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**Diabetes: A Reference for the Primary Eyecare Clinician**

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Diabetes: A Reference for the Primary Eyecare Clinician

Description
With the prevalence of diabetes in the United States increasing and expected to climb higher in coming years, eyecare practitioners should have a thorough understanding of the treatment and management of diabetic patients. Eyecare providers form part of a team of practitioners, that includes primary care medical doctors, endocrinologists, and podiatrists, who should be involved in the regular management of diabetic patients.

A detailed understanding of the clinical manifestations, treatment, and pathogenesis of diabetes is of importance to the primary eyecare practitioner. This document is designed to provide a fundamental and accessible resource for the clinician, with an emphasis on ocular signs and diabetic retinopathy.

Disciplines
Optometry

Comments
Advisor: Lee Ann Remington, O.D., M.S.

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Diabetes:
A Reference for the Primary Eyecare Clinician

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Pacific University College of Optometry
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Introduction

With the prevalence of diabetes in the United States increasing and expected to climb higher in coming years, eyecare practitioners should have a thorough understanding of the treatment and management of diabetic patients. Eyecare providers form part of a team of practitioners, that includes primary care medical doctors, endocrinologists, and podiatrists, who should be involved in the regular management of diabetic patients. As evidenced by the table below, ocular involvement in diabetes is incredibly common and increases with duration. In fact, studies have shown that duration of diabetes is the single largest risk factor for development of diabetic retinopathy.

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration</th>
<th>Ocular Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;10 years</td>
<td>60% have some retinopathy</td>
</tr>
<tr>
<td></td>
<td>&gt;15 years</td>
<td>Virtually all patients have some degree of retinopathy; 25% progress to proliferative DR</td>
</tr>
<tr>
<td></td>
<td>&gt;20 years</td>
<td>50% progress to proliferative DR</td>
</tr>
<tr>
<td>2</td>
<td>At diagnosis</td>
<td>20% have retinopathy</td>
</tr>
<tr>
<td></td>
<td>&gt;4 years</td>
<td>4% progress to proliferative DR</td>
</tr>
<tr>
<td></td>
<td>&gt;15 years</td>
<td>60%-80% have some retinopathy; up to 20% progress to proliferative DR</td>
</tr>
</tbody>
</table>

Table 1. Duration of Diabetes and Risk of Ocular Complications. Adapted from the pamphlet Care of the Patient with Diabetes Mellitus, American Optometric Association, 2009.

A detailed understanding of the clinical manifestations, treatment, and pathogenesis of diabetes is of importance to the primary eyecare practitioner. This document is designed to provide a fundamental and accessible resource for the clinician, with an emphasis on ocular signs and diabetic retinopathy.

Essential pathogenesis of diabetic retinopathy

Hyperglycemia (elevated blood glucose levels) is at the core of tissue damage resulting from diabetes mellitus. Chronically increased blood glucose has been shown to damage blood vessels and nerve cells, leading to further complications, including neovascularization, as shown in Figure 1. Several biochemical pathways have been identified within this framework. Some of the mechanistic pathways thought to play a role in diabetic retinopathy are summarized in Figure 2.
Figure 1. Chain of Events in Diabetes Leading to Ocular Tissue Damage. Adapted from Fig 6.2, Diabetes and the Eye. (Steele, Steel, & Waine, 2008, p. 62).
Figure 2. Mechanisms of Diabetic Retinopathy. Created by Lee Ann Remington, O.D., M.S. Clinical manifestations of diabetic retinopathy.
Management of diabetic ocular complications is dependent upon the severity of clinical signs. Some of the most common clinical signs of diabetic retinopathy are listed below; relevant information pertaining to their genesis and recognition is included.

**Cotton Wool Spots (CWS)**

Cotton Wool Spots are so termed due to their fluffy white appearance on fundoscopy.

**Why a cotton wool spot is white:** “An arrest of the axoplasmic transport will result in an accumulation of intracellular organelles that are transported retrogradely from the terminal end of the axon in the lateral geniculate body” (Bek, 2010). Swelling of the nerve fiber layer in the affected area will cause incoming light to be scattered, accounting for the white appearance and indistinct borders.

**VF loss with CWS:** While small scotomas are possible, they are fairly rare. This is probably due to the redundancy of the nerve fiber layer around the affected area. It is even more rare to have an arcuate scotoma due to the fact that, “in spite of the disturbance in the axoplasmic transport, the conduction of axon potential in the retinal nerve fibers in the affected area has remained intact (Bek, 2010).
**Hard Exudates**

Hard exudates appear as focal, well-defined yellowish-brown flecks or spots during fundoscopy. When surrounding the fovea, these spots may resemble a star-like pattern due to orientation of the outer plexiform layer fibers in this region. These exudates are composed of precipitated serum lipid and protein from surrounding retinal vasculature, and are indicative of a breakdown in vessel architecture and increased hydrostatic pressure due to hyperperfusion. Hard exudates are predominantly located in the outer plexiform layer of the retina. Discrete hard exudates are removed by macrophages in 4-6 months; confluent exudates, however, may take up to a year to resolve. Extreme amounts of hard exudates in severe retinopathy may require surgical intervention for timely removal.

The Early Treatment of Diabetic Retinopathy Study (ETDRS) showed that an increase in serum lipid levels increases the risk of hard exudates in patients with diabetic retinopathy. In accordance with this, some case study reports show significant regression of hard exudates with lowering of serum lipid levels via medication.

**Macular Edema**

Macular edema is the single greatest cause of visual impairment in diabetics. It is caused by an abnormal accumulation of fluid in retinal tissues because of a disruption in the normal balance of hydrostatic, electric and osmotic forces across the vascular wall. The fluid that leaks from these vessels enters Müller cells, causing them to swell. Fluid also accumulates in the outer plexiform and inner nuclear layers. Other possible causes of damage include liquefaction necrosis or hypertrophy of endothelial cells, and pericyte degeneration. When Müller cells swell, they sometimes rupture and can cause pockets of fluid in a condition known as cystoid macular edema (CME).

“Several factors are known to cause and influence the development of diabetic macular edema due to damage of the retinal vasculature. Leukocytes mediate damage to endothelial cells by platelets binding to these cells and inducing the expression of adhesion molecules (P-selectin, E-selectin, VCAM-1 and ICAM-1). Furthermore, they increase leukostasis, being one of the first histological changes in diabetic retinopathy, occurring prior to any apparent clinical pathology. Adherent leukocytes directly induce endothelial cell death in capillaries, causing vascular obstruction and vascular leakage. Angiogenic factors, mainly VEGF, cause vascular hyperpermeability by leukocyte-mediated endothelial injury. This results in the opening of interendothelial junctions and the induction of fenestrations as well as the formation of vesiculovacuolar organelles” (Scholl, Kirchhoff, & Augustin, 2010).
**Microaneurysms**

Microaneurysms are usually less than 100 microns in size and often no larger than 10-25 microns. “The differentiation of a microaneurysm from a small well defined dot hemorrhage cannot be done on the basis of ophthalmoscopy alone, but requires F.A. by which a microaneurysm fills with fluorescein, whereas a hemorrhage remains dark” (Bek, 2010). A microaneurysm starts with a localized dilation of a retinal capillary, probably secondary to increased hydrostatic pressure in the vessel and weakening of the structure of the capillary wall. The microaneurysm fills with thrombotic material and hemoglobin as erythrocytes become trapped. Vascular walls remain thickened at the site of damage. It is possible that microaneurysms may be aborted attempts at neovascularization due to loss of pericytes, which are presumed to inhibit endothelial cell proliferation.

**Intraretinal Microvascular Abnormalities (IRMA)**

Ophthalmoscopically, IRMA looks like an area of flattened neovascularization and is often found near cotton wool spots. Unlike neovascularization however, which looks like a tangled cord, IRMA will appear more like a detour around an area of capillary occlusion. During fluorescein angiography, an area of IRMA will not leak and it is thought that it serves as a germination bed for neovascularization elsewhere (NVE).

**Venous Beading**

On fundus examination, venous beading appears as segmentary enlargement or dilation of retinal veins, and is often difficult to identify due to its subtlety. Very little is known about the exact physiology of venous beading in diabetic retinopathy, although some scientists have suggested that it may be an adaptation to increased blood flow. More pronounced venous changes may be a result of metabolic acidosis from peripheral ischemia secondary to capillary occlusion.

**Neovascularization (NVI, NVD, NVE)**

Retinal capillary pericytes most likely play a significant role in inhibiting retinal neovascularization. As shown in Figure 2, hyperglycemia can lead to pericyte loss, permitting new retinal vessels to arise from venules (rarely from arterioles). This usually occurs at the borders of an area of capillary nonperfusion.

If the neovascular membrane lies flat on the internal surface of neural retina, it is categorized as epiretinal. If the area in question is elevated, the membrane is termed preretinal. Neovascularization usually begins as epiretinal, but may break through the internal limiting membrane (ILM) and be kept in check only by the vitreous. Proteinases associated with
endothelial cells may cause local areas of disruption in the ILM and facilitate angiogenesis. With time, vitreal shrinkage may cause the new vessels to tear and result in a hemorrhage, thus patients with vitreal detachment are at a lower risk for hemorrhage. Vitreal detachments are more common in diabetics and tend to occur at an earlier age. “The neovascular growth pattern resembles that of fetal angiogenesis where new vessel formation is stimulated by the relative ischemia that develops in parallel with the increasing number of metabolically active cells during retinal development. The proliferation of endothelial cells from the larger venules forms vascular fronts that connect with the arteriolar counterparts to form the microcirculation. However, in the mature retina, the newly formed vessels are unable to grow inside the retinal tissue to replace occluded vessels. Therefore, the new vessels grow into the vitreous body where they may branch extensively and never get to connect with an arteriole to allow circulation of the blood” (Bek, 2010).

**Focal retinal depressions**

“Some young patients (<45 years old) exhibit focal depressions in the macular reflex, termed the ‘retinal depression sign’. This manifestation results from small retinal depressions that reflect light away from the observer so that the macula appears slightly darker than the surrounding retina. The feature is best observed by slit-lamp biomicroscopy and is also noted on fundus photographs, particularly with red-free filters. This finding may contribute to paracentral scotomas and may be confused with epiretinal membranes or macular edema” (Scott & Flynn, 2010).

**Treatment of diabetic retinopathy**

There are currently many different surgical and pharmacologic treatments for diabetic retinopathy. The choice of treatment modality is dependent largely on the severity of the retinopathy as well as other systemic considerations. The primary treatment modalities for DR are listed below with a brief discussion of the procedure and its use intended for a referring eyecare clinician.

**Focal laser treatment**

This laser treatment, also known as photocoagulation, can stop or slow the leakage of blood and fluid in the eye by using laser burns. It is performed in-office and is usually done in a single session. The patient’s vision will be blurry for about a day after the procedure, and they will sometimes be aware of small spots in their visual field that are related to the laser treatment. These usually disappear within weeks. Blurred vision from swelling of the central macula before surgery, however, may prevent recovery of completely normal vision.
**Scatter laser treatment**

This laser treatment, also known as panretinal photocoagulation, can shrink abnormal blood vessels. Also performed in-office, areas of the retina away from the macula are treated with scattered laser burns. The burns cause the abnormal new blood vessels to shrink and scar. Scatter laser treatment is usually performed in two or more sessions. Blurred vision is common for about a day after the procedure. Some loss of peripheral vision or night vision after the procedure is possible.

**Vitrectomy**

This procedure can be used to remove blood from the middle of the eye (vitreous) as well as any scar tissue that’s tugging on the retina. It is performed in a surgery center or hospital under local or general anesthesia. During the procedure, the doctor makes a tiny incision in order to remove scar tissue and blood in the eye with delicate instruments, and replace it with a salt solution. The salt solution helps maintain the eye’s normal shape. Sometimes a gas bubble must be placed in the cavity of the eye to help reattach the retina. If a gas bubble was placed in the eye, the patient may need to remain in a facedown position until the gas bubble dissipates — often several days. The patient will be required to wear an eye patch and use medicated eyedrops for a few days or weeks. Vitrectomy may be followed or accompanied by laser treatment.

**Management of diabetic patients**

The management of diabetic patients is dependent upon the severity of the disease, as well as additional factors such as the presence of clinically significant macular edema (CSME) and systemic health risks. Each case should be considered individually, and a more cautious approach to treatment, with input from specialists if necessary, is generally recommended.

Several studies, most notably the ETDRS, have been instrumental in helping to define standards for the grading of diabetic retinopathy. These standards are listed in the table below, and the corresponding standard photos may be viewed in stereo at the website for the University of Wisconsin-Madison’s Fundus Photograph Reading Center. Table 2 is a reference of clinical findings in diabetic retinopathy by level of severity of the disease.
<table>
<thead>
<tr>
<th>Severity of Diabetic Retinopathy</th>
<th>Clinical Findings</th>
</tr>
</thead>
</table>
| Mild Non-proliferative Diabetic Retinopathy (<span class="highlight">
NPDR</span>) | Microaneurysms only |
| Moderate NPDR | More severe than mild NPDR, but less than severe NPDR |
| Severe NPDR | Any one of the following without PDR:  
• >20 intraretinal hemorrhages in all four quadrants  
• Venous beading in 2 quadrants  
• IRMA in one quadrant |
| Proliferative diabetic retinopathy (PDR) | One or more of the following:  
• Any neovascularization of the iris (NVI), disc (NVD), angle (NVA), or elsewhere (NVE)  
• Vitreous/preretinal hemorrhage |
| High-Risk PDR^ | PDR with any one of the following:  
• NVD greater than 1/4 to 1/3 of disc area in size  
• Any NVD associated with preretinal or vitreous hemorrhage  
• NVE > ½ of disc area and associated with preretinal or vitreous hemorrhage  
• Any NVI  
• Any neovascularization of the angle |
| Diabetic macular edema (DME)* | Macular edema not qualifying as CSME |
| Clinically significant macular edema (CSME)* | Any one of the following:  
• Retinal thickening within 500um (~1/3 disc diameter) of center of fovea  
• Hard exudates within 500um of center of fovea and adjacent to an area of retinal thickening  
• Retinal thickening over one disc area in size, any part of which is within one disc diameter of foveal center |

^High-risk PDR requires treatment by panretinal photocoagulation  
*DME and CSME may be present in any stage of diabetic retinopathy

Table 2. Clinical Findings in Diabetic Retinopathy.
A number of guidelines have been published to direct eyecare practitioners in appropriate management of diabetic retinopathy. The following table is adapted from information in the American Academy of Ophthalmology’s Preferred Practice Pattern document on Diabetic Retinopathy. We encourage downloading the original document, free to practitioners, which clarifies the information found below, here.

<table>
<thead>
<tr>
<th>Severity of Diabetic Retinopathy</th>
<th>Recommended Follow-up</th>
<th>PRP</th>
<th>FA</th>
<th>Focal/Grid Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or Trace NPDR - No CSME</td>
<td>12 mo</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mild-moderate NPDR - No CSME</td>
<td>6-12 mo</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mild-moderate NPDR - CSME</td>
<td>2-4 mo</td>
<td>No</td>
<td>Usually</td>
<td>Usually</td>
</tr>
<tr>
<td>Severe NPDR - No CSME</td>
<td>2-4 mo</td>
<td>Sometimes</td>
<td>Rarely</td>
<td>No</td>
</tr>
<tr>
<td>Severe NPDR - CSME</td>
<td>2-4 mo</td>
<td>Sometimes</td>
<td>Usually</td>
<td>Usually</td>
</tr>
<tr>
<td>Non-high risk PDR - No CSME</td>
<td>2-4 mo</td>
<td>Sometimes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Non-high risk PDR - CSME</td>
<td>2-4 mo</td>
<td>Usually</td>
<td>Usually</td>
<td>Usually</td>
</tr>
<tr>
<td>High-risk PDR - No CSME</td>
<td>2-4 mo</td>
<td>Usually</td>
<td>Rarely</td>
<td>No</td>
</tr>
<tr>
<td>High-risk PDR - CSME</td>
<td>2-4 mo</td>
<td>Usually</td>
<td>Usually</td>
<td>Usually</td>
</tr>
</tbody>
</table>

Table 3. Management of Diabetic Retinopathy.

For the referring eyecare clinician, it is generally recommended that a patient with diabetic retinopathy be sent for a consultation with a diabetes specialist (i.e. retinal surgeon) based on the following timeframe by clinical signs:

- Refer within 2-4 weeks if: macular edema, early PDR, very severe NPDR
- Refer within 24 hours if: high risk PDR or vitreous hemorrhage

In addition to managing the ocular aspects of diabetes, eyecare practitioners should be keenly aware of the general systemic guidelines for diabetes management. Encouraging diabetic patients to actively monitor their blood glucose and blood pressure levels reinforces for these patients the importance of maintaining their health and avoiding advanced complications of the disease. Published guidelines for systemic control of diabetes are listed in the table below. Individual patients may have differing guidelines based upon their primary care practitioner’s or endocrinologist’s recommendations.
### Glycemic control

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>&lt; 7.0%</td>
</tr>
<tr>
<td>Preprandial plasma glucose (before a meal)</td>
<td>70–130 mg/dl (5.0–7.2 mmol/l)</td>
</tr>
<tr>
<td>Postprandial plasma glucose (after a meal)</td>
<td>&lt; 180 mg/dl (&lt;10.0 mmol/l)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt; 130/80 mmHg</td>
</tr>
</tbody>
</table>

### Lipids

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>&lt; 100 mg/dl (&lt;2.6 mmol/l)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 150 mg/dl (&lt;1.7 mmol/l)</td>
</tr>
<tr>
<td>HDL</td>
<td>&gt; 40 mg/dl (&gt;1.1 mmol/l)</td>
</tr>
</tbody>
</table>

|Table 4. Recommended Values for systemic markers of diabetic health. Adapted from the American Diabetic Association.|

### A reference for common diabetes medications

It is valuable for practitioners managing diabetic patients in any capacity to recognize and have basic familiarity with common medications used in treating diabetes. General information regarding some of the more common diabetic insulins are listed below:

**Insulins (not exhaustive):**

- Lispro – extremely fast-acting
- Aspartate – extremely fast-acting
- Glulisine – extremely fast-acting
- Lantus – long duration allows for 24-hr control
- Levimir – long duration allows for 24-hr control
- Humulin – intermediate-acting
- Iletin – intermediate-acting
- Novolin – intermediate-acting
Note that insulin may be delivered in any of the following methods:

- Syringe (subcutaneous)
- Insulin Pens
- Continuous Subcutaneous Insulin Infusion (for highly committed, responsible patients)
- Inhalation

Oral medications are the first line of treatment for type 2 diabetics. The following table lists the major classes of oral medications for diabetes, along with the most common drugs within each class and their mechanism of action.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medications</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinedione (TZD)</td>
<td>Rosiglitazone (Actos)</td>
<td>Improves action of insulin in liver and skeletal muscles</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone (Avandia)</td>
<td></td>
</tr>
<tr>
<td>Biguanide (first-line therapy)</td>
<td>Metformin (Glucophage/XL)</td>
<td>Decreases liver gluconeogenesis and increases glucose uptake by skeletal muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Glimiperide (Amaryl)</td>
<td>Stimulate release of insulin from beta cells in the pancreas</td>
</tr>
<tr>
<td></td>
<td>Glyburide (Macronase, DiaBeta)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glipizide (Glucotrol/XL, Glynase)</td>
<td></td>
</tr>
<tr>
<td>Alpha-Glucosidase Inhibitor</td>
<td>Acarbose (Precose)</td>
<td>Slows carbohydrate breakdown, decreases glucose absorption</td>
</tr>
<tr>
<td></td>
<td>Miglitol (Glyset)</td>
<td></td>
</tr>
<tr>
<td>DPP4 Inhibitor</td>
<td>Sitagliptin</td>
<td>Slows incretin inactivation, which increases insulin secretion and decreases glucagon release</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Repaglinide (Prandin)</td>
<td>Short-acting; stimulates insulin secretion</td>
</tr>
<tr>
<td></td>
<td>Nateglinide (Starlix)</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Overview of Oral Medications in Diabetes.

In addition to the above medications, a number of newer combination medications including two or more of the above are available.
Summary

With the current prevalence of diabetes and its anticipated increase in the future, primary eyecare practitioners are placed at the forefront of detection and management of a major public health concern. It is imperative that primary eye clinicians are skilled in understanding the complex pathology, diagnosis, and treatment course of diabetes and its effects on the eye as well as throughout the body. Further exploration of the topics covered in this manual is encouraged, and the list of references that follows is recommended. It is the authors’ hope that readers of this manual will be motivated to offer the best of care to diabetic patients by keeping appraised of updates and advances in the medical sciences as they develop, and particularly as pertaining to the primary eyecare clinician’s role in the management of diabetes.
Sources


AAO Preferred Practice Guidelines document:
http://one.aao.org/ce/practiceguidelines/ppp_content.aspx?cid=d0c853d3-219f-487b-a524-326ab3cecd9a

AOA Optometric Clinical Practice Guideline: Care of the Patient with Diabetes Mellitus:

http://www.ophthobook.com/chapters/retina


http://diabetes.acponline.org/clinician/CL-CT-DT.html

http://www.diabeteshealth.com/media/pdfs/PRG0107/Type2-Meds-PRG-0107.pdf

http://diabetes.about.com/od/equipmentandbreakthroughs/a/med_ref_chart.htm

http://www.lifeclinic.com/focus/diabetes/oral.asp


http://www.diabetesinmichigan.org/Chapters/PDF/Chapter%205%20oral%20meds.pdf