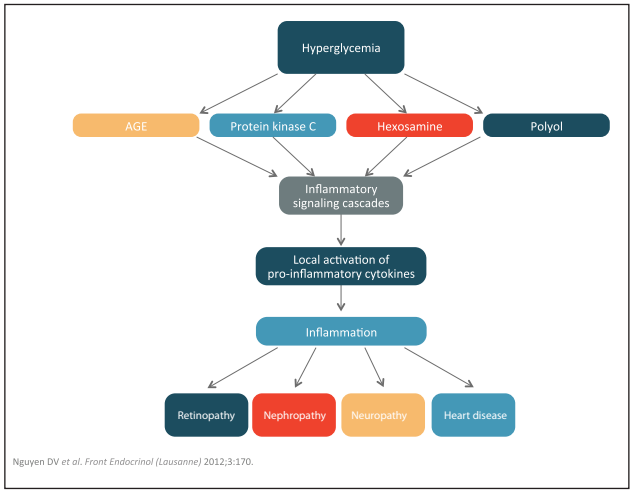


Figure 1. Chronic hyperglycemia mediates multiple cellular pathways, causing upregulation of proinflammatory cytokines, chemokines, and adhesion molecules.

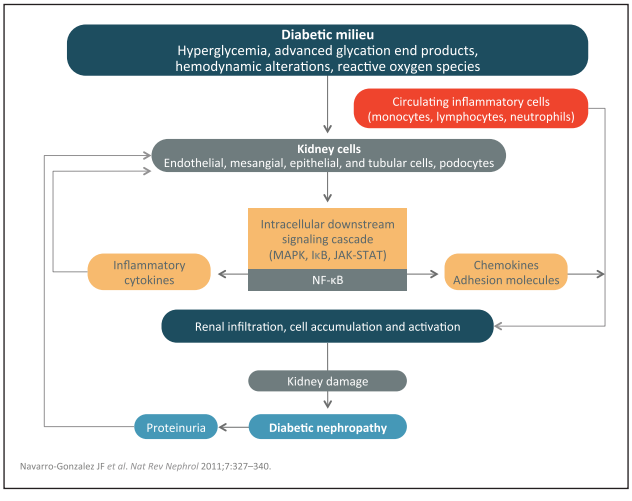
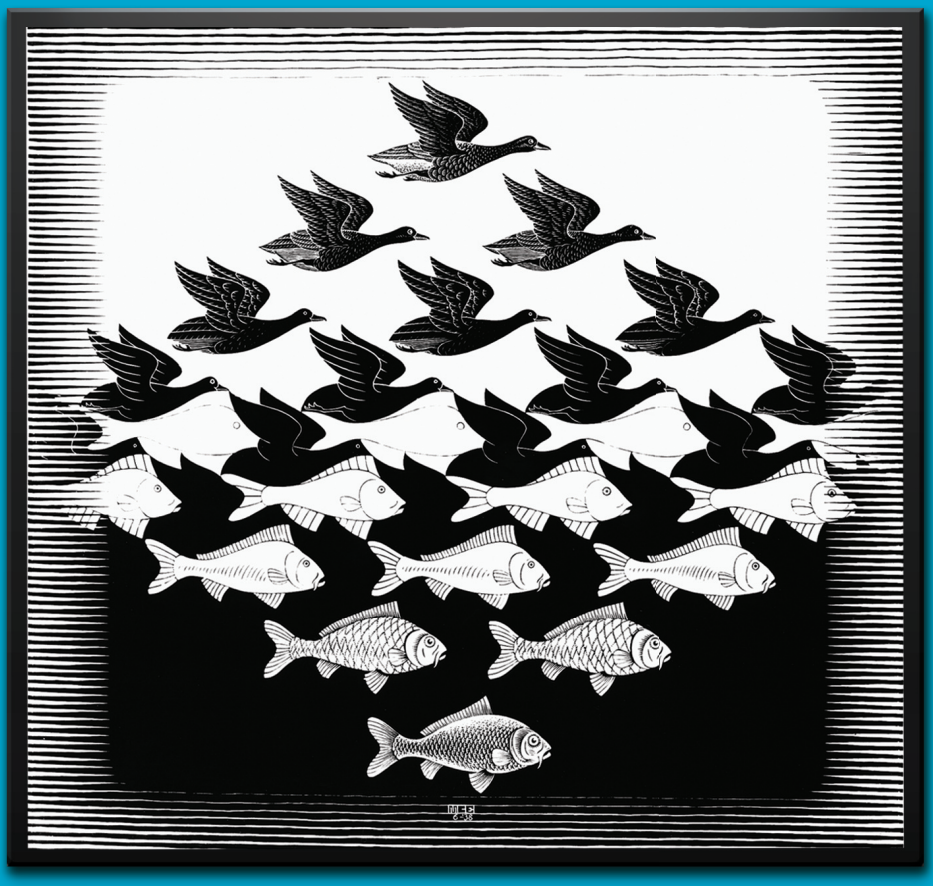


Figure 2. Chronic hyperglycemia activates inflammatory signaling pathways, releasing cytokines and adhesion molecules that recruit inflammatory cells, eventually leading to kidney damage.

A different perspective can have the power to change your approach



Indication and Usage
Diabetic Macular Edema
OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

Dosage and Administration
FOR OPHTHALMIC INTRAVITREAL INJECTION.
The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

IMPORTANT SAFETY INFORMATION
Contraindications
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions
Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Adverse Reactions
Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous

SEE DME Differently.

- **The pathophysiology**
  — An **inflammatory cascade** plays a key role[1-5]
- **The therapeutic targets**
  — Suppress multiple **inflammatory cytokines**[6]
- **The clinical results**
  — Achieve clinically significant **3-line gains** in BCVA[6,*]

The #1 steroid in U.S. market share for DME[7,†]

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® (dexamethasone intravitreal implant) patients versus 4% of sham patients. 42% of the patients who received OZURDEX® (dexamethasone intravitreal implant) were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6-month period).

Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® (dexamethasone intravitreal implant) group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects versus 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

Please see Brief Summary of full Prescribing Information on next page.

*Best-corrected visual acuity.
†Based on U.S. market share of DME patients treated with intravitreal steroids: December 2014.[7]

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

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ALLERGAN Retina

Ozurdex.com APC08XA15 150986

OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE

Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Diabetic Macular Edema

OZURDEX® is indicated for the treatment of diabetic macular edema.

CONTRAINDICATIONS

Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product *[see Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection *[see Patient Counseling Information]*.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses *[see Adverse Reactions]*.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids including OZURDEX® include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Retinal Vein Occlusion and Posterior Segment Uveitis

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients

MedDRA Term	OZURDEX® N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)
Ocular hypertension	23 (5%)	3 (1%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Following a second injection of OZURDEX® (dexamethasone intravitreal implant) in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

Diabetic Macular Edema

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in the table below were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Ocular		
Cataract[1]	166/243[2] (68%)	49/230 (21%)
Conjunctival hemorrhage	73 (23%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry eye	15 (5%)	7 (2%)
Vitreous detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

[2] 243 of the 324 OZURDEX® subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

	Treatment: N (%)	
IOP	**OZURDEX® N=324**	**Sham N=328**
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization,1 laser iridotomy, 1 surgical iridectomy
Sham: 1 laser iridotomy

Cataracts and Cataract Surgery

At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period).

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 3 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal treatment with OZURDEX® is low. It is not known whether intravitreal treatment with OZURDEX® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when OZURDEX® is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of OZURDEX®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells *in vitro* or in the *in vivo* mouse micronucleus test. Adequate fertility studies have not been conducted in animals.

PATIENT COUNSELING INFORMATION

Steroid-related Effects

Advise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects

Advise patients that in the days following intravitreal injection of OZURDEX®, patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

an influx of leukocytes into the retina, all of which alter vascular permeability.[10,20-22] These lead to pericyte loss, which is the earliest histologic marker of diabetic retinopathy, as well as changes in retinal vascular permeability, microaneurysms, capillary damage and occlusion, and eventually neovascularization.[21]

In addition to retinopathy and diabetic macular edema, which may occur at any stage of retinopathy, patients with diabetes are also more likely to develop cataracts and glaucoma.[22,23]

METABOLIC CONTROL IS KEY

Inflammation plays a prominent role in the etiology and complications of diabetes. An individualized approach aimed at maintaining metabolic control is key for patients to minimize complications. Although we have good tools to help patients manage their disease, it is still important to educate them about making necessary lifestyle changes—controlling blood sugar, blood pressure, and lipids, for example—as early as possible.■

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Clinical Relevance of the Proinflammatory State

Real-world cases reflect the multifactorial nature of diabetic macular edema.

BY THOMAS A. ALBINI, MD

Traditionally, the defining features of diabetic macular edema (DME) are vessel hyperpermeability, vascular leakage, edema, and retinal thickening.[1] What do these signs tell us about the pathophysiology of DME? In clinical practice, we cannot detect inflammation directly, nor can we see cytokines or leukocytes. We do not have markers to noninvasively detect these signs; however, we can consider the timing of disease and the implications for the pathophysiology. To do this, we use complementary imaging modalities, including fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT).[2] Looking at both the vasculature and the neuronal effects allows for a more comprehensive characterization of DME than was possible in the past, helping us to make the best treatment decisions for our patients.

The following cases are examples of how these technologies, along with knowledge gained from the literature and our own clinical experience, help shape how we think about DME.

CASE No. 1: SEVERE NPDR IN TYPE 2 DIABETES

A 65-year-old man with type 2 diabetes has decreased visual acuity (20/60) in his right eye. Fundus photography (Figure 1) shows evidence of severe nonproliferative diabetic retinopathy (NPDR), including intraretinal hemorrhages, lipid exudates, and some microaneurysms.

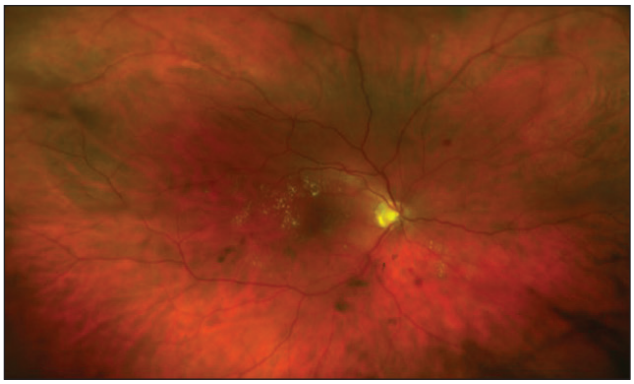

Figure 1. The patient's right eye shows severe NPDR, including intraretinal hemorrhages, lipid exudates, and microaneurysms.

Ultra widefield FA reveals severe NPDR with center-involved DME, and a close-up of the peak-phase angiogram (Figure 2) shows leakage from microaneurysms as well as diffuse leakage. The presence of these leaks in the absence of neovascularization suggests a weakening of the existing vasculature and a breakdown of the blood-retinal barrier (BRB).[1] The late-phase FA (Figure 3) confirms substantial leakage.

OCT is an important imaging tool for the diagnosis and management of DME.[3] It enables us to quantify increased macular thickness, and it can pinpoint fluid accumulation, along with cyst size, location, and reflectivity. OCT also reveals the presence of subretinal fluid, intraretinal hyperreflective spots, and vitreomacular traction.

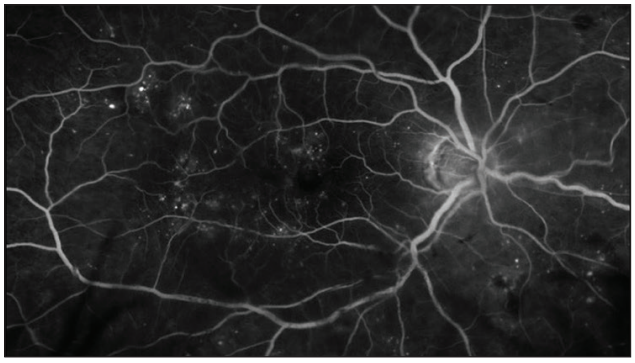

Figure 2. A close-up of the peak-phase angiogram shows leakage from microaneurysms and diffuse leakage.

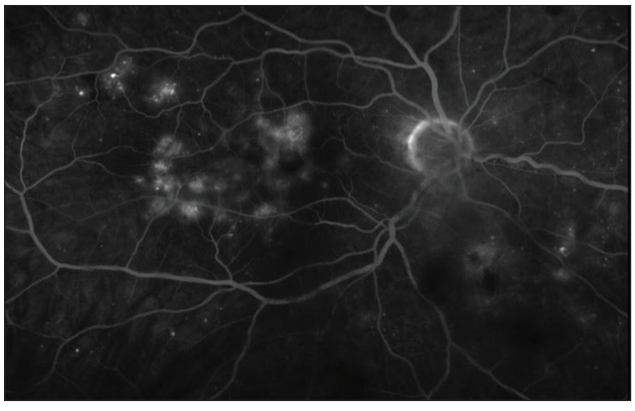

Figure 3. Late-phase FA confirms substantial leakage.

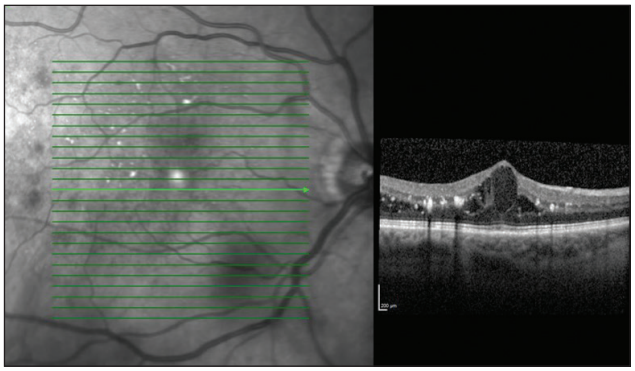

Figure 4. OCT reveals cystoid edema and some hyperreflective spots.

The eyes of 36 subjects (12 healthy controls, 12 diabetics with no retinopathy, and 12 diabetics with diabetic retinopathy) were examined by spectral-domain OCT

Percentage of eyes with hyperreflective spots

Retinal microglial activation	Control (n=12)	Diabetic	
		No DR (n=12)	NPDR (n=12)
Inner limiting membrane-ganglion cell layer	3%	55%	90%
Inner nuclear layer-outer plexiform layer	1%	35%	75%
Outer nuclear layer	–	10%	25%

Figure 5. Vujosevic and colleagues found that hyperreflective spots are present in diabetic eyes even when clinical retinopathy is undetectable.

Compared with time-domain OCT, spectral-domain OCT shows better differentiation and visualization of retinal structures. This is important because the literature suggests that the specific location of the fluid and persistent changes in the outer versus inner retinal layer are particularly important to assess the severity of disease and, potentially, clinical outcomes.[2,3]

This patient's OCT shows cystoid edema and some hyperreflective spots (Figure 4). Hyperreflective spots have been shown in the retinas of diabetic patients without detectable diabetic retinopathy to a greater extent than in healthy controls, and the prevalence is even higher in patients with diabetic retinopathy (Figure 5).[4] We do not know exactly what hyperreflective spots are, but one hypothesis is that they are aggregates of activated microglial cells.[4] If that is the case, their presence in early diabetic retinopathy may suggest that an inflammatory state exists before chronic DME develops.

Despite the obvious importance of OCT, we need to exercise caution when interpreting results. To date, no correlation has been shown between OCT thickness and visual acuity (Figure 6).[5] Therefore, a patient may have a wet macula with good visual acuity or a dry macula with poor visual acuity. Likewise, a reduction in edema does not necessarily always result in vision improvement and vice versa (Figure 7).[5] The extent of visual acuity recovery

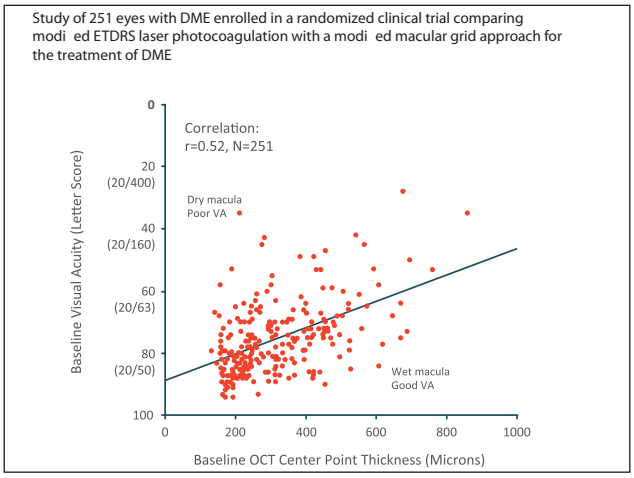

Figure 6. Researchers have found no direct correlation between retinal thickness measured by OCT and visual acuity.

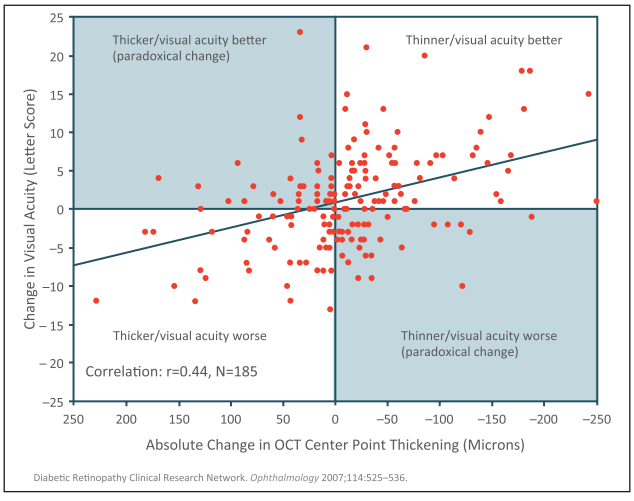

Figure 7. A reduction in edema does not necessarily result in vision improvement and vice versa.

depends on the neuroretinal damage that has accumulated through diabetic retinopathy and DME. Although it is intuitive that the duration of edema may play a role in terms of the extent of the damage, the extent of the macular damage may not correlate directly to macular thickness but rather to the underlying pathophysiology.[5] Vision loss is complicated and cannot be explained by the presence of edema alone.[5]

CASE No. 2: SEVERE BILATERAL NPDR IN TYPE 2 DIABETES

A 58-year-old woman with type 2 diabetes has severe NPDR and decreased visual acuity in both eyes (20/120 OD; 20/150 OS). Fundus photography shows some lipid exudates, intraretinal hemorrhages, and microaneurysms in both eyes, with no obvious neovascularization (Figure 8).

Widefield early-phase FAs show evidence of severe NPDR (Figure 9). Peak-phase angiograms (Figure 10) show predominantly diffuse leakage, which is confirmed

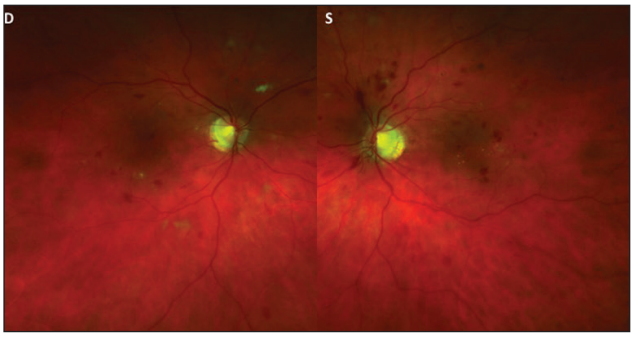

Figure 8. Fundus photos show some lipid exudates, intraretinal hemorrhages, and microaneurysms OU, with no obvious neovascularization.

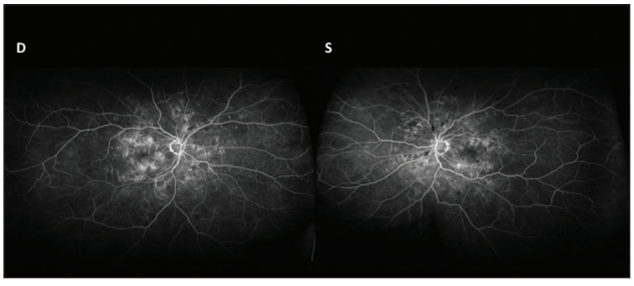

Figure 9. Widefield early-phase FAs show evidence of severe NPDR.

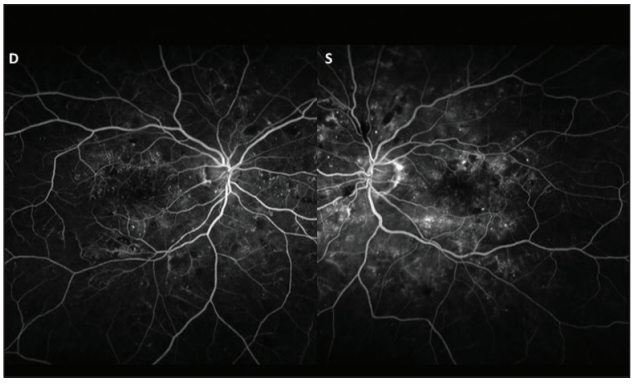

Figure 10. Peak-phase angiograms show predominantly diffuse leakage.

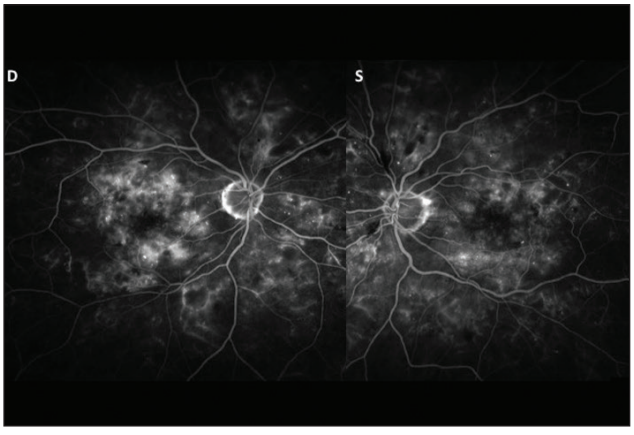

Figure 11. Late-phase angiograms confirm predominantly diffuse leakage.

by the late-phase angiograms (Figure 11). OCT shows intraretinal edema in the right eye and subretinal fluid in the left eye (Figure 12).

Improved OCT methods enable us to investigate the correlation between the type of edema seen on OCT and the patient's prognosis.[3] In particular, the presence of subretinal fluid, as seen in this patient's left eye, has been reported as a negative prognostic factor for patients with DME in terms of vision improvement.[2] Also, we can see that despite this patient's poor visual acuity, the macular thickness is not pronounced, which is consistent with study results that demonstrate a lack of correlation between visual acuity and macular thickness.[5]

CASE No. 3: MODERATE NPDR IN TYPE 1 DIABETES

A 45-year-old woman with type 1 diabetes has moderate NPDR and blurry vision (visual acuity 20/40) in her left eye. Fundus photography shows lipid exudates, intraretinal hemorrhages, some microaneurysms, and no obvious neovascularization (Figure 13).

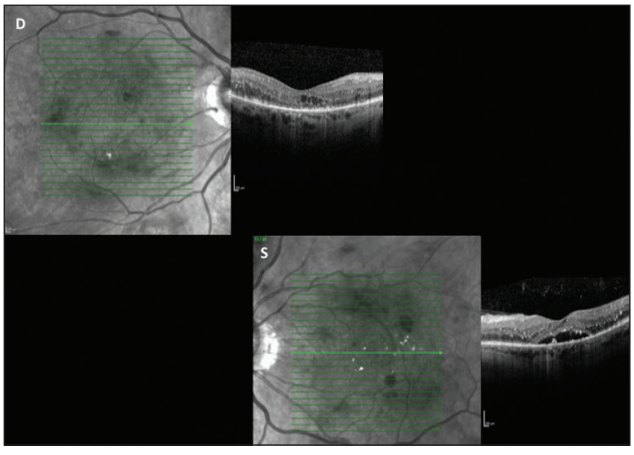

Figure 12. OCT shows intraretinal edema OD and subretinal fluid OS.

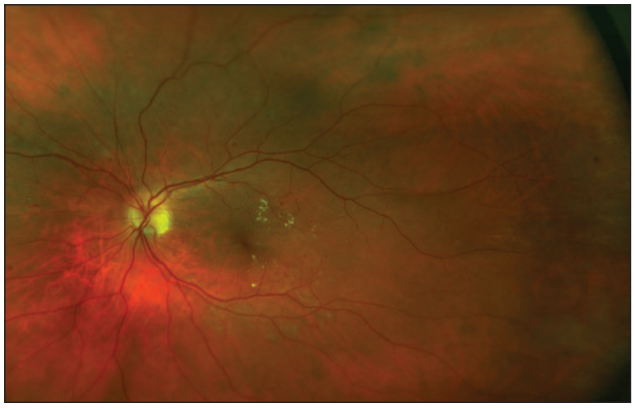

Figure 13. Fundus photo shows lipid exudates, intraretinal hemorrhages, some microaneurysms, and no obvious neovascularization.

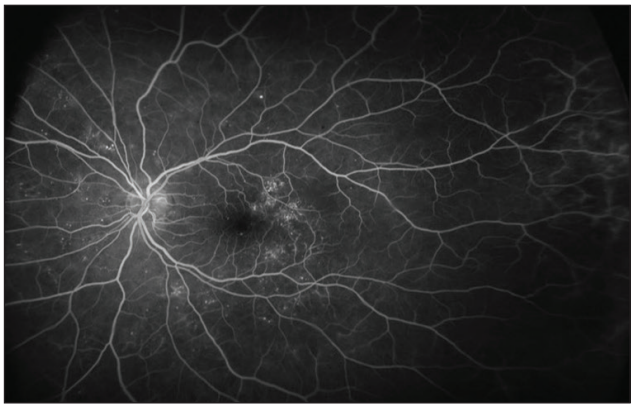

Figure 14. Widefield peak-phase angiogram shows evidence of moderate NPDR with diffuse leakage and some areas of capillary nonperfusion.

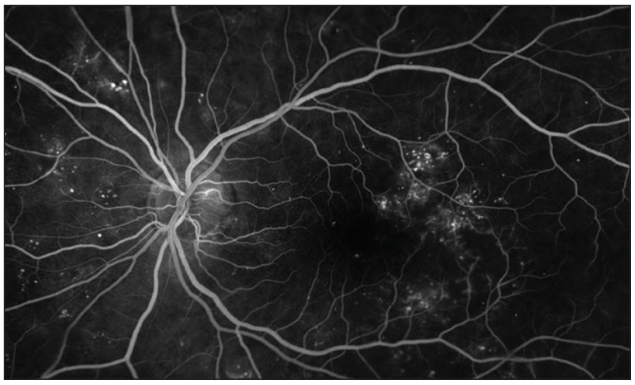

Figure 15. Close-up of peak-phase angiogram suggests leakage from microaneurysms as well as diffuse leakage.

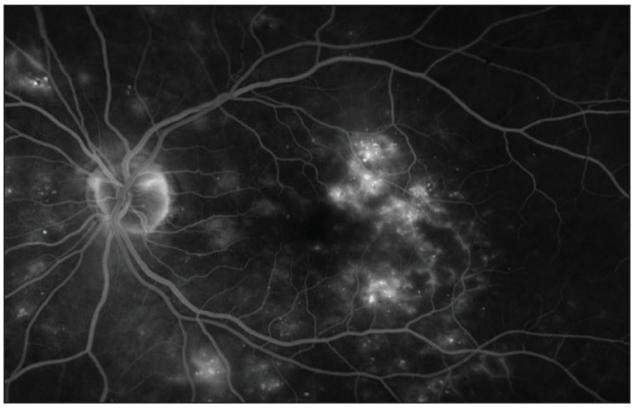

Figure 16. Late-phase angiogram confirms presence of leakage from microaneurysms as well as diffuse leakage.

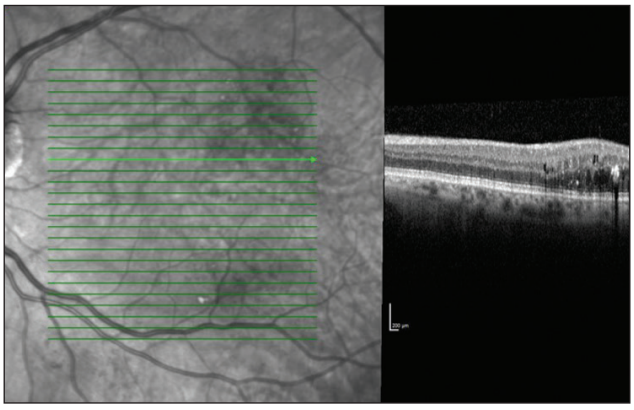

Figure 17. OCT shows intraretinal fluid and hyperreflective spots.

Widefield peak-phase FA shows evidence of moderate NPDR with diffuse leakage and some areas of capillary nonperfusion (Figure 14). A close-up of the peak-phase angiogram suggests leakage from microaneurysms and diffuse leakage, as well, (Figure 15), and that is reinforced in the late phase (Figure 16). Again, in the absence of neovascularization, this indicates a breakdown in the BRB. OCT shows intraretinal fluid and hyperreflective spots (Figure 17). The macular thickness is not pronounced in this case; however, the visual acuity is much better than for the patient in case No. 2.

SUMMARY

DME has a complex pathophysiology that can occur at any stage of retinopathy, even prior to observable vascular changes in the retina.[6] Although our understanding of DME is still evolving, what we observe in the clinic is consistent with the multifactorial inflammatory disease described in the literature, and this has important clinical implications that should be considered.

Given the different treatment options in our armamentarium, such as laser, anti-VEGF agents, and steroids, understanding the pathophysiology and clinical characteristics of each patient enables us to tailor therapy to that patient's individual needs.[7-11]■

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Insights Into the Pathophysiology of Diabetic Macular Edema

A growing body of scientific evidence reveals multiple therapeutic targets.

BY DAVID S. BOYER, MD

Chronic hyperglycemia can cause microvascular and macrovascular complications in multiple organs and cell types in the body. Here, I focus on the effects of hyperglycemia in the eye and discuss how inflammatory events culminate in the ocular fundus associated with diabetes.

HYPERGLYCEMIA-INDUCED INFLAMMATION

Four major pathogenic mechanisms are responsible for hyperglycemia-induced damage: the polyol pathway, the hexosamine pathway, the protein kinase C pathway, and the advanced glycation end-product pathway. These metabolic pathways are activated by increased levels of different glucose metabolites within the glycolysis pathway.[1] Increased activity in each of these pathways causes increased cellular oxidative stress and, subsequently, increased production of inflammatory mediators, such as cytokines and intercellular adhesion molecules (ICAM) as well as increased microglial activation.[2-4] Each of these pathways may be linked with the pathogenesis of diabetic retinopathy.[2] Diabetic macular edema (DME) can occur at any stage of diabetic retinopathy.[5]

Both systemic and local inflammatory events may contribute to diabetic retinopathy and DME, and these events may have different effects.[6] Systemic proinflammatory cytokines generally have low-grade activity and are produced by visceral fat and macrophages that infiltrate the adipose tissue in insulin resistance states, such as obesity and type 2 diabetes.[7] In contrast, local proinflammatory cytokines are produced by retinal pigment epithelium and glial cells.[6] Common sets of inflammatory factors—notably, interleukin-6 (IL-6), IL-8, vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-alpha), and monocyte chemoattractant protein-1 (MCP-1)—are upregulated in both the systemic and local environments in patients with diabetic retinopathy.[6]

ICAM-1, P-selectin, and vascular cell adhesion molecule-1 (VCAM-1) all facilitate leukocyte adhesion to endothelial cells, which is the first step toward damaging the endothelium, causing the endothelial wall to break down and fluid to leak out. IL-8 activates neutrophils and T lymphocytes and promotes angiogenesis, while IL-6 increases VEGF production. VEGF promotes retinal neovascularization and the breakdown of the blood-retinal barrier (BRB), stimulates leukostasis, and increases vascular permeability. MCP-1 induces leukocyte recruitment and activation. Angiopoietin-2 promotes breakdown of the BRB and sensitizes epithelial cells to TNF-alpha. TNF-alpha promotes breakdown of the BRB and promotes ICAM-1 expression.[6,8,9]

> Both systemic and local inflammatory events may contribute to diabetic retinopathy and DME.

What cytokine changes are associated with diabetes? Figure 1 illustrates the relative concentrations of 27 cytokines in the aqueous humor of people with and without diabetes.[10] In another study[11] (Figure 2), researchers showed that inflammatory cytokines were expressed at higher levels in the vitreous of eyes with DME versus eyes with nondiabetic ocular diseases or eyes of patients with diabetes without retinopathy. Based on these findings, it becomes immediately apparent that IL-6, MCP-1, and ICAM-1 play major roles in DME, as does VEGF. We have also learned that reducing these inflammatory cytokines reduces the foveal thickness and resolves the DME.[9]

Inflammation mediates both neural and vascular dysfunction, which contribute to the development of DME. Some of the key events of DME occurring in the neural component of the retina include: microglial activation, Müller cell gliosis and dysfunction, and ganglion cell death.[12-16] In the vascular component of the retina, leukocyte adhesion to endothelial cells in the retinal vasculature, alterations in tight junctions between cells, retinal pigment endothelial cell death, and pericyte

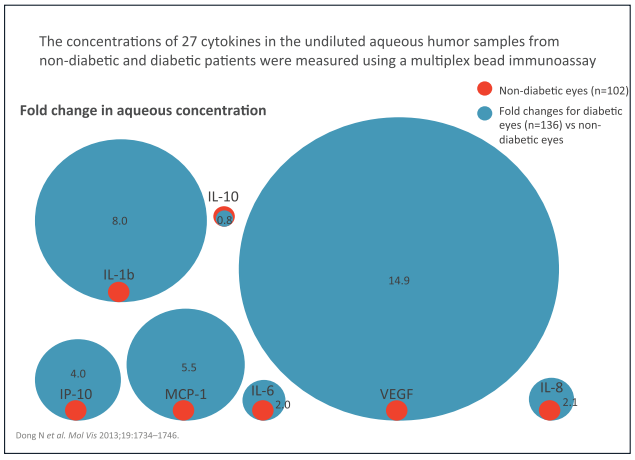

Figure 1. Studies have indicated that a number of inflammatory cytokines significantly increases in the aqueous humor of diabetic eyes versus nondiabetic eyes.

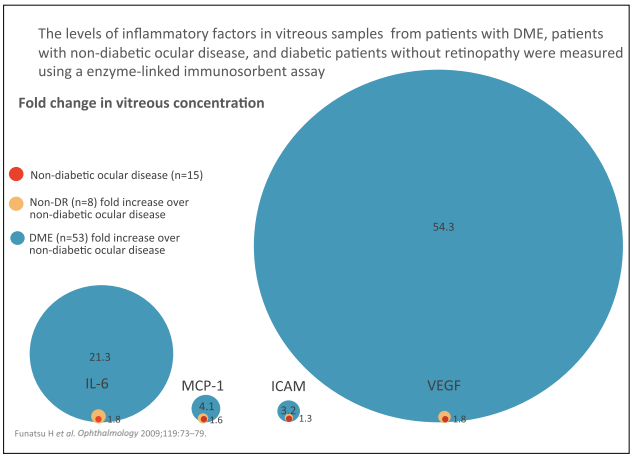

Figure 2. Inflammatory cytokines were expressed at higher levels in the vitreous of eyes with DME versus eyes with non-diabetic ocular diseases or eyes of patients with diabetes without retinopathy.

death play a role in vascular injury and the development of DME.[16]

Glial cells, including Müller cells and astrocytes, act as the interface between the neurons and the vasculature, and are key regulators of neural metabolism.[12] In eyes with DME, they show altered contact with vessels, and release inflammatory mediators.[16] They also have impaired glutamate metabolism.[15,16] Microglia are normally found in the inner retina. In eyes with DME, microglia increase in number, activate inflammatory mediators, and are found throughout the retina, including the subretinal space.[4] Ganglion cell death and axonal atrophy are also features of the neural component dysfunction during DME.[16]

DME also affects the vascular components of the retina, resulting in altered tight junctions and RPE cell and pericyte death.[16]

VASCULAR COMPONENT

There are three main stages to the microvascular changes that result from inflammation:

1. Dilation of the capillaries to increase blood flow;
2. Microvascular structural changes and escape of plasma proteins from the bloodstream;
3. Leukocyte transmigration through the endothelium, and accumulation at the site of injury.[8]

Vascular dysfunction in diabetic retinopathy and DME is primarily caused by leukostasis, which is the recruitment and adhesion of leukocytes to the retinal vasculature.[6] Leukostasis is the first step in a sequence of adhesion and activation events that lead to extravasation of the leukocyte through the endothelium.[6] Leukocytes involved in leukostasis induce vascular permeability by releasing cytokines, including VEGF and TNF-alpha, altering endothelial junction proteins, increasing reactive oxidative species levels, and inducing the death of pericytes and astrocytes surrounding the endothelial cells.[6,17] Furthermore, the accumulation of leukocytes leads to vessel occlusion and subsequent injury.[18]

Following leukostasis, the alteration of adherens and tight junctional proteins disrupts the integrity of the endothelial cell monolayer.[6] This breakdown of the inner BRB results in vascular permeability and escape of leukocytes and inflammatory mediators into the extravascular space of the retina.[6,19] Furthermore, the death of pericytes and astrocytes surrounding the endothelium leads to further breakdown of the BRB and even more pronounced vascular leakage.[6]

NEURAL COMPONENT

The effects of inflammation in the neural components of the retina can be detected early in diabetic retinopathy and DME.[15,20-22] The key changes are microglial activation and Müller cell dysfunction. These effects in particular lead to impaired glutamate metabolism in glia, altered contact between glia and vessels, and neuron and ganglion death.[15,20] The accumulation of activated microglia in the subretinal space and their production of inflammatory factors leads to progression of DME pathology.[4]

Under normal resting conditions, retinal microglia are located almost exclusively in the inner retinal layers up to the outer plexiform layer. Under conditions of injury, disease, and aging, however, activated microglia can migrate across retinal lamina and into the subretinal space.[4,23] This results in the accumulation of subretinal microglia, which is of particular concern within this region, given that activated microglia can release inflammatory factors important for leukostasis and can

exert cytotoxic effects, thereby increasing vascular permeability.[4]

A clinical histology image shows a normal eye (Figure 3) with a few ramified parenchymal (arrows) and perivascular (arrowhead) microglial cells present in the inner retinal layers.[24] In DME (Figure 3), proliferated microglia extend throughout the retina and subretinal space. The cells in the epiretinal membrane are also heavily stained with all three microglial markers tested (arrows).[24]

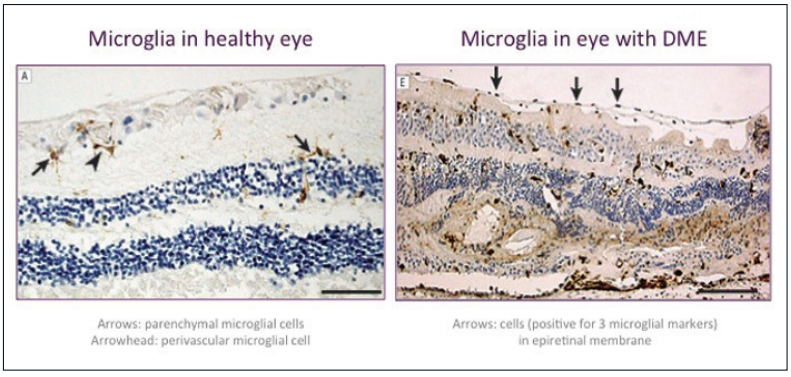

Figure 3. In DME, proliferated microglia extend throughout the retina and the subretinal space.

Müller cells are affected by proinflammatory factors.[25] This leads to swelling and reduced fluid clearance from the inner retinal tissue.[13-15] This impaired fluid clearance, which is accompanied by increased vascular leakage because of the breakdown of the BRB, contributes to the development of macular edema.[15,26] Furthermore, Müller cells contribute to survival of ganglion cell neurons and photoreceptors, stabilization of the retinal structure, and modulation of inflammatory and immune responses.[22]

Müller glial cells regulate ion and water transport to help maintain the homeostasis of the retinal extracellular environment.[13,15] Müller cells work to "dehydrate" the inner retinal tissue by mediating transcellular water transport from the retinal interstitium through the cell bodies into the vasculature.[15] K+ ions are taken up by Müller cells and released into the fluid-filled space outside of the neural retina through potassium (Kir4.1) channels; water osmotically coupled to K+ currents flows into the blood through aquaporin-4 (AQP4) water channels in the plasma membrane.[13,15]

In response to proinflammatory stimuli, however, Müller cells undergo gliosis and are unable to control osmotic water transport.[21,25] Müller cells in diabetic retinas downregulate the expression of potassium (Kir4.1) channels, disrupting the release of potassium ions (K+) into the blood; however, Müller cells continue to take up potassium ions via Kir2.1 channels.[13,15] The resulting osmotic difference favors water influx, which leads to swelling of Müller cells.[15] Disruption of ion and water transport results in decreased fluid clearance from the inner retinal tissue and contributes to the development of edema.[13]

SUMMARY

Diabetic retinopathy and DME result from the interaction between and overlap of vascular and neural processes caused by hyperglycemia. It is not known if vascular or neural cell defects occur first; most likely they are interdependent.[12] Until recently, no unifying hypothesis linked these mechanisms or showed an obvious connection between any of these mechanisms.[3]

Evidence suggests that the inflammatory process underlies several shared mechanisms that contribute to early neuronal damage or death and microvascular impairment.[20] Moreover, there is overlap between the neural and vascular effects.[20] For example, the release of inflammatory factors causes leukostasis in the vasculature or elicits neuronal cell death, as in the case of activated microglia in the subretinal space. When the neurodegenerative process is initiated, there is accumulation of glutamate and loss of neuroprotective factors.[20]

By means of complex underlying mechanisms, this contributes to BRB breakdown, vasoregression, and impairment of the hemodynamic response (or timely delivery of blood to active neural tissues), leading to early microvascular impairment.[20] Increased microvascular impairment leads to neuronal loss, further solidifying the link between these processes.[20]

TREATMENT INSIGHTS

The pathogenesis of DME provides insights into our three major treatment classes—laser, corticosteroids, and anti-VEGF agents—which target different aspects of DME.

- **Laser.** The mechanism of action of laser therapy is not well understood, but it may promote the regression of abnormal blood vessels.[27,28]
- **Anti-VEGF agents.** These agents inhibit the biologic activity of VEGF and target a key aspect of the vascular dysfunction: tight junction integrity and angiogenesis.[9,29]
- **Corticosteroids.** Treatment with corticosteroids has been associated with reductions in several inflammatory mediators, including TNF-α, IL-6, MCP-1, and VEGF.[6,9,29] Much of this activity is mediated by regulating the local expression of proinflammatory and anti-inflammatory mediators.[6]

INFLAMMATION'S PROMINENT ROLE

Evolving evidence suggests that for diabetic retinopathy and DME, inflammation and vascular leakage play prominent roles in the beginning of the disease, and inflammation is also a significant contributor to processes that cause vascular leakage.[6] In contrast, VEGF plays a more prominent role in other retinal disorders such as wet AMD.[30]

Inflammation is a critical element in neural and vascular elements of DME. Microvascular and neural events increase fluid accumulation in the retina and reduce fluid efflux, resulting in the physiological presentation of macular edema.[13,20] Consideration of all of the events in DME pathophysiologies suggests that inflammation plays an important role in the development of this disease.■

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