



Evidence-Based Clinical Practice Guideline

Eye Care of the Patient With

# DIABETES MELLITUS



American Optometric Association

# OPTOMETRY: THE PRIMARY EYE CARE PROFESSION

The American Optometric Association represents approximately 36,000 doctors of optometry, optometry students and paraoptometric assistants and technicians. Optometrists serve individuals in nearly 6,500 communities across the country, and in 3,500 of those communities, they are the only eye doctors. Doctors of optometry provide two-thirds of all primary eye care in the United States.

Doctors of optometry are on the frontline of eye and vision care. They examine, diagnose, treat and manage diseases and disorders of the eye. In addition to providing eye and vision care, optometrists play a major role in an individual's overall health and well-being by detecting systemic diseases such as diabetes and hypertension.

The mission of the profession of optometry is to fulfill the vision and eye care needs of the public through clinical care, research and education, all of which enhance the quality of life.



## Disclosure Statement

This Clinical Practice Guideline was funded by the American Optometric Association (AOA) without financial support from any commercial sources. All Committee, Guideline Development Group, and other guideline participants provided full written disclosure of conflicts of interest prior to each meeting and prior to voting on the strength of evidence or clinical recommendations contained within.

## Disclaimer

Recommendations made in this guideline do not represent a standard of care. Instead, the recommendations are intended to assist the clinician in the decision-making process. Patient care and treatment should always be based on a clinician's independent professional judgment, given the individual's circumstances, state laws and regulations.

The information in this guideline is current as of the date of publication.

**EYE CARE OF THE PATIENT WITH**  
**DIABETES MELLITUS**

**Developed by the AOA Evidence-Based Optometry Guideline Development Group.**

**Approved by the AOA Board of Trustees, February 7, 2014**

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## EVIDENCE-BASED CLINICAL GUIDELINES

### A. What is the Evidence-Based Process?

As a result of the Medicare Improvement for Patients and Providers Act of 2008, Congress commissioned the U.S. Secretary of Health and Human Services to create a public-private program to develop and promote a common set of standards for the development of clinical practice guidelines (CPGs). These standards address the structure, process, reporting, and final products of systematic reviews of comparative effectiveness research and evidence-based clinical practice guidelines.

The Institute of Medicine (IOM), through the Agency for Healthcare Research and Quality (AHRQ), issued two reports in March 2011: *Clinical Practice Guidelines We Can Trust* and *Finding What Works in Health Care: Standards for Systematic Reviews*.

In *Clinical Practice Guidelines We Can Trust*,<sup>1</sup> the IOM redefined CPGs as follows:

*“Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options.”*

The report states that to be trustworthy, guidelines should:

- Be based on a systematic review of existing evidence.
- Be developed by a knowledgeable, multidisciplinary panel of experts and key stakeholders.
- Consider important patient subgroups and preferences as appropriate.
- Be based on a transparent process that minimizes conflicts of interest and biases.
- Provide a clear explanation of the logical

relationships between alternative care options and health outcomes.

- Provide a grading of both the strength of the quality of evidence and the strength of the clinical recommendation.
- Be revised as appropriate when new evidence warrants modifications of recommendations.

Based on the IOM reports, the American Optometric Association (AOA) Evidence-Based Optometry (EBO) Committee developed a 14-step process to meet the new evidence-based recommendations for trustworthy guidelines.

<b>AOA's 14 Steps to Evidence-Based Clinical Practice Guideline Development</b>	
1.	<u>Guideline Development Group</u> : Select a multidisciplinary panel of experts, including patient and public representatives, for Guideline Development Group (GDG).
2.	<u>Transparency and COI</u> : Manage conflict of interest (COI).
3.	<u>Clinical Questions**</u> : Explore and define all clinical questions through a Question Formulation Meeting and define search criteria (GDG).
4.	<u>Search for Evidence</u> : Send clinical questions for query (outside researchers) and provide all papers to the Guideline Development Reading Group (GDRG). There should be no inclusion of Systematic Review (SR) writers in the Guideline Development Group (No intersection of GDG with SR writers; not applicable to AOA at this time).
5.	<u>Grade Evidence and Clinical Recommendations</u> : Read and grade papers (2 GDRG readers per paper, randomly selected) according to pre-designed evidence quality values. Make clinical recommendation(s) from each paper and grade the strength of each (GDRG).
6.	<u>Articulate Clinical Recommendations**</u> : Review all clinical recommendations and articulate each for inclusion in the guideline during an "Articulation of Recommendations" meeting and document identified gaps in medical research (GDRG).
7.	<u>Write Draft</u> : Send to writer for development of draft 1.
8.	<u>Draft Review and Edits**</u> : Read draft 1, discuss and edit (GDG).
9.	<u>Rewrite/Final Drafts</u> : Send to writer for writing/revisions for draft 2, then final reading / changes/rewrites as necessary.
10.	<u>Approval for Peer Review</u> : Send to the AOA Board of Trustees for approval to post for peer and public review. Post on the AOA website, announce the review period, and solicit comments.
11.	<u>Final Document Produced</u> : Review and revise final document (include peer review comments or identify issues for review when preparing next edition).
12.	<u>Final Approval and Legal Review</u> : Send to the AOA Board of Trustees and AOA Legal Counsel for approval (same management of COI).
13.	<u>Post Guideline</u> : Submit to the National Guideline Clearinghouse and website for public use, accompanied by AOA written process and documents. Post to the AOA website.
14.	<u>Schedule Reviews</u> : Review all previously identified gaps in medical research and any new evidence, and revise guideline every 2 to 5 years.
	<u>** Denotes face-to-face meeting</u>

## B. HOW TO USE THIS GUIDELINE

The following table provides the grading system used in this guideline for rating evidence-based clinical statements. Grades are provided for both strength of the evidence and clinical recommendations.

Key to Strength of Evidence and Clinical Recommendation Grading	
GRADE	STRENGTH OF EVIDENCE
<b>A</b>	Data derived from well-designed, multiple randomized clinical trials, meta-analyses (Systematic Review) or diagnostic studies of relevant populations. Randomized Control Studies (RCTs), Systematic Reviews with meta-analysis when available, Diagnostic Studies.
<b>B</b>	RCTs or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies. Weaker RCTs (weak design but multiple studies confirm). Cohort Study (this may include retrospective and prospective studies).
<b>C</b>	Studies of strong design, but with substantial uncertainty about conclusions, or serious doubts about generalization, bias, research design, or sample size; or retrospective or prospective studies with small sample size.
<b>D</b>	Expert opinion, case reports, reasoning from principles. No evidence is available that directly supports or refutes the conclusion. Cross-sectional studies, case series/ case reports, opinion or principle reasoning.
GRADE	CLINICAL RECOMMENDATION
<b>A</b>	Clinicians should follow this recommendation unless clear and compelling rationale for an alternative approach is present. There is a <i>clinically important outcome</i> and the <b>study population is representative</b> of the focus population in the recommendation. The quality of evidence may not be excellent, but there is clear reason to make a recommendation.
<b>B</b>	Clinicians should generally follow this recommendation, but should remain alert for new information. There is a <i>clinically important outcome</i> but it may be a <b>validated surrogate outcome or endpoint</b> . The benefits exceed the harm or vice versa, but the quality of evidence is not as strong.
<b>C</b>	Clinicians should be aware of this recommendation, and remain alert for new information. The <b>evidence quality that exists is suspect</b> or the studies are not that well-designed; <b>well conducted studies have demonstrated little clear advantage of one approach versus another</b> .
<b>D</b>	Clinicians should be aware of this recommendation. The <b>outcome is an invalid surrogate</b> for a clinically important population, or the <b>applicability of the study is irrelevant</b> . There is <b>both a lack of pertinent evidence and an unclear balance between benefit and harm</b> .



As you navigate through the guideline, note the following:

Grades are displayed with the evidence strength listed first, followed by the strength of the clinical recommendation. A statement with a strength of evidence of “B” and a clinical recommendation of “A” is shown as B/A.

Evidence-based Clinician Action Statements will be highlighted in an “Action” box, with the strength of evidence and clinical recommendation grades listed.

**ACTION:** Individuals with diabetic macular edema (DME), but without clinically significant macular edema (CSME), should be re-examined at 4- to 6-month intervals. Once CSME develops, treatment with focal laser photocoagulation or intravitreal anti-VEGF injection is indicated.<sup>178</sup> [Evidence Strength: A, Recommendation: A]

Consensus-based Clinician Action Statements, based on consensus by the Guideline Development Reading Group (GDRG), will be highlighted in an “Action” box, without any strength of evidence or clinical recommendation grade listed.

**ACTION:** Women with pre-existing diabetes who are planning pregnancy or who become pregnant should have a comprehensive eye examination prior to a planned pregnancy or during the first trimester, with follow-up during each trimester of pregnancy.

## I. INTRODUCTION

Type 2 diabetes is the most prevalent form of diabetes mellitus and often goes undiagnosed for many years because high blood glucose levels develop gradually and initially are often not severe enough for a person to notice any of the symptoms of diabetes. However, during this time, individuals are at risk of developing microvascular and macrovascular complications of diabetes, including visual impairment and blindness, hypertension, renal failure, heart disease, and stroke.

Diabetic retinopathy, the most common microvascular complication of diabetes, is the leading cause of new cases of blindness and low vision among Americans 20 to 74 years of age. Diabetic retinopathy accounts for approximately 12 percent of all new cases of blindness each year.<sup>2</sup>

Intensive treatment to maintain blood glucose concentrations close to the normal range has been

shown to decrease the risk of the development of diabetic retinopathy by as much as 76 percent.<sup>3</sup> However, as many as 40 percent of people with diabetes don't know they have the disease.<sup>4</sup> For some, signs of diabetes found during an eye examination may be the initial indication of the presence of the disease.<sup>5</sup>

Optometrists are often the first health care practitioners to examine persons with undiagnosed diabetes mellitus or ocular manifestations of diabetes. This Evidence-Based Clinical Practice Guideline on Eye Care of the Patient with Diabetes Mellitus provides doctors of optometry with examination and management recommendations designed to preserve vision and reduce the risk of vision loss in persons with diabetes, through timely diagnosis, appropriate management and referral.

## A. GUIDELINE OBJECTIVES

This Guideline will assist optometrists in achieving the following objectives:

- Identification of individuals at risk for diabetes
- Identification of individuals with undiagnosed diabetes mellitus
- Identification of individuals at risk of vision loss from diabetes
- Preservation of vision by reducing the risk of vision loss in persons with diabetes through timely diagnosis, intervention, determination of need for future evaluation, and appropriate referral
- Improvement in the quality of care rendered to persons with diabetes
- Education of individuals and health care practitioners regarding the ocular complications of diabetes
- Dissemination of information and education of individuals on the benefits of vision rehabilitation
- Provision of vision rehabilitation services or referral for care of persons with vision loss from diabetes

## II. CLASSIFICATION, EPIDEMIOLOGY AND RISK FACTORS FOR DIABETES MELLITUS

### A. DISEASE DEFINITION

**D**iabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects of insulin secretion and/or increased cellular resistance to insulin. It is a chronic disease with long-term macrovascular and microvascular complications, including diabetic nephropathy, neuropathy, and retinopathy.<sup>6</sup>

Diabetes is a significant, costly, and potentially

preventable public health problem. It is the seventh leading cause of death in the United States and the direct and indirect cost of care for persons with diabetes exceeds \$245 billion annually.<sup>7</sup> An estimated 25.8 million Americans (8.3 percent of the population) have diabetes. In 2010, about 1.9 million new cases of diabetes were diagnosed in people aged 20 years or older in the United States.<sup>8</sup> If the current trend continues, one in three adults in the United States will have diabetes by 2050.<sup>9</sup>

Because it can lead to blindness, diabetic retinopathy is the most significant vision threatening complication of diabetes. While advances in the management of diabetes and diabetic retinopathy have reduced the risk of vision loss and blindness,<sup>10</sup> as many as 1/3 to 1/2 of persons with diabetes don't receive an annual eye examination.<sup>11,12</sup> In addition, about 20 to 40 percent of individuals with type 2 diabetes have retinopathy at the time of first diagnosis of diabetes.<sup>13,14</sup>

These findings are particularly important as the Diabetic Retinopathy Study (DRS),<sup>15-27</sup> the Early Treatment Diabetic Retinopathy Study (ETDRS),<sup>28-50</sup> the Diabetic Retinopathy Vitrectomy Study (DRVS),<sup>51-55</sup> the United Kingdom Prospective Diabetes Study (UKPDS),<sup>56-59</sup> the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies,<sup>3,60-63</sup> and the Diabetic Retinopathy Clinical Research Network (DRCR.net)<sup>64-71</sup> provide evidence-based care interventions that rely on early referral for eye care with prompt and appropriate intervention to lessen the risk for and the severity of vision loss related to diabetes. Timely diagnosis, intensive diabetes treatment, and consistent, long-term follow-up evaluations for persons with diabetes are essential for effective care, which can preserve vision and substantially lower the risk of vision loss.

### B. DESCRIPTION AND CLASSIFICATION OF DIABETES MELLITUS

#### 1. Classification

The definitions and categories of diabetes used

in this document are based on the most recent classifications reported by the American Diabetes Association (ADA).<sup>6</sup>

### **a. Type 1 Diabetes Mellitus**

Type 1 diabetes (formerly called insulin-dependent or juvenile diabetes) occurs when the body's immune system attacks and destroys insulin-producing beta-cells in the pancreas. It accounts for approximately 5 to 10 percent of individuals with diabetes in the United States.<sup>8</sup> The primary characteristic of type 1 diabetes is absolute dependence on exogenous insulin to prevent profound hyperglycemia and ketoacidosis.

Type 1 diabetes, although generally diagnosed in children and young adults, can occur at any age. It may be caused by genetic, environmental, or other factors, and currently there is no known way to prevent it.

There are two forms of type 1 diabetes, both of which are characterized by destruction and/or loss of secretory function by insulin producing pancreatic beta-cells. One form is an immune-mediated disease with autoimmune markers such as islet cell antibodies (ICAs), insulin autoantibodies (IAAs), and autoantibodies to glutamic acid decarboxylase (GAD65). As many as 85 to 90 percent of individuals with fasting hyperglycemia are positive for one or more of these markers. Strong human leukocyte antigen (HLA) associations also exist.

The second form of type 1 diabetes, called idiopathic diabetes, has no known causes. Only a minority of persons fall into this group, and they are predominantly of African and Asian origin. Idiopathic diabetes is strongly inherited, but it lacks autoimmune markers and it is not associated with HLA.

### **b. Type 2 Diabetes Mellitus**

Type 2 diabetes (formerly termed non-insulin dependent or adult-onset diabetes) occurs when

the body does not produce enough insulin (relative insulin deficiency) or cannot use the insulin it makes effectively (insulin resistance). It is the most common form of diabetes worldwide and its prevalence is increasing.

Type 2 diabetes accounts for 90 to 95 percent of diabetes cases.<sup>8</sup> In contrast to type 1 diabetes, with this form of the condition, autoimmune destruction of beta-cells does not occur.

Type 2 diabetes develops more frequently in adults than in children. However, the prevalence of type 2 diabetes in children is increasing, especially in high-risk ethnic groups, such as American Indians, Hispanic Americans, African Americans, Alaska Natives, Asian Americans, Native Hawaiians and Other Pacific Islanders. Most of these children are between 10 and 19 years old, have infrequent or mild diabetic ketoacidosis, are obese and have a strong family history of diabetes.<sup>72</sup>

### **c. Pre-Diabetes**

Individuals, whose blood glucose levels do not meet the criteria for diabetes but are higher than those considered normal, are classified as having pre-diabetes. They have an increased risk of developing type 2 diabetes, heart disease, and stroke.<sup>8</sup>

Persons with pre-diabetes have impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) levels, as described below:

#### [Impaired Glucose Tolerance](#)

A diagnosis of IGT can only be made with the Oral Glucose Tolerance Test (OGTT), which measures the body's ability to metabolize glucose. Serial testing shows that individuals with IGT may improve, remain stable, or worsen. In persons with IGT, the 2-hour plasma glucose value in the 75-g OGTT is 140 mg/dl (7.8 mmol/L) to 199 mg/dl (11.0 mmol/L).<sup>6</sup>

### Impaired Fasting Glucose

IFG signifies the zone between the upper limit of normal fasting plasma glucose (FPG) and the lower limit of diabetic FPG. IFG includes those persons whose fasting glucose is 100 mg/dl (5.6 mmol/L) to 125 mg/dl (6.9 mmol/L).<sup>6</sup>

Long used as the test of choice for the management of diabetes, the glycosylated hemoglobin (A1C) test is now also recommended for use in its diagnosis.<sup>73</sup> A1C indicates a person's average blood glucose level for the previous 2 or 3 months by measuring the percentage of blood glucose attached to hemoglobin. An A1C test level between 5.7 percent and 6.4 percent is considered pre-diabetes.<sup>8</sup>

#### **d. Gestational Diabetes Mellitus**

Gestational diabetes mellitus (GDM) refers to any degree of glucose intolerance with onset or first diagnosis during pregnancy. GDM is caused by the hormones secreted during pregnancy or by a shortage of insulin. It occurs predominantly in African American, Hispanics, and American Indian women, as well as women who are obese or have a family history of type 2 diabetes.<sup>9</sup>

GDM usually is diagnosed during the second or third trimester. Approximately 5 to 10 percent of all pregnancies are complicated by GDM. Glucose tolerance typically returns to normal within 6 weeks after pregnancy ends. Due to the relatively short and temporary duration of GDM, it does not lead to the development of diabetic retinopathy. However, women who have had GDM have a 35 to 60 percent chance of developing type 2 diabetes in the subsequent 10 to 20 years.<sup>8</sup>

#### **e. Other Specific Types of Diabetes**

Diabetes can also occur secondary to genetic defects in beta-cell function or insulin action, pancreatic diseases or other endocrinopathies, medications, toxic chemicals, infections, or uncommon forms of immune-mediated diabetes

(e.g., "stiff man syndrome" or anti-insulin-receptor antibodies).<sup>6</sup> These forms of the condition account for 1 to 5 percent of all diagnosed cases of diabetes.<sup>8</sup>

## **2. Background**

### **a. Natural History of Diabetes Mellitus**

The development of diabetes involves several processes. These range from autoimmune destruction of beta-cells of the pancreas causing insulin deficiency to abnormalities that result in resistance to insulin action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same individual. Therefore, it is often unclear which abnormality is the primary cause of the hyperglycemia.

#### Type 1 Diabetes Mellitus

The rate of beta-cell destruction in type 1 diabetes varies. Some individuals develop ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can change rapidly to severe hyperglycemia and/or ketoacidosis as the result of infection or other stress.

Some individuals retain sufficient residual beta-cell function to prevent ketoacidosis for many years. However, they eventually become dependent on insulin for survival. In the later stage of the disease, there is little or no insulin secretion.<sup>6</sup>

In type 1 diabetes, persons tend to be acutely symptomatic at onset, often complaining of polydipsia, polyphagia, polyuria, unexplained weight loss and dry mouth.

#### Type 2 Diabetes Mellitus

The metabolic processes leading to type 2 diabetes occur years or even decades before the development of hyperglycemia. These processes progress from an asymptomatic stage, with insulin resistance, to mild

postprandial hyperglycemia, and finally to diabetes.

Initially, pancreatic beta-cells can compensate by increasing insulin levels (hyperinsulinemia), keeping glucose levels normalized for a period (up to several years), but eventually IGT develops for a period of up to several years, but in mild hyperglycemia, IGT eventually develops. As compensatory insulin resistance worsens, greater difficulty with insulin secretion occurs resulting in increased hyperglycemia. Together, these defects lead to further increases in fasting blood glucose. Over time, the beta-cells are unable to compensate for insulin resistance, resulting in type 2 diabetes.<sup>74</sup>

#### **b. Diagnostic Criteria**

Due to a lack of a more specific biological marker to define diabetes, plasma glucose estimation remains the basis for diagnosis. The cutoff glycemic levels used to diagnose diabetes are based on the observed association between certain glucose levels and a dramatic increase in the prevalence of microvascular complications (retinopathy and nephropathy).<sup>75</sup>

For decades, the diagnosis of diabetes has been based on glucose level criteria, using either the FPG or the 75-g OGTT. However, A1C testing is now also considered an accepted method of diagnosis as it may be a better biochemical marker for the disease than FPG or 2-hour plasma glucose testing.<sup>73</sup>

The current ADA diagnostic criteria for diabetes<sup>6</sup> are:

- A1C  $\geq$  6.5 percent. The test should be performed in a laboratory using a method that is certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.\*

or

- A random plasma glucose level  $\geq$  200 mg/dl (11.1 mmol/l) in a person with classic symptoms of hyperglycemia (polyuria, polydipsia, and weight loss) or hyperglycemic crisis. Random is defined as any time of the day without regard to time since the last meal.

or

- Fasting plasma glucose level  $\geq$  126 mg/dl (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.\*

or

- Two-hour plasma glucose level  $\geq$  200 mg/dl (11.1 mmol/L) during an OGTT.\*

\* *In the absence of unequivocal hyperglycemia, these results should be confirmed by repeat testing.*

#### Gestational Diabetes Mellitus

A 75-g OGTT taken at 24 to 28 weeks of pregnancy is recommended by the International Association of Diabetes and Pregnancy Study Group and the American Diabetes Association (ADA) for diagnosis of gestational diabetes.<sup>76</sup>

The American College of Obstetricians and Gynecologists recommends a two-step process for the screening and diagnosis of GDM. All pregnant women should be screened by patient history, clinical risk factors, or a 50-g 1-hour glucose challenge test at 24 to 28 weeks of gestation. The diagnosis of GDM can be made on the basis of a 100-g, 3-hour OGTT.<sup>77</sup>

The ADA recommends that women with a history of GDM have lifelong screening for the development of diabetes or pre-diabetes at least every 3 years.<sup>78</sup>

## C. EPIDEMIOLOGY OF DIABETES MELLITUS

### 1. Prevalence and Incidence

Diabetes mellitus is a large and growing health care problem in the United States and around the world. The prevalence of diagnosed and undiagnosed diabetes in the United States (2010)<sup>8</sup> is shown in Table 1:

<b>TABLE 1</b>	
<b>Prevalence of Diagnosed and Undiagnosed Diabetes: Americans Aged 20 Years or Older (2010)</b>	
<b>Group</b>	<b>Number or percentage who have diabetes</b>
Aged 20 years or older	25.6 million, or 11.3% of all people in this age group
Aged 65 years or older	10.9 million, or 26.9% of all people in this age group
Men	13.0 million, or 11.8% of all men ages 20 years or older
Women	12.6 million, or 10.8% of all women ages 20 years or older
Non-Hispanic Whites	15.7 million, or 10.2% of all non-Hispanic whites ages 20 years or older
Non-Hispanic Blacks	4.9 million, or 18.7% of all non-Hispanic blacks ages 20 years or older

Source: Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: National estimates and general information on diabetes and prediabetes in the United States, 2011*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

The number of people with diabetes worldwide increased from 153 million in 1980 to 347 million in 2008.<sup>79</sup> This number is expected to grow to 429 million by 2030, owing to the rising frequency of

obesity, increasing life span, and improved detection of the disease.<sup>80</sup>

In developing countries, the largest number of people with diabetes is in the age group 45 to 64 years, while in developed countries the largest number is found in those aged 65 and over. Worldwide rates of diabetes are similar in men and women, although they are slightly higher in men less than 60 years of age and in women over age 65.<sup>81</sup>

#### a. Type 1 Diabetes Mellitus

It is estimated that approximately 20 million people worldwide, mostly children and young adults, have type 1 diabetes. The incidence of type 1 diabetes is increasing at a rate of approximately 3 percent per year.<sup>82</sup>

The annual incidence of type 1 diabetes in children from birth to 16 years of age in the United States varies with ethnicity and is approximately 3 to 26 new cases per 100,000 persons. For example, in Blacks in San Diego, CA, it is 3.3 per 100,000 and in whites in Rochester, MN, it is 20.6 per 100,000. Approximately 0.3 percent of the population in the United States develops the disease by 20 years of age.<sup>83</sup>

#### b. Type 2 Diabetes Mellitus

Type 2 diabetes is more common in the elderly, especially those who are overweight. Diabetes rates vary by race and ethnicity. American Indian, Alaska Native, Black, Hispanic/Latino, Asian American, Native Hawaiian and other Pacific Islander adults are nearly twice as likely as non-Hispanic white adults to have type 2 diabetes.<sup>9</sup> People of Caribbean and Middle Eastern descent also have an increased risk of developing type 2 diabetes.

The annual incidence of type 2 diabetes in the United States is approximately 2.4 per 1,000 persons over age 20. By 65 years of age, 26.9

percent of the population may have type 2 diabetes.<sup>84</sup>

### c. Pre-Diabetes

An estimated 35 percent of adults 20 years or older in the United States have pre-diabetes. The rate increases to 50 percent of adults aged 65 years or older. Therefore, approximately 79 million American adults ages 20 years or older have pre-diabetes.<sup>8</sup>

#### Impaired Glucose Tolerance

The prevalence of IGT varies among different age groups and the condition typically is more common in women than in men. The prevalence of IGT increases from 2.9 percent in 30- to 39-year-old men to 15.1 percent in 70- to 79-year-old men; and from 4.5 percent in 30- to 39-year-old women to 16.9 percent in 70- to 79-year-old women.<sup>75</sup>

#### Impaired Fasting Glucose

The prevalence of IFG also varies among different age groups and the condition occurs more frequently in men than in women. It increases from 5.2 percent in 30- to 39-year-old men to 10.1 percent in 50- to 59-year-old men and then decreases to 3.2 percent in 80- to 89-year-old men. The prevalence increases from 2.6 percent in 30- to 39-year-old women to 5.9 percent in 70- to 79-year-old women.<sup>75</sup>

## D. RISK FACTORS FOR DIABETES MELLITUS

### 1. Type 1 Diabetes Mellitus

Specific risk factors for type 1 diabetes are unclear. However, possible factors include:<sup>8</sup>

- **Family history of diabetes** - Having a parent or sibling with type 1 diabetes.
- **Viral exposure** - Exposure to Epstein-

Barr virus, coxsackie virus, mumps virus, or cytomegalovirus may trigger the autoimmune destruction of islet cells, or the virus may directly infect the islet cells.

- **Autoimmune conditions** - Individuals having another condition that affects the immune system (e.g., Grave's disease, Addison's disease, celiac disease, Crohn's disease, rheumatoid arthritis).

### 2. Type 2 Diabetes Mellitus

The risk factors for type 2 diabetes include:<sup>6,8</sup>

- **Family history of diabetes** - First-degree relatives of individuals with type 2 diabetes are three times more likely to develop the disease.
- **Being overweight** - Having a body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> (at-risk BMI may be lower in some ethnic groups).
- **Age** - Being 45 years old or older.
- **Ethnic background** - Being African American, Hispanic/Latino, American Indian, Alaska Native, Asian American, or Pacific Islander.
- **Gestational diabetes** - Having diabetes while pregnant or delivering a baby weighing more than 9 pounds.
- **Pre-diabetes** - Persons with IGT or IFG.
- **Hypertension** - Blood pressure  $\geq 140/90$  mm Hg.
- **Abnormal cholesterol levels** - HDL level  $< 35$  mg/dl and/or a triglyceride level  $> 250$  mg/dl.

### 3. Screening for Diabetes Mellitus

Due to the acute onset of symptoms, most cases of type 1 diabetes are detected soon after the onset of hyperglycemia. Therefore, widespread clinical testing of asymptomatic individuals for the presence

of autoantibodies related to type 1 diabetes is not recommended as a means to identify persons at risk.<sup>85</sup>

There is no direct evidence supporting the effectiveness of screening for type 2 diabetes or pre-diabetes in individuals without risk factors.<sup>86</sup> However, due to the high prevalence of type 2 diabetes and the increased morbidity and mortality associated with the disease, the ADA recommends that all adults aged 45 years and older be screened.<sup>85</sup> In high-risk individuals (as described above), screening at a younger age should be considered at younger ages and performed more frequently. In addition, all pregnant women not known to have diabetes should be screened for GDM.

Screening using the FPG test following an 8-hour overnight fast, a 2-hour OGTT (75-g glucose load), or the A1C test. Individuals whose results are normal according to a single test, but who have retinal findings consistent with diabetic retinopathy, should receive additional laboratory testing to exclude diabetes. Persons whose results are normal should be re-screened at the 3-year point.<sup>85</sup> Individuals with positive results need to be retested. Screening of urine glucose levels is not recommended.

#### 4. Early Detection and Prevention

The Diabetes Prevention Program showed that weight loss through moderate diet changes and physical activity can delay and prevent type 2 diabetes.<sup>87,88</sup> People with pre-diabetes who lose 5 to 7 percent of their body weight and participate in at least 150 minutes a week of moderate physical activity can reduce the risk of developing type 2 diabetes by 58 percent over four years.<sup>89</sup> However, the risk reduction drops to 34 percent after 10 years.<sup>90</sup>

Early detection and treatment can reduce the risk of complications associated with diabetes. Improving glycemic control can benefit people with either type 1 or type 2 diabetes. In general, every percentage point reduction in A1C test results can reduce the risk of microvascular complications by nearly 40 percent.<sup>60,62,91,92</sup>

In addition, control of hypertension reduces the risk of cardiovascular disease and microvascular complications. For every 10 mm Hg reduction in systolic blood pressure, the risk of complications related to diabetes is reduced by 12 percent.<sup>6,93</sup>

Diabetic retinopathy is the leading cause of preventable vision loss in persons of working age in the United States<sup>94</sup>. Early diagnosis of diabetes and diabetic retinopathy is essential in reducing the potential for vision loss. Timely detection and appropriate treatment of diabetic retinopathy reduces the risk of severe vision loss (i.e., best corrected visual acuity of 5/200 or worse) in most individuals with diabetes.

### III. OCULAR COMPLICATIONS OF DIABETES MELLITUS

#### A. DIABETIC RETINAL DISEASE

**D**iabetic retinal disease, primarily manifesting as diabetic retinopathy and/or diabetic macular edema (DME), is the most common microvascular complication of diabetes.<sup>95</sup> Despite the availability of highly effective treatments, diabetic retinopathy remains a leading cause of moderate and severe visual loss among working-aged adults in the United States and other industrialized countries.

Diabetic retinopathy is a highly specific retinal vascular complication of diabetes mellitus. It is often asymptomatic early in the disease, and visual loss is primarily due to the development of diabetic macular edema, vitreous hemorrhage or traction retinal detachment (TRD).<sup>17</sup> Diabetes duration and sustained hyperglycemia are among the primary risk factors for the development of diabetic retinopathy.<sup>96</sup>

The progression of diabetic retinopathy occurs in well-defined stages. The condition may progress from mild non-proliferative diabetic retinopathy (NPDR), characterized by increased vascular permeability, to moderate and severe NPDR, with vascular closure, to proliferative diabetic retinopathy (PDR), with the growth of new vessels on the retina and posterior surface of the vitreous. Identifying the severity level



of diabetic retinopathy is important for determining the risk of progression and the appropriate care for preservation of vision.

Each level of NPDR is associated with a corresponding risk for progression to PDR and subsequent risk of severe visual loss.

Diabetic macular edema, which is the most common cause of vision loss in persons with diabetes, may be present at any severity level of non-proliferative or proliferative diabetic retinopathy. Diabetic macular edema is caused by the breakdown of the blood–retinal barrier that leads to intraretinal fluid accumulation in the macula, causing photoreceptor disruption, and if untreated, increased risk of loss of vision.<sup>28</sup>

Multiple biological pathways have been implicated in the development of diabetic retinopathy. Current studies have pointed to specific biochemical pathways, molecular mechanisms and hemodynamic alterations in early diabetes mellitus, that include the sorbitol pathway,<sup>97</sup> advanced glycation end-products (AGE),<sup>98</sup> protein kinase C (PKC) activation,<sup>99</sup> oxidative stress,<sup>100</sup> inflammatory markers,<sup>101</sup> retinal blood flow,<sup>102</sup> and growth factors, such as vascular endothelial growth factor (VEGF).<sup>103</sup> These studies demonstrate that changes in retinal biochemistry and physiology occur long before clinically evident disease is observed.

## **1. Epidemiology of Diabetic Retinal Disease and Vision Loss**

Nearly 86 percent of individuals with type 1 diabetes mellitus and 40 percent of those with type 2 diabetes mellitus have some form of clinically evident diabetic retinopathy.<sup>104</sup>

In 2005 to 2008, an estimated 4.2 million, or 28.5 percent of people with diabetes ages 40 years and over, had diabetic retinopathy and 655,000 of this group, or 4.4 percent, had advanced diabetic retinopathy that could lead to severe vision loss.<sup>105</sup> In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6 percent of younger-onset persons with type 1 diabetes and 1.6 percent of

older-onset persons with type 2 diabetes were legally blind.<sup>106</sup> The number of Americans 40 years or older with diabetic retinopathy and vision threatening diabetic retinopathy is projected to triple by 2050, from 5.5 million (in 2005) to 16 million for diabetic retinopathy and from 1.2 million (in 2005) to 3.4 million for vision threatening diabetic retinopathy.<sup>94</sup>

The prevalence of diabetic retinopathy and vision loss among persons with diabetes is highly associated with the duration of the disease rather than the person's age.<sup>107,108</sup> Diabetic retinopathy occurs more frequently in individuals with longstanding disease (over 10 years). However, the actual duration of diabetes for individuals with type 2 diabetes can be difficult to determine because the initial diagnosis is typically made after a 5- to 10-year period of asymptomatic or clinically undetected diabetes. Table 2 summarizes the estimated proportion of persons with diabetic retinopathy and diabetic macular edema by diabetes type and diabetes duration.<sup>109-112</sup>

TABLE 2		
Duration of Diabetes Mellitus and Presence of Diabetic Retinopathy and Diabetic Macular Edema		
Diabetes	Duration of Disease	Ocular Complication
Type 1	> 5 years	17 to 29% have some retinopathy
	> 10 years	60% have some retinopathy
	> 15 years	78 to 97% have some degree of retinopathy; 25% progress to proliferative diabetic retinopathy
	> 20 years	50 to 60% progress to proliferative retinopathy
	> 25 years	29% have diabetic macular edema; 17% have clinically significant macular edema
Type 2	At diagnosis	20 to 39% have some retinopathy
	> 4 years	4% progress to proliferative retinopathy
	> 10 years	25% of individuals on insulin have diabetic macular edema; 14% on oral medications have diabetic macular edema
	> 15 years	60 to 80% have some retinopathy; up to 20% progress to proliferative retinopathy

## 2. Classification and Signs of Diabetic Retinopathy

Diabetic retinopathy is broadly classified as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). In addition, diabetic macular edema (DME) can occur at any stage of retinopathy.

Characteristic lesions of diabetic retinopathy:

- Retinal blood flow alteration is one of the early changes resulting from diabetes.<sup>113,114</sup> However, changes in retinal blood flow are not readily observed in routine clinical settings.
- Saccular outpouchings of retinal capillaries, termed microaneurysms, are frequently the earliest clinically evident sign of diabetic retinopathy. These microaneurysms result from

the loss of intramural pericytes of the retinal capillaries, which weakens the capillary walls.

- Retinal hemorrhages are usually caused by ruptured or leaking microaneurysms or retinal capillaries. Hemorrhages due to diabetes typically lie deep in the retina (within the inner nuclear and outer plexiform layers), wherein the arrangement of cells is more compact and perpendicular to the surface of the retina, causing the hemorrhages to assume a pinpoint or dot shape.
- Intraretinal microvascular abnormalities (IRMA) represent either new vessel growth within the retina or, more likely, pre-existing vessels with endothelial cell proliferation that serve as “shunts” through areas of nonperfusion.

The development of severe IRMA commonly indicates severe ischemia and frank neovascularization is likely to occur on the surface of the retina or optic disc within a short time.

- Venous caliber abnormalities are indicators of severe retinal hypoxia. These abnormalities can take the form of venous dilation, venous beading (VB), or loop formation. Large areas of nonperfusion can appear adjacent to these abnormal veins and are indicative of a substantial risk factor for progression to proliferative diabetic retinopathy.
- The growth of new vessels, either at or near the optic disc (NVD), or elsewhere in the retina (NVE), signify the presence of proliferative diabetic retinopathy, with an increased risk for visual loss due to the development of vitreous hemorrhage or traction retinal detachment.

The following classification of diabetic retinopathy and diabetic macular edema is based on the ETDRS grading system<sup>38,40</sup> for diabetic retinopathy and DME. (See Appendix Figure 3 for ETDRS standard photographs 2A, 6B, 8A, 10A and macular edema).

#### **a. Non-proliferative Diabetic Retinopathy (NPDR)**

Non-proliferative diabetic retinopathy is characterized by the presence of hemorrhages and/or microaneurysms (H/Ma), hard exudates (HE), soft exudates (cotton wool spots), intraretinal microvascular abnormalities (IRMA), venous looping, and/or venous beading (VB). In the absence of macular edema or ischemia, NPDR typically does not present a threat to vision. However, the presence of severe H/Ma, VB, and IRMA confers a substantial risk for progression to PDR, with a corresponding increased risk for severe vision loss.<sup>40</sup> (See Table 3).

##### Mild NPDR

Mild NPDR is marked by at least one retinal microaneurysm. However, the severity of H/Ma

is less than that depicted in ETDRS standard photograph 2A.<sup>21,38,40</sup>

No other diabetic retinal lesion or abnormality associated with diabetes is present.

##### Moderate NPDR

Moderate NPDR is characterized by H/Ma greater than that depicted in ETDRS standard photograph 2A in one to three retinal quadrants and/or soft exudates, VB, or IRMA definitely present.<sup>38,40</sup>

##### Severe NPDR

Severe NPDR is based on the extent and severity of H/Ma, VB and IRMA, and is characterized by any one of the following lesions:

- H/Ma  $\geq$  than ETDRS standard photograph 2A in **four** retinal quadrants.
- VB (exemplified by that in standard photograph 6B) in **two** or more retinal quadrants.
- Prominent IRMA ( $\geq$  than ETDRS standard photograph 8A) in at least **one** retinal quadrant.<sup>38,40</sup>

This “4-2-1” rule is an important clinical tool for determining the risk of progressing to proliferative diabetic retinopathy.

##### Very Severe NPDR

In very severe NPDR, two or more criteria for severe NPDR are met, in the absence of frank neovascularization.

#### **b. Proliferative Diabetic Retinopathy (PDR)**

The most severe sight-threatening form of diabetic retinopathy is proliferative diabetic retinopathy. Most individuals with PDR are at substantial risk for severe vision loss. Without appropriate treatment, 50% of eyes with PDR are blind within

5 years, as reported by ETDRS.

Characteristics of PDR include new vessels on or within one disc diameter of the disc (NVD), new vessels elsewhere on the retina i.e. not on or within one disc diameter of the optic disc (NVE), fibrous proliferation on or within one disc diameter of the optic disc (FPD) or elsewhere on the retina (FPE), preretinal hemorrhage (PRH), and/or vitreous hemorrhage (VH).<sup>38,40</sup>

**PDR**

Early proliferative diabetic retinopathy has one or more of the following:

- NVE or NVD < ETDRS standard photograph 10A.
- PRH and NVE < one-half disk area (DA), without NVD.

**High-Risk PDR**

High-risk PDR is characterized by one or more of the following:

- NVD ≥ one-fourth to one-third DA in size (ETDRS standard photograph 10A).
- NVD < one-fourth DA in size with fresh VH or PRH present.

- NVE ≥ one-half DA in size with VH or PRH present.

Table 3 provides a listing of the 1- and 5-year course of progression for the levels of diabetic retinopathy. The risk for progression described in Table 3 is based on estimates derived from the ETDRS, which was conducted in the 1980s. Current risk for progression may be lower given changes in management of diabetes that have resulted in overall improved glycemic, blood pressure and lipid control.<sup>105,115</sup>

TABLE 3		
Severity of Condition	Natural Course Rate of Progression to	
	PDR (1 year)	HR PDR (5 years)
Mild NPDR	5%	15%
Moderate NPDR	12 to 27%	33%
Severe NPDR	52%	60 to 75%
Non-high-risk PDR		75%

Twenty-five to forty percent of individuals with high-risk proliferative diabetic retinopathy (HR PDR) develop severe vision loss within 2 years.

### c. Diabetic Macular Edema

Diabetic macular edema (DME) is the collection of intraretinal fluid in the macular area of the retina, with or without lipid exudates or cystoid changes. Visual acuity is generally compromised when DME affects the fovea.

Macular edema is classified as:

#### Macular Edema

Retinal thickening within two disk diameters (DD) of the center of the macula.

#### Clinically Significant Macular Edema (CSME)

One or more of the following are present:

- Thickening of the retina  $\leq 500$  microns (1/3 DD) from the center of the macula.
- Hard exudates  $\leq 500$  microns (1/3 DD) from the center of the macula with thickening of the adjacent retina.
- A zone or zones of retinal thickening  $\geq 1$  DA in size, any portion of which is  $\leq 1$  DD from the center of the macula.<sup>31</sup>

The term clinically significant macular edema (CSME) was introduced in the ETDRS to signify an increased risk for moderate visual loss (defined as doubling of the visual angle, e.g. from 20/40 to 20/80).<sup>28</sup> A further increased risk for visual loss was observed in eyes with DME that have retinal thickening involving the center of the macula (center-involved DME), which is an important factor in determining short- and long-term visual acuity outcomes. Data from the ETDRS have shown that by one year of follow-up, eyes with center-involved CSME had nearly a ten-fold greater risk for developing moderate visual loss compared to eyes without center involvement, stressing the importance of determining center involvement in eyes with macular edema.

## B. NON-RETINAL OCULAR COMPLICATIONS

### 1. Classification and Signs of Non-retinal Ocular Complications

Diabetic eye disease is an end-organ response to a systemic medical condition. All structures of the eye and many aspects of visual function are susceptible to the deleterious effects of diabetes. These effects are summarized as follows:

#### a. Visual Function

##### Loss of visual acuity

Reductions in visual acuity can occur due to refractive shifts, cataracts, ischemic optic neuropathy, papillopathy, macular edema, ocular surface disease, or other diabetes-related ocular changes.

##### Refractive error changes

Persons with diabetes may experience transient changes in their refractive status. The fluctuations may be myopic or hyperopic in association with hyperglycemia or hypoglycemia.<sup>116,117</sup> These changes are thought to involve fluid absorption by the crystalline lens.

Refractive shifts often occur as a symptom or sign of undiagnosed diabetes. This shift can be several diopters or more. Regardless of the magnitude or direction of the changes, the refractive status tends to normalize within weeks of initiation of treatment for diabetes.<sup>118</sup>

##### Changes in color vision

Color vision changes may appear in persons with diabetes and can precede the development of diabetic retinopathy. Acquired color vision changes can occur in both blue-yellow and red-green discrimination and, when diabetic retinopathy is present, have been shown to correlate with the duration of diabetes.<sup>119</sup>

### Accommodative dysfunction

Accommodative ability may be altered in persons with diabetes.<sup>120</sup> A decrease of accommodation is usually transient and improves with control of glucose levels.

A reduction in accommodation has also been reported in persons who undergo panretinal (scatter) laser photocoagulation.<sup>120</sup>

### Visual field changes

Loss of visual field can occur in individuals with diabetes secondary to preretinal and vitreous hemorrhages, new vessel growth and fibrous proliferation on the retina, neovascular or primary open angle glaucoma, posterior vitreous detachment, papillopathy, or ischemic optic neuropathy.<sup>121</sup>

In addition, persons undergoing scatter (panretinal) laser photocoagulation may experience a reduction in their visual fields.<sup>122</sup>

## **b. Eye Movement Anomalies**

Ocular motility disorders may occur in individuals with diabetes secondary to diabetic neuropathy involving the third, fourth or sixth cranial nerves. Mononeuropathies present a significant diagnostic challenge, since a substantial number that occur in persons with diabetes are not due to the diabetes itself.<sup>120</sup> Therefore, other potential causes need to be ruled out.

Palsies of the third nerve are generally more common than fourth or sixth nerve palsies.<sup>120</sup> They generally are accompanied by a ptosis, with exotropia and hypotropia of the affected eye. Acute pain may be associated with onset of the palsy. Pupil sparing is also an important, but not the only, diagnostic feature in helping to distinguish diabetes-related third nerve palsy from intracranial aneurysms or tumors.

Persons with sixth nerve palsy usually present with horizontal diplopia. The affected eye is esotropic

and may be unable to abduct past the mid-line. Patients may turn their heads in the direction of their paretic field of action in order to eliminate diplopia.

Persons with fourth nerve palsy usually complain of vertical diplopia, which is typically sudden in onset and initially worsens. The vertical deviation increases with downward gaze or lateral gaze away from the affected muscle when the head is tilted toward the side of the affected muscle.

Full ocular motility recovery generally occurs within three to six months.<sup>118,120</sup> However, recurrences are common.<sup>123</sup>

## **c. Pupillary Reflexes**

Diabetes may affect sympathetic innervation of the iris. Persons with diabetes may exhibit sluggish pupillary reflexes.<sup>118</sup> Also, pupils may be more miotic and have a weaker reaction to topical mydriatics.

## **d. Conjunctiva**

Microaneurysms in the bulbar conjunctiva are more common in persons with diabetes. In addition, individuals with diabetes are at increased risk of developing conjunctival bacterial infections.<sup>118</sup>

## **e. Tear Film**

Tear film abnormalities occur frequently in persons with diabetes, leading to an increased incidence of dry eye.<sup>118</sup> Tear break-up time may be diminished, affecting tear film stability. The presence of an abnormal tear film may contribute to discomfort and to the increased risk of ocular surface epithelial defects.

In addition, persons with diabetes may exhibit reduced corneal sensitivity, due to neuropathy of the ophthalmic division of the trigeminal nerve, which may reduce reflex tear secretion,<sup>118</sup> decrease subjective symptomatology and increase risk of neurotrophic keratitis. Longstanding diabetes may also damage the microvascular supply to the

lacrimal gland, impairing lacrimation.

## **f. Cornea**

### Corneal wound healing

The cornea of a person with diabetes is more susceptible to injury and slower to heal after injury than the cornea of a person without diabetes.<sup>120</sup> Therefore, persons with diabetes are at higher risk of corneal complications, including superficial punctate keratitis, recurrent corneal erosions, persistent epithelial defects and corneal endothelial damage. These complications have been linked to tear secretion abnormalities, decreased corneal sensitivity, and poor adhesion between epithelial cells and the basement membrane.

### Reduced corneal sensitivity

Persons with diabetes often have reduced corneal sensitivity.<sup>118,120</sup> This may result in increased susceptibility to corneal ulceration or abrasion in individuals with dry eye syndrome or in those who wear contact lenses.

### Corneal abrasions

Corneal abrasions in persons with diabetes are more likely to be recurrent and to involve detachment of the basement membrane.<sup>118</sup> In addition, persons with diabetes experience delayed re-epithelization of the cornea due to abnormal adhesion of the epithelium to the underlying basement membrane.

### Contact lens wear

Diabetes increases the risk of contact lens-related microbial keratitis, especially in those who use extended wear contact lenses.<sup>118</sup> In addition, persons with diabetes may not recover as readily from contact lens-induced corneal edema. However, studies have concluded that daily wear contact lenses are a safe option for vision correction for persons with diabetes.<sup>124,125</sup> However, individuals with

diabetes need to be evaluated initially and on a continuing basis by their eye care provider.

## **g. Iris**

### Depigmentation

Depigmentation of the iris may result in pigment deposits on the corneal endothelium.<sup>118</sup>

### Neovascularization of the iris (Rubeosis iridis)

Neovascularization of the iris (NVI) is a serious complication marked by a growth of new blood vessels. These vessels are usually first observed at the pupillary margin, but may be present in the filtration angle without any visible vessels on the pupil border. NVI can involve the entire iris surface and angle.

If NVI progresses, a fibrovascular network of vessels may grow over the iris tissue and into the filtration angle of the eye. The new vessels and accompanying fibrosis may occlude the trabecular meshwork, resulting in neovascular glaucoma.

### Neovascular glaucoma

Studies have shown a consistent association between diabetes and neovascular glaucoma (NVG). NVG is a sequella of PDR that is thought to develop because of VEGF-induced neovascularization of the iris and angle.<sup>126</sup>

## **h. Lens**

### Cataracts

Cataracts are a major cause of vision impairment in people with diabetes and tend to develop earlier and progress more rapidly, compared to persons without diabetes.<sup>120</sup> The risk of cataract development increases with the duration of diabetes and the severity of hyperglycemia.<sup>123</sup>

Studies<sup>127-129</sup> have reported an increased prevalence and incidence of posterior subcapsular and cortical cataracts in persons with diabetes. Deposition of advanced glycation end-products (AGEs) in the lens has been postulated as one possible mechanism for diabetic cataract.

Type 2 diabetes is strongly associated with the development of nuclear sclerosis and cortical cataract. Compared with nondiabetic persons, individuals with type 2 diabetes have a substantially higher use of statins, which are associated with the development of age-related cataracts (nuclear sclerosis and posterior subcapsular cataract). In addition, cataracts tend to occur earlier in persons with type 2 diabetes using statins, compared with persons without diabetes who don't use statins.<sup>130</sup>

Metabolic Syndrome (MetS) has also been found to contribute to an increased incidence of cortical cataracts and posterior subcapsular cataract over 5 years. Among MetS components, low HDL cholesterol has been linked to an increase in the 10-year incidence of cortical cataract and elevated glucose was positively associated with the incidence of posterior subcapsular cataract over 10 years.<sup>131</sup>

#### Reversible opacities and snowflake cataracts

Although rare, reversible lenticular opacities related to diabetes have been reported and are frequently related to poor metabolic control of diabetes. These cataracts are usually bilateral and are characterized by dense bands of white, subcapsular spots that are snowflake in appearance.<sup>123</sup>

#### **i. Vitreous**

Persons with diabetes may exhibit vitreous degeneration and posterior vitreous detachment (PVD), which may play a role in PDR. New vessel growth on the surface of the retina may project into the posterior vitreous causing biochemical

changes in the vitreous. The vitreous may exert traction on these vessels resulting in vitreous hemorrhage.

Proliferative diabetic retinopathy is associated with an increased incidence of PVD. Partial vitreous detachment may result in vitreous hemorrhage, an increase in retinal neovascularization and tractional retinal detachment.<sup>120</sup>

#### **j. Optic Disc**

##### Papillopathy

Diabetic papillopathy is a distinct clinical entity that must be distinguished from papilledema or other etiologies of optic disc swelling.<sup>132</sup> The papillopathy is characterized by unilateral or bilateral hyperemic disc swelling, which may present with or without an afferent pupillary defect or visual field defect.<sup>133</sup>

Diffuse microangiopathy may be associated with the etiology of diabetic papillopathy, although there appears to be no correlation between diabetic papillopathy and either the degree of diabetic retinopathy or the level of clinical control of the individual's diabetes.<sup>132-134</sup> However, diabetic papillopathy is a risk factor for the progression of diabetic retinopathy.<sup>123</sup>

Visual acuity is usually moderately reduced and the prognosis for improvement upon resolution is good. In most individuals, diabetic papillopathy resolves without treatment within a year and visual acuity improves to a level of  $\geq 20/30$ .<sup>123</sup>

##### Ischemic optic neuropathy

Diabetes represents an independent risk factor for the development of nonarteritic anterior ischemic optic neuropathy (NAION) and has been shown to increase the risk of NAION among individuals over 67 years of age.<sup>135</sup>

Diabetes-related anterior ischemic optic neuropathy usually presents with optic disc



pallor, swelling and hemorrhages, sudden decreased vision, an afferent pupillary defect, and an altitudinal visual field defect. The condition often results in optic atrophy and reduced visual acuity. The clinical appearance of early anterior ischemic optic neuropathy is difficult to distinguish from diabetic papillopathy,<sup>133</sup> although younger age is more consistent with the latter. Persons with diabetes are also susceptible to retrobulbar ischemic optic neuropathy. As many as 25 percent of persons with anterior ischemic optic neuropathy have a history of diabetes.<sup>123</sup>

#### [Open angle glaucoma](#)

Diabetes has been found to be associated with elevated intraocular pressure (IOP). However, current evidence suggesting that diabetes is a risk factor for glaucoma is conflicting.<sup>118</sup>

Diabetes can influence ocular vasculature in individuals with open angle glaucoma and may contribute to the disease process. Persons with diabetes who have open angle glaucoma (OAG) may have lower retrobulbar flow in the central retinal artery, as well as possible higher retinal microcirculation flow, specifically in the inferior retinal sector. These ocular diabetic vascular abnormalities could contribute to glaucomatous optic neuropathy.<sup>136</sup>

In addition, persons with diabetes often have concomitant hypertension that may potentially affect vascular perfusion of the optic nerve head. Formation of advanced glycation end-products (AGEs) within the trabecular meshwork and the lamina cribrosa of the optic nerve may further increase the risk of both ocular hypertension and damage to the optic nerve axons.<sup>137</sup>

## **IV. DIAGNOSIS OF OCULAR COMPLICATIONS OF DIABETES MELLITUS**

The components of patient care described in this Guideline are not intended to be all-inclusive. Professional judgment and individual patient symptoms and findings may have a substantial impact on the nature, extent and course of the services provided and/or recommended.

### **A. INDIVIDUALS WITH UNDIAGNOSED DIABETES MELLITUS**

An eye examination may be the basis for the initial diagnosis of the individual who is unaware of having a diabetic condition.

#### **1. Patient History**

The patient history is used to investigate any ocular and systemic complaints and symptoms related to diabetes:

- Common ocular symptoms of undiagnosed diabetes may include the recent onset of visual changes. Individuals may report blurred or fluctuating vision, improved near vision if they have a myopic shift and are presbyopic or new-onset diplopia. Symptoms of ocular surface disease and staphylococcal eyelid disease may also be more common, as a function of hyperglycemia.
- Systemic symptoms may include polyuria, polydipsia, polyphagia, unexplained weight changes, dry mouth, pruritus, leg cramps or pains, erectile dysfunction in men and reduced sexual response in women, delayed healing of bruises or wounds, and recurrent infections of the skin, genitalia, or urinary tract.

#### **2. Diabetes Risk Assessment**

Noninvasive risk assessment tools are available to help identify people at risk for the development of type 2 diabetes. These tools provide a risk

rating based on answers to a number of questions regarding variables such as age, gender, race, weight, body mass index (BMI), blood pressure, physical activity, and family history of diabetes.

Diabetes risk scores can be used to identify individuals with undiagnosed type 2 diabetes who might benefit from more comprehensive assessment, such as determination of blood glucose levels.<sup>138</sup>

Examples of validated risk assessment tools include the Diabetes Risk Calculator\*<sup>139</sup> and the Weill-Cornell Medical College Patient Self-Assessment Score for Diabetes.\*\*<sup>140</sup>

It should be noted that these tools are not diagnostic and further testing should be done to achieve a definitive diagnosis.

\* *The Diabetes Risk Calculator can be accessed online*

\*\* *The Weill-Cornell Medical College Patient Self-Assessment Score for Diabetes can be accessed online*

### 3. Ocular Examination

**ACTION:** The ocular examination of an individual suspected of having undiagnosed diabetes should include all aspects of a comprehensive eye examination\*\*\* with supplemental testing, as needed.

\*\*\**Refer to the Optometric Clinical Practice Guideline for Comprehensive Adult Eye and Vision Examination*

If, on the basis of the results of the eye examination or risk assessment tools, diabetes is suspected, the patient should be referred to his or her primary care physician for further evaluation, or an A1C test or fasting blood glucose analysis may be ordered.\*\*\*\* The use of A1C testing may help predict those at-risk for diabetes, diabetic retinopathy or other complications of diabetes.<sup>73</sup> (C/B)

**ACTION:** Persons without a diagnosis of diabetes who present with signs suggestive of diabetes during the initial examination should be referred to their primary care physician for

evaluation, or an A1C test or fasting blood glucose analysis may be ordered.

There is little direct evidence that identifying persons with pre-diabetes will lead to long-term health benefits.<sup>86</sup> (A/B) However, early identification and control of hyperglycemia and high blood pressure can prevent or delay long-term microvascular complications of diabetes.<sup>141</sup> (B/B) Tight glycemic and blood pressure control are the cornerstones of primary prevention of diabetic retinopathy.<sup>142</sup> (A/A)

\*\*\*\*Authority of Optometrists to Order Lab and Other Diagnostic Tests Unless there is a specific limitation in the Optometry Act or other section of state law regarding which diagnostic, laboratory, radiology or other tests they may order, optometrists may order any tests rational to the diagnosis of conditions of the eye, adjacent structures, the vision system, or for systemic conditions affecting the eyes, as defined by the applicable standard of care.

*American Optometric Association, State Government Relations Center, July 2009*

## B. INDIVIDUALS WITH DIAGNOSED DIABETES MELLITUS

**ACTION:** The ocular examination of a person with diabetes should include all aspects of a comprehensive eye examination,\*\*\* with supplemental testing, as indicated, to detect and thoroughly evaluate ocular complications.

\*\*\**Refer to the Optometric Clinical Practice Guideline for Comprehensive Adult Eye and Vision Examination*

### 1. Patient History

The patient history includes a review of both the ocular and systemic status of the patient:

- **Quality of the patient's vision** - including symptoms such as blurred, distorted, or fluctuating vision, diplopia, night vision problems and flashes or floaters.

- **Ocular history** - including previous ocular trauma, disease or surgery that might contribute to ocular complications associated with diabetes.
- **Medical history** - including obesity, pregnancy, and current medication taken. (See Appendix Table 2: Effect of Systemic Medications on Onset and Progression of Diabetic Retinopathy)
- **Duration of diabetes** - the risks for ocular complications are closely related to the duration of the diabetes.<sup>107-108</sup> Age at the time of onset of diabetes is not as significant as the duration of the disease in the prediction of complications.<sup>109,110,143</sup>
- **Recent values for the ABCs of diabetes** - A1C, blood pressure and cholesterol levels, and smoking. The A1C level, at initial examination, has been shown to be a strong predictor of the incidence and progression of any retinopathy or progression to proliferative retinopathy.<sup>144,145</sup>

In addition, individuals should be questioned about their use of tobacco. Smoking may be considered the final letter(s) in the ABCs of diabetes.

- **The patient's prescribed management of diabetes, including:**

1. Medical nutrition therapy
2. Exercise and physical activity
3. Oral or injectable medications
4. Insulin type, dosage and timing of administration
5. Method, frequency and results of self-monitoring of blood glucose.

This information provides insight into the patient's adherence to therapeutic regimens and control of diabetes, which may affect the

development of ocular complications.<sup>60,61,144</sup>

The presence of retinopathy, regardless of the person's diabetes status, may also indicate other underlying subclinical vascular disease.<sup>146</sup> (B/B) The clinician should consider other etiologies, especially cardiovascular disease, hypertension and smoking status.<sup>147</sup> (B/B)

**ACTION:** Patients should be questioned about the awareness of their personal diabetes ABCs (A1C, blood pressure, and cholesterol levels and their history of smoking).

Additional information useful for patient assessment includes a review of other medical problems, all prescribed medications, use of nutritional supplements and history of allergy to medications.

Contact information for the patient's other health care providers should be noted in their record to facilitate communication and coordination of care, when appropriate.

## 2. Ocular Examination

**ACTION:** The initial ocular examination should include, but is not limited to, the following evaluations:

- Best-corrected visual acuity
- Pupillary reflexes
- Ocular motility
- Refractive status
- Confrontation visual field testing or visual field evaluation
- Slit lamp biomicroscopy
- Tonometry
- Dilated retinal examination

### Tonometry

The central cornea of persons with diabetes may be thicker than in persons without diabetes. This possibility needs to be taken into consideration when measuring intraocular pressure in individuals with diabetes to ensure accuracy of measurement.<sup>148</sup>

In addition, persons with diabetes may display altered corneal biomechanics related to blood glucose concentrations. They may have significantly higher corneal response factors (CRF), which is strongly associated with corneal stiffness and may also alter tonometry readings.<sup>149</sup>

### Dilated Retinal Examination

Binocular indirect ophthalmoscopy or slit lamp biomicroscopy with condensing lens should be performed to examine the retina thoroughly for the presence of diabetic retinopathy.

**ACTION:** Retinal examinations for diabetic retinopathy should be performed through a dilated pupil.

Clinicians should use caution in administering topically applied drugs for pupillary dilation in pregnant women. Topically applied drugs for pupillary dilation, such as tropicamide, hydroxyamphetamine and phenylephrine are Pregnancy Category C drugs. When evaluation through a dilated pupil is necessary to assess diabetic retinal changes or unexplained decreased vision during pregnancy, the benefits of dilation may outweigh any potential risks. The use of digital punctal occlusion can minimize systemic absorption.

Proper documentation of retinal status, including the use of drawings or color photographs in the patient's record, is valuable for determining any progression or stability of the retinopathy at future examinations. Use of the standard protocol for color-coding retinal drawings is recommended.\*

It is advisable to note the presence (and the severity) or the absence of neovascularization of the iris (rubeosis iridis or NVI), retinal H/Ma, VB, IRMA,

retinal neovascularization and hard exudates or thickening in the macula. The presence and severity of these lesions determines the level of diabetic retinopathy and diabetic macular edema.

**ACTION:** When vitreous hemorrhage prevents adequate visualization of the retina, prompt referral to an ophthalmologist experienced in the management of diabetic retinal disease should be made for further evaluation.

*\*Click this link for the protocol for color coding retinal drawings*

### **3. Supplemental Testing**

Additional procedures in diagnosing and evaluating diabetic retinopathy may be indicated. Such procedures include, but are not limited to:

- **Fundus photography or retinal imaging**

Mydriatic ETDRS 7-field stereo 35 mm fundus photography is the gold standard for evaluating the presence and severity of diabetic retinopathy and DME. The transition to digital imaging, while utilizing the same imaging technique, has been shown to maintain comparable levels of agreement.<sup>150,151,152</sup> (A/A)

Retinal imaging following defined validated protocol for image acquisition and evaluation has been shown to correlate well with dilated stereoscopic examination by a trained examiner.<sup>153</sup> (C/B) Stereoscopic photography is useful for identifying lesions of diabetic retinopathy and for documenting retinal status.

The results of digital and film evaluations of diabetic retinopathy have been shown to be comparable for ETDRS severity levels and DCCT/EDIC study design outcomes.<sup>152</sup> (A/A) Similarly, the use of standardized retinal video recording evaluated using a defined protocol has been shown to be comparable to standard retinal photography in imaging and evaluating for diabetic retinopathy.<sup>154</sup> (B/B)

- **Optical coherence tomography**

Optical coherence tomography (OCT) is particularly useful in quantifying the degree of retinal thickening and for identifying retinal thickening that may not have been evident on clinical examination.<sup>155</sup> Also, OCT has become nearly indispensable in routine clinical practice to evaluate macular edema and vitreo-retinal interface abnormalities.<sup>156-159</sup> However, data suggest routine macular OCT imaging is not indicated in persons with no retinopathy or mild to moderate diabetic retinopathy, when retinal thickening is absent on clinical examination.<sup>160</sup>

Use of the OCT is an important tool in assessing DME, especially for monitoring the efficacy of treatment.<sup>153</sup> (C/B) However, clinicians should be aware that substantial discrepancies often exist between OCT results and the clinical examination of DME.<sup>161</sup> (B/B)

The assessment of macular thickness using OCT is clinically useful and demonstrates the degree of macular edema. However, central macular thickness only shows moderate correlation with visual acuity in eyes with DME.<sup>162</sup> This finding indicates that functional and structural determinants of visual function other than retinal thickness are present in quantifying visual loss from DME.

The use of central macular thickness, as measured by OCT, is not indicated in isolation to identify central CSME or to make treatment decisions in persons with DME.<sup>161</sup> (B/B) In patients with DME, spectral domain OCT provides easier observation of normal and abnormal retinal and vitreo-retinal findings than does time domain OCT.<sup>163</sup> (C/B)

- **Fluorescein angiography**

Fluorescein angiography (FA) may be used to identify vascular leakage and treatable lesions in eyes with DME. Fluorescein leakage (particularly diffuse), capillary loss and dilation and various

arteriolar abnormalities are associated with retinopathy severity and with the likelihood of progression to proliferative retinopathy.<sup>41</sup> (A/A)

Fluorescein angiography can also be used for determining the presence of foveal ischemia in cases where vision is reduced beyond that expected based on ophthalmoscopic appearance of the macula. However, fluorescein angiography is not indicated to confirm a suspected clinical diagnosis of PDR<sup>164</sup> (B/B) and should not be used for routine diabetic retinopathy evaluation.<sup>39</sup> In addition, the use of FA for assessing DME is not recommended, since it offers little additional information beyond that provided by OCT imaging.<sup>153</sup> (C/B) However, FA may be helpful in guiding treatment of DME.

- **Fundus autofluorescence**

Fundus autofluorescence (FAF) is a noninvasive “in vivo” imaging method for metabolic mapping of fluorophores of the fundus. FAF is increasingly used to detect and objectively quantify disease severity in patients with nonexudative age-related macular degeneration.<sup>165</sup> Evidence suggests that FAF may provide information beyond that obtained by fundus photography, fluorescein angiography and OCT in eyes with DME.<sup>166</sup> However, usefulness of FAF for assessing and managing diabetic retinal disease remains uncertain.

- **Ocular ultrasound**

Ocular ultrasound (ultrasonography) can be helpful in detecting retinal detachment when viewing of the retina is obscured by cataract, vitreous hemorrhage or other media opacity.

- **Contrast sensitivity testing**

Contrast sensitivity testing can be used as an early indicator of changes in the retina not shown by visual acuity measurements.<sup>167</sup> Deficits in contrast sensitivity may occur before the

onset of clinically detectable retinopathy.<sup>168</sup>

- **Blood pressure measurement**

As hypertension is more prevalent in persons with diabetes and is a potential risk factor for the development and progression of diabetic retinopathy,<sup>87,169</sup> blood pressure may be measured at the time of the eye examination, particularly in individuals who may not be under regular medical care.

Slight variations in optimum blood pressure for people with diabetes are found in the literature. Blood pressure of <140/80 mmHg has been recommended for most patients with diabetes.<sup>78</sup> No evidence was shown that a more aggressive blood pressure goal (e.g. systolic blood pressure <130 mmHg) is beneficial.<sup>170</sup> (A/B)

- **Color vision testing**

Changes in color perception may occur in persons with diabetes. Therefore, color vision testing may be appropriate. However, the use of color vision testing for the diagnosis of diabetic retinopathy is not recommended.<sup>171</sup> (B/B)

**ACTION:** The individual's primary care physician should be informed of eye examination results following each examination, even when retinopathy is minimal or not present.

## C. OCULAR EXAMINATION SCHEDULE

### 1. Persons with Diabetes Mellitus

The frequency of ocular examination is determined on the basis of several factors, including, but not limited to:

- Type of diabetes
- Duration of the disease
- Age of the patient

- Level of patient adherence to, and understanding of, their treatment plan
- Concurrent medical status
- Both non-retinal and retinal ocular findings and symptoms
- Subjective changes in vision

**ACTION:** As diabetes may go undiagnosed for many years, any individual with type 2 diabetes should have a comprehensive dilated eye examination soon after the diagnosis of diabetes.<sup>78</sup>

**ACTION:** Individuals with diabetes should receive at least annual dilated eye examinations. More frequent examination may be needed depending on changes in vision and the severity and progression of diabetic retinopathy.

The clinical signs of diabetic retinopathy can appear early in the natural history of the disease. Unfortunately, individuals may not experience symptoms until relatively late, at which time treatment may be less effective. The success of appropriate intervention and management strategies depends upon accurate and timely detection of diabetic eye disease.

The main risk factor of diabetic retinopathy worsening during pregnancy is the baseline severity of diabetic retinopathy.<sup>60,172</sup> (C/B) In general, individuals with GDM do not develop retinopathy. Therefore, retinal evaluation for diabetic retinopathy in these patients is not indicated.

**ACTION:** Women with pre-existing diabetes who are planning pregnancy or who become pregnant should have a comprehensive eye examination prior to a planned pregnancy or during the first trimester, with follow-up during each trimester of pregnancy.

## **2. Persons with Non-retinal Ocular Complications of Diabetes Mellitus**

**ACTION:** Examination of persons with non-retinal ocular complications of diabetes should be consistent with current recommendations of care for each condition.

See Table 5 for a brief outline of the management of non-retinal ocular complications.

## **3. Persons with Retinal Complications of Diabetes Mellitus**

### Mild NPDR (with no DME)

An annual dilated eye examination is generally sufficient for monitoring the patient with mild NPDR, as long as there are neither DME nor coincident medical risk factors such as hypertension, renal disease or pregnancy, that may predispose patients to progression.

### Moderate NPDR

For patients with moderate NPDR, fundus photography is strongly suggested, and repeat evaluation in 6 to 8 months is appropriate in the absence of DME or complicating medical or risk factors.

If DME is present, but does not meet the criteria for CSME, follow-up every 2 to 4 months is advisable.

### Severe or Very Severe NPDR

Follow-up every 2 to 3 months in consultation with an ophthalmologist experienced in the management of diabetic retinal disease is advisable for patients with severe or very severe NPDR.

### Proliferative Diabetic Retinopathy

Consultation with an ophthalmologist experienced in the management of diabetic retinal disease is indicated if PDR or DME is suspected or if there is an unexplained loss of visual acuity.

Follow-up every 2 to 3 months in consultation with an ophthalmologist experienced in the management of diabetic retinal disease is recommended.

**ACTION:** Prompt referral to a vitreo-retinal surgeon is indicated when a vitreous hemorrhage, a retinal detachment or other evidence of proliferative diabetic retinopathy is present.

A summary of follow-up visits for management of patients with retinal complications of diabetes can be found in Table 4. Patient education and written or electronic communication with the patient's primary care physician are integral to the management of diabetic retinopathy.

**TABLE 4:**  
**Frequency and Composition of Evaluation and Management Visits for**  
**Retinal Complications of Diabetes Mellitus**

Severity of Condition	Natural Course Rate of Progression to		Frequency of Follow-up	Components of Follow-up Evaluations	
	PDR (1 year)	HRC * (5 years)		Fundus Photography	OCT/ Fluorescein Angiography
<b>Mild NPDR</b>	5%	15%			
No macular edema			12 months	No	No
Macular edema			4 to 6 months	Yes	Based on clinical judgment
CSME			2 to 4 months**	Yes	Yes
<b>Moderate NPDR</b>	12-27%	33%			
No macular edema			6 to 8 months	Yes	No
Macular edema (not CSME)			4 to 6 months	Yes	Based on clinical judgment
CSME			2 to 4 months**	Yes	Yes
<b>Severe NPDR</b>	52%	60-75%			
No macular edema			3 to 4 months	Yes	No
Macular edema (not CSME)			2 to 3 months	Yes	Based on clinical judgment
CSME			2 to 3 months**	Yes	Yes
<b>Very Severe NPDR</b>	75%	75%			
No macular edema			2 to 3 months	Yes	No
Macular edema (not CSME)			2 to 3 months	Yes	Based on clinical judgment
CSME			2 to 3 months**	Yes	Yes
<b>Non-high-risk PDR</b>		75%			
No macular edema			2 to 3 months	Yes	No
Macular edema			2 to 3 months	Yes	Based on clinical judgment



**TABLE 4 (continued)**

CSME			2 to 3 months**	Yes	Yes
<b>High-risk PDR</b>					
No macular edema			2 to 3 months	Yes	No
Macular edema			1 to 2 months	Yes	Yes
CSME			1 to 2 months**	Yes	Yes

\*HRC = High-risk category

\*\*Follow-up is typically monthly for the first year of treatment if intravitreal anti-VEGF injections are given.

#### 4. Clinical Recordkeeping

Electronic Health Records (EHRs) are helpful for identifying at-risk populations for preventive care and intervention.<sup>173</sup>(B/B) The use of EHRs to support clinical decision-making has been shown to improve glucose control and some aspects of blood pressure control in adults with type 2 diabetes.<sup>174</sup>(B/B)

When compared to paper record-based practices, the use of electronic health records (EHRs) may improve the quality of care and outcomes for patients with diabetes.<sup>175</sup>(C/B) EHRs can also be used to identify clusters of risk factors for diabetes and coronary heart disease in patients in large health care networks.<sup>173</sup>(B/B)

## V. TREATMENT AND MANAGEMENT

### A. MANAGEMENT OF OCULAR COMPLICATIONS OF DIABETES MELLITUS

#### 1. Basis for Treatment

Treatment recommendations depend upon the nature and severity of the patient’s ocular condition and desired visual outcome. Treatment decisions should reflect the patient’s preferences and values. Appendix Figure 1 presents a flowchart for the management of the patient with undiagnosed diabetes. Appendix Figure 2 presents a flowchart outlining the optometric management of the patient diagnosed with diabetes.

##### a. Persons with Undiagnosed Diabetes Mellitus

Patients suspected of having diabetes need to be

screened for high blood glucose levels:

- A1C values between 4.0 percent and 5.6 percent usually indicate adequate blood glucose levels. Values between 5.7 percent and 6.4 percent are considered pre-diabetes. Values of 6.5 percent or greater indicate the need for further evaluation or treatment.
- A patient with fasting blood glucose values of greater than or equal to 110 mg/dl, but less than 126 mg/dl, has IFG and needs to be retested. Fasting blood glucose values of 126 mg/dl or greater indicate the need for further evaluation or treatment.

Most pregnant women should be screened for glucose intolerance. Because as a pregnant patient is usually under medical care, her prenatal care provider should coordinate this evaluation.

##### b. Persons with Non-retinal Ocular Complications

Management of non-retinal ocular complications of diabetes should be consistent with current recommendations of care for each condition. Although a comprehensive discussion of these therapy regimens is beyond the scope of this Guideline, Table 5 briefly reviews current clinical practice for management of common non-retinal ocular and visual complications.

**ACTION:** Treatment protocols for persons with non-retinal ocular and visual complications should follow current recommendations for care, and include education on the subject and recommendations for follow-up visits.

**TABLE 5**

**Management of Non-retinal Ocular Complications of Diabetes**

Category	Ocular /Visual Complications	Management*
Functional	Loss of visual acuity	Assess visual acuity as recommended in the <b>Optometric Clinical Practice Guideline</b> on Adult Eye and Vision Examination, Pediatric Eye and Vision Examination, or Care of the Patient with Visual Impairment.
	Refractive error changes	Assess refractive error, distance and near and pinhole acuity as recommended in the <b>Optometric Clinical Practice Guidelines</b> on Care of the Patient with Myopia and Care of the Patient with Hyperopia.  Change in spectacle or contact lenses prescription, as indicated by the patient's visual requirements, with special attention to the person's level of glycemic control.  Counsel patients about variable refractive status due to fluctuations in blood glucose.
Functional	Changes in color vision	Perform color vision assessment that is sensitive to acquired (i.e., generally blue/yellow) color vision loss.
	Changes in visual fields	Assess visual field changes and manage as recommended in the <b>Optometric Clinical Practice Guideline</b> on Care of the Patient with Visual Impairment.  Rule out other causes of visual field changes.
Eye movement anomalies	Cranial nerve palsies	Assess multiple diagnostic positions of gaze; tests of smooth pursuits (versions and ductions), and saccades.  Rule out other cranial nerve palsies or other etiologies.
Pupils	Sluggish pupillary reflexes Afferent pupillary defects	Rule out optic neuropathy and other neurological etiologies.
Conjunctiva	Bulbar microaneurysms	Monitor

**TABLE 5 (continued)**

Category	Ocular /Visual Complications	Management*
Tear film	Dry eye syndrome	<p>Recommend use of artificial tears, ocular lubricants, and other dry eye management techniques as recommended in the <b>Optometric Clinical Practice Guideline</b> on Care of the Patient with Ocular Surface Disease.</p> <p>Monitor for corneal complications.</p>
Cornea	Reduced corneal sensitivity	<p>Monitor for abrasions, keratitis, or ulcerations.</p> <p>Monitor contact lens wear as recommended in the <b>Optometric Clinical Practice Guideline</b> on Care of the Patient with Contact Lenses.</p>
	<p>Basement membrane anomalies</p> <p>Recurrent corneal erosions</p>	<p>Recommend lubricating drops/artificial tears.</p> <p>Prescribe sodium chloride solution/ointment or ocular surface lubricant.</p> <p>Bandage contact lenses or patching, as necessary.</p>
Iris	Rubeosis iridis (neovascularization on the iris)	<p>Gonioscopy to rule out anterior chamber angle involvement and neovascular glaucoma.</p> <p>Dilated retinal examination to evaluate proliferative diabetic retinopathy.</p> <p>Refer to an ophthalmologist experienced in the management of diabetic retinal disease for possible panretinal photocoagulation and/or anti-VEGF agents.</p>
Eyelids	Ptosis	Determine etiology (neurologic, mechanical, immunological).

**TABLE 5 (continued)**

Category	Ocular /Visual Complications	Management*
Lens	Cataracts	<p>Assess and monitor degree of lens opacification.</p> <p>Refraction to obtain best visual acuity. If functional deficits remain, manage as recommended in the <b>Optometric Clinical Practice Guideline</b> on Care of the Patient with Visual Impairment.</p> <p>Surgery may be indicated, if adequate visualization of the retina is no longer possible or if visual acuity is decreased secondary to the cataract.</p> <p>Refer to <b>Optometric Clinical Practice Guideline</b> on Care of the Adult Patient with Cataract for more information.</p>
Vitreous	Premature syneresis/degeneration Hemorrhage Detachment	<p>Dilated retinal examination.</p> <p>Ultrasound, if retinal view is obscured.</p> <p>Consultation with an ophthalmologist experienced in the management of diabetic retinal disease.</p>
Optic Disc	Papillopathy Ischemic optic neuropathy	<p>Management of diabetic papillopathy or ischemic optic neuropathy may require consultation with a neuro-ophthalmologist or neurologist to rule out all other potential etiologies.</p>

\* Communication with the patient's health care provider regarding ocular and visual findings, and patient education are an integral part of management for all conditions.

**ACTION:** As part of the proper management of diabetes, the optometrist should make referrals for concurrent care when indicated.

**c. Persons with Retinal Complications**

Major clinical trials provide the scientific basis for clinical management of diabetic retinopathy:

- The Diabetic Retinopathy Study (DRS, 1971–1975)<sup>15-27</sup>
- The Early Treatment Diabetic Retinopathy Study (ETDRS, 1979–1990)<sup>28-50</sup>
- The United Kingdom Prospective Diabetes Study (UKPDS, 1977–1998)<sup>56-59</sup>

- The Diabetes Control and Complications Trial (DCCT, 1983–1993)<sup>3,60,61</sup> and its extended follow-up, the Epidemiology of Diabetes Interventions and Complications trial (EDIC, 1994-present)<sup>62,63</sup>
- Diabetic Retinopathy Clinical Research Network Clinical Trials (DRCR.net, 2003-present)<sup>64-71</sup>

These studies have guided the current treatment and management of diabetic retinal disease. The DRS and ETDRS established the efficacy and appropriate timing for panretinal laser photocoagulation to prevent severe vision loss from diabetic retinopathy. The development of

endolaser photocoagulation and small gauge vitrectomy have made the results of the DRVS less applicable.

The DCCT and UKPDS established the benefits of intensive control of blood glucose levels to reduce the risks of onset and progression of retinal complications of diabetes in type 1 and type 2 patients, respectively.

One of the most important contributions that arose from the DRS and ETDRS was standardized classification of the varying levels of diabetic retinopathy based on the modified and extended Airlie House classification of diabetic retinopathy.<sup>38,40</sup> This modification formed the basis of an overall diabetic retinopathy severity scale<sup>38</sup> that ranges from the absence of diabetic retinopathy to advanced PDR with VH.

To simplify the classification of diabetic retinopathy and diabetic macular edema, and to standardize communication between health care providers, a Consensus Panel developed an International Classification of Diabetic Retinopathy and Diabetic Macular Edema Severity Scale<sup>176</sup> (see Appendix Table 1).

This simplified classification scale provides a practical and valid method of grading the severity of diabetic retinopathy that is appropriate in most eye care settings and provides a useful scale for clinicians to use in assessing risk for vision loss. Retinal specialists typically are familiar with the ETDRS-derived classification system and continue to use ETDRS levels.

## 2. Treatment of Retinal Complications

The current treatment options for diabetic retinopathy and DME include careful retinal examination and follow-up, timely laser photocoagulation, monitored regimens of intravitreal injections (anti-VEGF) for diabetic macular edema and appropriate use of vitrectomy surgery in clearing vitreous hemorrhage, removing fibrous tissue and relieving tractional retinal detachment.

### a. Laser Photocoagulation

Panretinal or scatter photocoagulation (PRP), in which approximately 1200-2400 laser burns are scattered throughout the retina, sparing the macula, is the current standard of care for the treatment of high-risk PDR. PRP may also be considered in eyes approaching high-risk PDR.<sup>177</sup> (A/A)

While the benefits of PRP are notable in patients with proliferative retinopathy, PRP is not indicated for DME.<sup>177</sup> (A/A) The presence of DME requires more frequent evaluation, consultation with an eye care provider experienced in the management of diabetic retinal complications and in the presence of center-involved diabetic macular edema, focal/grid laser photocoagulation or a regimen of intravitreal anti-VEGF treatment.

In eyes receiving focal/grid laser for DME and PRP, the addition of intravitreal triamcinolone injection or intravitreal ranibizumab injections is associated with improved visual acuity and decreased macular edema.<sup>69</sup> (A/A) Coexisting center-involved DME and PDR may be treated with combined PRP, focal/grid laser and intravitreal injections.

Complications and side effects of PRP include visual field constriction, night blindness, color vision changes, decreased accommodation, scotoma, anisocoria, glaucoma and traction retinal detachment. There is evidence to suggest that in patients with center-involved macular edema, PRP may worsen retinal thickening in some cases. In eyes without center-involved macular edema, the risk for significant worsening of the edema following PRP is low.<sup>66</sup> (B/B)

### Non-proliferative Diabetic Retinopathy

While PRP is effective at reducing the risk of severe vision loss in patients with PDR, it may also be considered for severe NPDR. Patients with severe NPDR or worse will invariably require laser photocoagulation.<sup>178</sup> (B/B) However, PRP is

not indicated for patients with mild or moderate NPDR.<sup>37</sup> (A/A)

Panretinal laser photocoagulation can exacerbate DME in some individuals. Since the relative risk of vision loss in patients without high-risk characteristics is low, treatment of CSME or center-involved DME should be considered before panretinal laser photocoagulation is used.<sup>177</sup> (A/A)

**ACTION:** Panretinal photocoagulation may be considered in patients with severe or very severe non-proliferative diabetic retinopathy (NPDR), or early proliferative diabetic retinopathy (PDR) with a high risk of progression (e.g. pregnancy, poor glycemic control, inability to follow-up, initiation of intensive glycemic control, impending ocular surgery, renal impairment and rapid progression of retinopathy).<sup>177</sup> [Evidence Strength: A, Recommendation: A]

### *Proliferative Diabetic Retinopathy*

Proliferative diabetic retinopathy is marked by new vessel growth on the optic disc or elsewhere on the retina, VH, pre-retinal hemorrhage, or the proliferation of fibrous tissue on the optic disc or elsewhere on the retina. Scatter (panretinal) laser photocoagulation is generally indicated when high-risk proliferative diabetic retinopathy is present.

**ACTION:** Patients with high-risk proliferative diabetic retinopathy (PDR) should receive referral to an ophthalmologist experienced in the management of diabetic retinal disease for prompt scatter (panretinal) photocoagulation.<sup>37</sup> [Evidence Strength: A, Recommendation: A],<sup>178</sup> [Evidence Strength: B, Recommendation: B]

**ACTION:** Eyes in which PDR has not advanced to the high-risk stage should also be referred for consultation with an ophthalmologist experienced in the management of diabetic retinal disease.<sup>37</sup> [Evidence Strength: A, Recommendation: A],<sup>178</sup> [Evidence Strength: B, Recommendation: B]

The management of patients following laser treatment needs to be coordinated with the recommendations of an eye care provider experienced in the management of diabetic eye diseases due to the high rate of patients that may subsequently need laser or surgical intervention. Long-term follow-up of the ETDRS patients over a median of 16.7 years has shown that in patients who have received PRP, more than 60 percent will require laser treatment of DME and 17 percent will require vitrectomy.<sup>178</sup> (B/B)

Patients receiving PRP for PDR have similar risks of development of macular edema, whether the PRP is delivered in a single session or 4 sessions over 12 weeks.<sup>66</sup> (B/B)

Patients with diabetic retinopathy who require laser photocoagulation need aggressive follow-up examinations and intervention to achieve good visual acuity outcomes and because of a dramatically increased risk of mortality.<sup>178</sup> (B/B)

**ACTION:** Following successful treatment with panretinal photocoagulation (PRP), patients should be re-examined every 2 to 4 months. The follow-up interval may be extended based on disease severity and stability.

### *Diabetic Macular Edema*

The management of patients with DME has evolved substantially in recent years. The ETDRS established the efficacy of focal/grid photocoagulation for the treatment of CSME.<sup>28</sup> (A/A) The DRCR.net demonstrated that center-involved DME, with vision reduced to 20/32 or worse, is best treated with intravitreal anti-VEGF followed by either prompt or deferred (up to six months) focal laser photocoagulation. Treatment is generally recommended for all eyes with CSME. Frequent follow-up is needed to determine whether additional treatment is necessary for persistent CSME.<sup>28</sup> (A/A)

**ACTION:** Following focal photocoagulation for DME, re-examination should be scheduled in 3 to 4 months.

In the ETDRS, focal/grid laser treatment of CSME substantially reduced the risk of moderate visual loss, increased the chance of visual improvement, decreased the frequency of persistent macular edema, and caused only minor visual field losses. However, despite focal/grid laser treatment, 16 percent of patients may continue to experience vision loss. Recent data demonstrated that a regimen of sequential intravitreal anti-VEGF injections is more effective than focal/grid laser alone in the treatment of center-involved DME.<sup>67</sup> (A/A), <sup>179</sup> (A/B)

Eyes with center-involved DME and visual impairment should be considered for possible initiation of a regimen of anti-VEGF injections with prompt or deferred focal/grid laser. An average of 8 to 9 intravitreal injections may be needed in the first year of treatment. This number may be reduced to 2 to 3 and 1 to 2 injections in the second and third years of follow-up, respectively. However, the full benefit of macular laser treatment or intravitreal injection may not be manifest until the second year of treatment.<sup>180</sup> (A/A)

**ACTION:** Patients with center-involved diabetic macular edema (DME) should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible treatment.

The Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus (RISE and RIDE) studies demonstrated that ranibizumab significantly reverses vision loss from DME. In addition, patients treated with ranibizumab experienced fewer complications such as vitreous hemorrhage and fewer developed PDR or underwent panretinal photocoagulation.<sup>179</sup> (A/B)

The presence or absence of CSME is the most important factor in determining when people with maculopathy and mild to moderate NPDR should be treated. Before development of CSME, the risk of vision loss is very low and there is no evidence that early focal laser macular photocoagulation provides any additional benefit.<sup>177</sup> (A/A)

Focal/grid laser is typically not indicated in eyes without CSME. Such patients should be re-examined within 4 to 6 months. Follow-up for proper management of the retinopathy can be more frequent, if required.<sup>28,29,31,33</sup> Patients judged to be at high short-term risk for progression of DME should be followed in consultation with an ophthalmologist experienced in the management of diabetic retinal disease.

**ACTION:** Individuals with diabetic macular edema (DME), but without clinically significant macular edema (CSME), should be re-examined at 4- to 6-month intervals. Once CSME develops, treatment with focal laser photocoagulation or intravitreal anti-VEGF injection is indicated.<sup>177</sup> [Evidence Strength: A, Recommendation: A]

#### **b. Vitrectomy**

Vitrectomy is used for treating vitreous hemorrhage and PDR with non-clearing vitreous hemorrhage or fibrosis, areas of traction threatening the macula and persistent DME with vitreous traction. Less frequently, vitrectomy may be used for DME that is nonresponsive to focal laser treatment.

Vitrectomy can result in a reduction in macular thickening<sup>68</sup> (C/B) and can improve visual acuity in DME when the pre-operative acuity is < 20/80 and there is an epiretinal membrane or vitreo-retinal adhesion.<sup>181</sup> (C/B)

While the use of vitreo-retinal procedures for the management of the late complications of PDR remains a common treatment, for many patients the visual results are guarded.<sup>182</sup> (B/B) Early vitrectomy appears more effective than deferred vitrectomy at improving visual acuity in people with recent severe vitreous hemorrhage. The trend to operate in patients earlier and on those with better vision has also been associated with better visual outcomes.<sup>182</sup> (B/B)

**ACTION:** Eyes with vitreous hemorrhage (VH), traction retinal detachment (TRD), macular traction or an epiretinal membrane should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for evaluation for possible vitrectomy.

Potential complications of vitrectomy include neovascular glaucoma, retinal detachment, vitreous hemorrhage, retinal tear formation, cataract and endophthalmitis.<sup>68</sup> (C/B),<sup>177</sup> (A/A),<sup>182</sup> (B/B) Glaucoma is more likely to occur in people with associated preoperative retinal detachment.<sup>177</sup> (A/A)

### c. Intraocular Steroids

The pathogenesis of diabetic retinopathy and DME is multifactorial, involving both angiogenic and inflammatory pathways. The anti-inflammatory and anti-angiogenic properties of intraocular corticosteroids may provide benefit in the treatment of PDR and DME. However, the exact role of intraocular steroids in the treatment for PDR and DME remains to be fully established.<sup>183</sup>

The use of intravitreal triamcinolone acetonide (IVTA) injections and intraocular corticosteroid sustained release drug delivery systems for the treatment of DME has been shown effective in decreasing macular thickness and improving visual acuity.<sup>177</sup> (A/A),<sup>184</sup> (B/B),<sup>185</sup> (B/B)

The use of 4 mg intravitreal triamcinolone acetonide shows a beneficial effect for DME, but repeated injections are needed every 3 to 4 months to maintain the benefit, which decreases to baseline by 6 months.<sup>178</sup> (B/B) The use of IVTA has been associated with a substantial risk of adverse events. In particular, the risk of elevated intraocular pressure and the rates of visually significant cataracts were substantially higher compared to eyes receiving focal/grid laser treatment.<sup>64</sup> (A/A)

IVTA injections given as monotherapy for DME have been shown to result in inferior outcomes compared to focal/grid laser treatment. Focal/

grid photocoagulation is more effective with respect to both visual acuity and OCT-measured retinal thickening and has fewer side effects than intravitreal triamcinolone in most patients with DME.<sup>64</sup> (A/A) When combined with focal/grid laser treatment, the benefit of IVTA injections is comparable to anti-VEGF injections only in pseudophakic eyes.<sup>67</sup> (A/A) Triamcinolone plus prompt grid photocoagulation is effective in pseudophakic eyes.<sup>67</sup> (A/A) There is no evidence that lower doses of intravitreal triamcinolone acetonide than the standard 4 mg dose have more benefits or fewer adverse effects.

Intravitreal steroid implants may avoid the complications resulting from repeat injections of IVTA and may have a more sustained effect. However, they also increase the risk of cataract progression and elevated IOP.<sup>184</sup> (B/B)

### d. Vascular Endothelial Growth Factor Inhibitors

The use of anti-VEGF agents has substantially changed the treatment of DME. Intraocular injection of anti-VEGF agents is considered to be the standard of care in patients with center-involved DME and best corrected visual acuity of 20/32 or worse.<sup>64</sup> (A/A) Repeated intravitreal administration of anti-VEGF agents has been shown to be more effective than conventional focal/grid laser alone in the treatment of DME.<sup>67</sup> (A/A)

**ACTION:** The current standard of care for treatment of center-involved diabetic macular edema (DME) in persons with best corrected visual acuity of 20/32 or worse, is anti-VEGF injections.<sup>64,67</sup> [Evidence Strength: A, Recommendation: A]

The combination of anti-VEGF injection of ranibizumab plus prompt or deferred photocoagulation provides better visual outcomes than grid photocoagulation alone.<sup>67</sup> (A/A)

Anti-VEGF treatment for CSME combined with either prompt or delayed focal laser photocoagulation provides improved visual acuity



outcomes compared to prompt laser treatment alone, through at least two years of follow-up.<sup>71</sup>(A/B).

Deferral of focal/grid laser following anti-VEGF treatment for at least 24 weeks may achieve better visual outcomes compared to eyes receiving prompt focal/grid laser treatment, since nearly 50 percent of eyes do not need laser treatment.<sup>71</sup>(A/B)

Focal/grid laser at the initiation of intravitreal ranibizumab is no better, and possibly worse, than deferring laser for at least 24 weeks in eyes with DME involving the fovea with vision impairment. Intravitreal ranibizumab injections with or without prompt laser at 1 year are more effective compared to prompt laser alone for the treatment of DME involving the central macula with visual impairment. Furthermore, focal/grid laser at the initiation of intravitreal ranibizumab is no better, and is possibly worse than, deferring laser for at least 24 weeks in these eyes. The beneficial effect has been shown to continue to at least 3 years with a reduction in the number of injections at years 2 and 3.<sup>71</sup>(A/B)

Following ischemic events, VEGF has a pivotal role in promoting collateral vessel formation, which is particularly important in persons with diabetes who are at increased risk of having cardiovascular and peripheral vascular events. Therefore, long-term systemic VEGF inhibition can result in increased risk of ischemic and thromboembolic events. The risk of such events with systemic administration was found to be 5 percent. However, these patients received anti-VEGF intravenous doses that were several hundredfold what is typically given intravitreally. Commonly administered intravitreal doses of anti-VEGF therapy are approximately 1/400 or less of the usual systemic dose. Nevertheless, the possibility of systemic adverse side effects exists.<sup>186</sup>

Currently available anti-VEGF agents:

- Pegaptanib (Macugen®) is FDA approved for the treatment of wet age-related macular degeneration and is used off-label for other

indications, including DME.

- Ranibizumab (Lucentis®) is FDA approved for treatment of wet age-related macular degeneration, retinal vein occlusion and DME. The dose for DME is 0.3 mg, compared to the 0.5 mg dose for wet age-related macular degeneration and retinal vein occlusion.
- Aflibercept (Eyelea®) is FDA approved for the treatment of wet age-related macular degeneration and central retinal vein occlusion. The dose is 2 mg in 0.05 mL given intravitreally.
- Bevacizumab (Avastin®) is approved for treatment of cancer and its systemic use is known to be associated with an increased risk of stroke. It is unknown if a substantially smaller dose, when used intravitreally, has any significant systemic toxicity.<sup>177</sup>(A/A) It is used off-label for the treatment of DME. Intravitreal bevacizumab results in superior visual outcomes compared to focal/grid laser treatment over 2 years.<sup>180</sup>(A/A)

Ocular adverse events resulting from the intravitreal injection itself include endophthalmitis, ocular inflammation, retinal detachment, vitreous hemorrhage and traumatic cataract. Data from more than 2,009 injections administered in clinical trials employing the same standardized procedure for the preparation and intravitreal injection using preservative-free triamcinolone in pre-filled syringes has reported only one case of endophthalmitis (0.05 percent).<sup>187</sup>

Multiple studies suggest that there are significant benefits from anti-VEGF treatment for DME in terms of visual acuity improvement and decrease in retinal edema. Two- and three-year data on safety and efficacy of anti-VEGF therapies for DME have reported significantly better outcomes compared to focal/grid laser while maintaining limited adverse events. However, focal/grid laser treatment still remains an effective treatment modality in patients with noncenter involved DME

or in patients unable to tolerate intravitreal injection modality in patients with noncenter involved DME (e.g. those with noncenter involved CSME or vision better than 20/32) or in patients unable to tolerate intravitreal injections.

### 3. Telehealth Programs

Ocular telehealth programs can be an integral component of primary care for patients with diabetes. Telehealth programs can increase access and adherence to demonstrated standards of care among individuals with diabetes.<sup>188</sup> Studies across multiple populations demonstrate that the prevalence of blindness and visual impairment among patients with diabetes is lowest among populations with a national telehealth program that provides retinal evaluations for all patients with diabetes.<sup>189-191</sup>

The implementation of national coverage of universal retinal evaluation for all patients with diabetes mellitus has been shown to reduce the incidence of blindness among patients with diabetes by as much as 95 percent.<sup>192,193</sup> Telehealth programs have been largely used in these initiatives and rely on the digital capture and transmission of standardized ocular images and patient health information for interpretation and evaluation by trained observers who can generate a treatment and care plan. These programs may substantially assist in the accurate detection and evaluation of individuals at risk for or having sight-threatening diabetic retinopathy.<sup>188</sup>

Ocular telehealth programs for diabetic retinopathy have the potential to preserve vision and prevent vision loss by increasing access to evaluation, educating patients and promoting appropriate follow-up and treatment. Telehealth has the potential to deliver economical, high quality eye care locally, nationally and internationally.<sup>194</sup> (B/A) These programs integrate appropriately validated digital retinal imaging systems with standardized methods of image acquisition and review that provide high levels of sensitivity and specificity, and agreement with dilated standard photography or clinical examination for the detection and assessment of the severity of diabetic retinal disease when implemented appropriately.<sup>188</sup>

However, telehealth-based retinal evaluations are not a substitute for a comprehensive eye examination by an eye care professional.

### 4. Patient Education

The vast majority of persons with diabetes will develop diabetic retinopathy at some point during the course of the disease. Therefore, it is important for them to learn about the disease process and the risks for developing ocular complications of diabetes that may result in vision loss. Individuals need to be aware that retinopathy may exist even when vision is good and in the absence of any symptoms.

Persons should be encouraged to report all ocular symptoms (e.g. blurred vision, flashes and floaters). Optometrists should help patients understand that timely follow-up examinations and management are critical for early diagnosis and intervention, when indicated, to reduce the risk of vision loss from diabetic retinopathy. Individuals should also be informed about their higher risk for other non-retinal ocular complications, such as cataracts, neovascular glaucoma and open angle glaucoma, and informed about available optometric vision rehabilitation care to address loss of visual function. Proper monitoring and timely treatment can result in subsequent saving of sight for persons with diabetes mellitus.

**ACTION:** Persons should be educated about the ocular signs and symptoms of diabetic retinopathy and other non-retinal complications of diabetes, and encouraged to comply with recommendations for follow-up eye examinations and care.

Individuals should also be encouraged to participate in diabetes education programs. Despite substantial improvement during the past decade, achieving the diabetes ABCs recommendations (A1C, blood pressure, cholesterol and smoking cessation) remain suboptimal among adults, particularly in some minority groups (Mexican Americans and non-Hispanic Blacks). Substantial opportunity exists to further improve diabetes control and, thus, to reduce diabetes-related morbidity and mortality.<sup>195</sup>

In addition, there is a clear need to increase the frequency of smoking cessation counseling for patients with diabetes, given the strong association between smoking and diabetes complications.<sup>196</sup>

**ACTION:** Individuals should be advised of the risks of smoking related to diabetes and encouraged to quit smoking and/or seek smoking cessation assistance.

Diabetes education programs should not just provide information, but involve the person in making well-informed choices. Research has shown that individuals with diabetes, who actively participate in an empowerment-based approach to diabetes education, are substantially more likely to accurately recall the meaning of the diabetes ABCs, recall their own personal ABCs, and know their clinical target ABCs, than those receiving traditional education.<sup>197</sup> (B/B)

Intensive diabetes education, defined as adoption of behaviors that allow for active engagement in diabetes self-management, is more effective in lifestyle behavior modification and glycemic control in newly or recently diagnosed individuals with diabetes compared to patients with a longer duration of diabetes.<sup>198</sup> (C/B) A structured, group-based educational program focusing on self-management can further improve A1C levels, even in patients who are well controlled.<sup>199</sup> (C/B) In addition, the use of culturally appropriate diabetes health education programs for socio-economically disadvantaged ethnic groups appears to be effective in improving glycemic control and increasing knowledge of diabetes and healthy lifestyles, at least in the short term.<sup>200</sup> (B/B)

Improved A1C control is associated with health care providers who more effectively communicate with persons who have type 2 diabetes.<sup>201</sup> (C/B) In addition, providing them with personalized clinical information during a consultation can increase their involvement and make them more likely to take the lead in discussing aspects of their diabetes care.<sup>202</sup> (B/B)

Persons should be informed of the relationship between the level of glycemic control and the risk of

developing ocular and other medical complications. Specific emphasis should be placed on the benefit of reduction in elevated A1C in lowering the risk of damage. A one percent rise in A1C (e.g. from 7 to 8 percent) increases the risk of progression of non-proliferative retinopathy by 44 percent over a 10-year period. For the individual with proliferative retinopathy, the same one percent increase in A1C results in 145 percent progression over 10 years.<sup>60,92,203</sup>

**ACTION:** Individuals should be educated about the long-term benefits of glucose control in saving sight, based on their individual medically appropriate A1C target.

Those with diabetic retinopathy have a measurable decline in health-related quality of life early in the disease process. This decline is much greater and more rapid in persons with bilateral moderately severe NPDR or worse, compared with those with no diabetic retinopathy or less severe diabetic retinopathy.<sup>204</sup> (C/B) Therefore, it is important to also consider psychological and emotional support for patients with diabetes mellitus, especially those with longer diabetes duration or diabetes complications, to maximize the effectiveness of diabetes education. Diabetes “burn-out” or diabetes-related stress influences patient self-care behaviors.<sup>198</sup> (C/B) Special care is also indicated in counseling elderly patients. Their risks and benefits may be different; therefore, as with all persons, the discussion and instruction should be individualized.<sup>205</sup>

The use of a team approach to providing supportive care for people with diabetes can help reduce risk factors for type 2 diabetes, improve diabetes management and lower the risk for chronic complications.<sup>206</sup> (C/B)

It is helpful to advise individuals about organizations that provide resources and support for people with diabetes. (A list of organizations is available from the AOA Clinical Resources Group.)

## 5. Prognosis and Follow-Up

Disability and premature death are not inevitable

consequences of diabetes.<sup>9</sup> Lifestyle and behavioral modification, and pharmacotherapy, can delay progression to type 2 diabetes among persons with prediabetes.<sup>86</sup> (A/B) Physical activity, dietary interventions, and, when needed, medications can also help control the effects of diabetes.

All persons with diabetes mellitus are at risk for the development of ocular-related complications. Adherence to treatment recommendations to maintain optimal control of blood glucose levels is a substantial factor in slowing the development and progression of complications of diabetes.

Recent studies indicate that the rates of progression to PDR and severe vision loss are substantially lower, especially in individuals with type 1 diabetes, than reported thirty or more years ago. These findings may be due to improvements in the management of risk factors (hyperglycemia, hypertension and hyperlipidemia) and overall diabetes care, along with earlier identification of diabetes.<sup>115</sup>

Regular retinal examinations can identify diabetic retinopathy before it causes visual loss. Epidemiological studies have shown that the major predictors of retinopathy progression are the presence and severity of retinopathy at the time of the patient's initial eye examination.<sup>207</sup>

The follow-up examination of persons with diabetic retinopathy should be scheduled in accordance with recommendations in this Guideline. Proper diagnosis is crucial because misdiagnosis by just one level underestimates a patient's risk of developing PDR in 1 year by 50 percent or more.

Laser photocoagulation greatly improves the prognosis for maintaining useful vision. Scatter (panretinal) laser photocoagulation reduces the risk of severe vision loss (best visual acuity  $\leq$  5/200) to less than 2 percent per patient. Anti-VEGF injections for center-involved diabetic macular edema reduce the risk of moderate visual loss to less than 5 percent, with nearly 50 percent of patients gaining 10 or more letters of visual acuity.

Appropriate communication with the patient's primary care physician (as with any referral consultant) is critical for proper coordination of the patient's care. Due to the nature of diabetes, a multidisciplinary approach to the management of individuals with diabetes is essential. All health care personnel involved with the individual's care should be aware of his or her overall medical status. Written letters or reports are useful in accomplishing this task. These letters also provide permanent documentation for the patient's record.

## **B. MANAGEMENT OF SYSTEMIC COMPLICATIONS AND COMORBIDITIES OF DIABETES MELLITUS**

The management of persons with diabetes mellitus includes individualized glucose targets and lifestyle modifications. The individual's age, weight, comorbidities, race/ethnicity, and physiologic differences need to be considered in determining treatment.<sup>78,208</sup> (C/B)

Some individuals with type 2 diabetes can achieve adequate glycemic control with weight reduction, exercise and/or oral glucose-lowering agents and do not require insulin. Others, who have only limited residual insulin secretion, often require insulin for adequate glycemic control. Individuals with type 1 diabetes, who have extensive beta-cell destruction and therefore no residual insulin secretion, require insulin for survival.<sup>6</sup>

### **1. Glycemic Control**

While previous standards for diabetes management emphasized the need to maintain glucose levels as near to normal as safely possible, current standards emphasizes individualization. According to the American Diabetes Association, reducing A1C levels to less than 7 percent has been shown to reduce microvascular complications; therefore, it is a reasonable goal for many nonpregnant adults.<sup>78</sup>

For individuals with short duration of diabetes, long life expectancy and no significant cardiovascular disease, a more stringent A1C goal (<6.5 percent)

may be reasonable, if it can be achieved without significant hypoglycemia. For individuals with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive co-morbid conditions, a less stringent A1C goal, such as <8 percent, may be appropriate.<sup>78</sup>

**ACTION:** The glycemic goal for persons with diabetes should be individualized, taking into consideration their risk of hypoglycemia, anticipated life expectancy, duration of disease and co-morbid conditions.<sup>78</sup>

A recent consensus statement for managing diabetes during pregnancy recommends that pregnant women with pre-existing type 1 or type 2 diabetes who become pregnant maintain an A1C goal of <6 percent throughout pregnancy, if it can be achieved without excessive hypoglycemia.<sup>209</sup>

In persons with type 2 diabetes mellitus, intensive glucose control may reduce microvascular disease, retinopathy, nephropathy, cataract and neuropathy,<sup>210</sup> (B/B) non-fatal myocardial infarction and lower extremity amputation. However, in light of recent trials such as ACCORD<sup>211</sup> ADVANCE<sup>212</sup> and VADT,<sup>213</sup> cardiovascular disease is less clearly impacted by the degree of glycemic control.

Intensive glucose control in individuals with type 2 diabetes and established cardiovascular disease or additional cardiovascular risk factors (hypertension, dyslipidemia, smoking) should not be recommended due to the increased risk for death.<sup>211</sup> (A/B)

In addition, intensive control has been shown to have no significant impact on the risk for nonfatal heart attack or stroke, as well as death from cardiovascular causes, and cannot be recommended as a strategy for reducing such events in individuals with type 2 diabetes.<sup>212</sup> (A/A) Intensive control (A1C of 6.5 percent versus 7.3 percent) also showed no benefit for reducing the risk of new or worsening retinopathy over 5 years.<sup>212</sup> (A/A)

While achieving tight glycemic control may reduce

some diabetes related complications, it also increases the relative risk of severe hypoglycemia by 30 percent.<sup>214</sup> (A/B) In addition, the added benefits of a 1 percent reduction in A1C (e.g. 8 to 7 percent) diminish with age.<sup>210</sup> (B/B)

Hypoglycemia is defined as a plasma glucose level below 70 mg/dL, which is confirmed when symptoms are relieved after eating. The classic symptoms of hypoglycemia are hunger, shakiness, nervousness, sweating, or weakness.<sup>215</sup> While hypoglycemia is more common in type 1 diabetes, the incidence is also high in individuals with type 2 diabetes who use insulin or secretagogues, particularly those with longer duration of diabetes.<sup>216</sup>

It is common for individuals with diabetes to experience symptoms suggestive of hypoglycemia even with above-normal glucose levels, if they have had chronically elevated blood glucose. However, as persons experience more frequent low blood glucose, they gradually lose the classic symptoms of hypoglycemia due to defective glucose counter regulation (hypoglycemia unawareness).<sup>216</sup> To help identify persons experiencing hypoglycemia, the staff should be alert for neuroglycopenic symptoms such as slow cognitive response, light-headedness, sleepiness, confusion, difficulty speaking, and anxiety. It may be prudent for optometrists' offices to maintain a blood glucose meter and single use lancet devices for confirming hypoglycemia and its resolution where state laws permit.

The treatment of a hypoglycemic episode may include:<sup>217</sup>

1. Check blood glucose to confirm hypoglycemia (blood glucose <70 mg/dL).
2. If patient is conscious, give 15 g of simple carbohydrates orally as immediate treatment. Options include 4 oz of fruit juice, 5 to 6 oz regular soda, 1 tablespoon of table sugar or honey, 7 to 8 Lifesaver candies, 3 tablespoons of jelly, 2 tablespoons of raisins, or 4 to 5 glucose tablets. If initial blood glucose is less than 50 mg/dL, give 30 g of simple

carbohydrates.

3. Re-check blood glucose after 10–15 minutes. If blood glucose is less than 70 mg/dL repeat the treatment (step 2) until blood glucose returns to at least 90 mg/dL.

4. Follow with a meal or snack such as 6 saltine crackers, 3 graham cracker squares or 1/2 peanut butter sandwich. Further glucose monitoring may be necessary.

5. Activate 911, if patient is unconscious. Inject glucagon intramuscularly, if it is available in the office.

6. When the person is alert enough to swallow, give fruit, fruit juice or sugar-sweetened soda immediately and follow steps 2 to 4.

**ACTION:** Optometrists should have a rapid-acting carbohydrate (e.g. glucose gel or tablets, sugar-sweetened beverage or fruit juice) in their office for use with diabetes patients who experience acute hypoglycemia during an eye examination.

## 2. Blood Pressure Control

Hypertension is a common comorbidity of diabetes mellitus and a major risk factor for cardiovascular disease (CVD) and microvascular complications. Slight variations in optimum blood pressure for people with diabetes can be cited in the literature. Blood pressure of <140/80 mmHg has been recommended for most patients with diabetes.<sup>78</sup> Lower systolic blood pressure of <130 mmHg may be appropriate for younger individuals. Treatment may include life style modifications, (e.g. weight loss, diet changes, exercise) along with pharmacological agents, when needed.<sup>78</sup>

The impact of blood pressure control on the progression of diabetic retinopathy is unclear. The ACCORD Eye Study<sup>218</sup> (B/B) and the ADVANCE Retinal Measurements Study<sup>219</sup> (B/B) looked at intensive blood pressure control versus standard blood pressure control. The studies did not find a significant effect on the progression of diabetic

retinopathy in patients with type 2 diabetes mellitus, although the ADVANCE study reported that a consistent trend toward a benefit was observed. However, the Wisconsin Epidemiologic Study of Diabetic Retinopathy showed that elevated blood pressure and A1C are directly related to the development of DME and CSME in type 1 diabetes mellitus, and persons with elevated blood pressure need to be evaluated earlier for DME and CSME and treated more aggressively.<sup>111</sup> (B/A)

## 3. Lipid-Lowering Treatment

Individuals with type 2 diabetes mellitus have an increased prevalence of lipid abnormalities, which contributes to a higher risk for CVD. Lowering LDL cholesterol to <100 mg/dL is a recommended goal for individuals without overt CVD. However, in individuals with overt CVD, LDL <70 mg/dL is recommended.<sup>78</sup> This level may be achieved through lifestyle modifications (e.g. reduction in saturated fats and cholesterol, weight loss, increased physical activity), along with statin therapy.<sup>78</sup>

**ACTION:** The majority of persons with diabetes are at risk of coronary heart disease and can benefit from reducing low-density lipoprotein (LDL) cholesterol levels to the currently recommended targets.<sup>220</sup> [Evidence Strength: B, Recommendation: B]

As a preventive approach, persons with diabetes should be treated as if they have cardiovascular disease. In the absence of severe hypertriglyceridemia, therapy targeting HDL cholesterol or triglycerides lacks the strong evidence base of statin therapy.<sup>78</sup>

Statins (e.g. simvastatin, lovastatin, atorvastatin) are the first choice agents for reducing high cholesterol. According to the ADA, statin therapy should be initiated for diabetic patients without regard for baseline lipid level in those with overt CVD or those without CVD who are over age 40 and have one or more other CVD risk factors (family history of CVD, hypertension, smoking or albuminuria).<sup>78</sup>

Combination therapy with a statin and other classes of lipid lowering agents may be used to further reduce LDL levels; however, this approach has not been demonstrated to provide additional cardiovascular benefit above statin therapy alone.<sup>78</sup> There is emerging evidence that normalizing blood lipid levels may also reduce the risk of retinopathy. Intensive treatment of dyslipidemia using a combination of simvastatin and fenofibrate, along with intensive glucose control, has been shown to slow the rate of progression of diabetic retinopathy in type 2 diabetes mellitus.<sup>218</sup> (B/B) Fenofibrate may also have a role in reducing the risk of diabetic retinopathy and its progression independent of its lipid modifying action.<sup>221</sup> (B/B)

#### 4. Cardiovascular Risk Reduction

The major cause of death and complications in individuals with type 2 diabetes mellitus is cardiovascular disease. Persons with type 2 diabetes have a substantially increased risk of cardiovascular disease compared with persons without diabetes of similar age and need to be treated aggressively.<sup>208</sup> (C/B), <sup>222</sup> (B/B)

Successful prevention and treatment of CVD risk factors have reduced the burden of coronary heart disease among U.S. adults with diabetes over the past decade.<sup>223</sup> Significant progress has been achieved when multiple risk factors such as blood pressure control, lipid management, antiplatelet agents and smoking cessation are addressed globally.<sup>224</sup>

#### 5. Physical Exercise

Exercise is a vital component for the prevention and management of type 2 diabetes. The benefits are greatest when used early in the course of the disease.<sup>225</sup>

Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss and improve well-being. Regular exercise may also help prevent type 2 diabetes in high-risk individuals.

It is recommended that all persons with diabetes participate in at least 150 minutes per week of moderate-intensity aerobic exercise, spread over at least 3-days per week, and unless contraindicated, perform resistance training at least twice per week.<sup>78</sup>

#### 6. Weight Management

Being overweight or obese is associated with increased risk of developing type 2 diabetes. It is important for individuals to understand this association, as well as how to prevent or remedy excess body weight through dietary modification and increased physical activity. Among those who have pre-diabetes or are at high risk for developing type 2 diabetes, a modest weight reduction of 5 to 7 percent combined with 150 minutes of physical activities per week significantly reduces the likelihood of developing diabetes.<sup>89</sup>

Very obese adults, who are at high risk for developing diabetes, can reduce their cardiometabolic risk with primary care weight management. Modest weight loss (5 percent to 9.9 percent) during a one-year period is an appropriate short-term goal for people who are severely obese.<sup>226</sup> (B/B) Behavioral modification such as medical nutrition therapy and physical activity are essential elements of weight loss programs and are especially critical in the weight maintenance phase.<sup>78</sup>

Although bariatric surgery is effective for reducing weight and may be considered for adults with BMI  $\geq 35$  kg/m<sup>2</sup> and type 2 diabetes, the long-term benefits, cost-effectiveness and risks of bariatric surgery need to be more rigorously studied.<sup>78</sup>

**ACTION:** When indicated, overweight individuals should be referred to a qualified health care provider for assistance with weight loss.

#### 7. Treatment Modalities

Among adults with either type 1 or type 2 diabetes, the percentage receiving treatment using one of the following methods<sup>8</sup> is:

- Insulin only – 12 percent

- Insulin and oral medications – 14 percent
- Oral medications only – 58 percent
- No insulin or oral medications – 16 percent

Specific treatment modalities include:

- **Medical nutrition therapy** - Dietary recommendations need to take into account the individual's total daily caloric requirements and promote weight control to achieve an ideal body weight. Recommended carbohydrate, protein and fat intake levels can be determined using ADA Guidelines.<sup>227</sup> If used early in the disease, nutritional therapy and weight loss may be sufficient for controlling type 2 diabetes in many individuals.

**ACTION:** Individuals with diabetes should receive nutrition and dietary recommendations preferably provided by a registered dietician who is knowledgeable about diabetes management.

- **Oral medications** – A variety of classes of medications are available to treat type 2 diabetes.<sup>228</sup> The specific agents are listed in Table 6:

**Biguanides**, which block hepatic glucose production (nocturnal gluconeogenesis), are a first-line pharmacological agent for treatment of diabetes.

**Sulfonylurea compounds**, which stimulate the pancreas to release more insulin. Their use also reduces hepatic glucose production and increases the number of insulin receptors.

**Alpha-glucosidase inhibitors**, which block starch, sucrose and maltose absorption.

**Meglitinides** (repaglinide, nateglinide) increase insulin secretion, but their effect typically is shorter than that of sulfonylureas.

**Thiazolidinediones** (pioglitazone, rosiglitazone), which decrease insulin resistance by enhancing insulin-mediated glucose disposal by muscle/fat.

**Dipeptidyl peptidase (DPP) 4 inhibitors** (sitagliptin, saxagliptin, linagliptin) are another category of oral medications that prolong the action of incretin hormones and regulate the level of insulin produced after a meal.

**Bile acid sequestrant** (colesevelam) is a medication that is a non-absorbed lipid and glucose lowering resin that binds bile acids in the digestive track. Its mechanism of action in reducing glucose levels is unknown.

**Dopamine agonist** (bromocriptine) works by modulating hypothalamic dopamine levels and reducing sympathetic tone, resulting in reduced postprandial glucose levels.


**SGLT2 inhibitor** (canagliflozin) lowers blood glucose by blocking re-absorption of glucose and increasing its excretion in urine.

**Amylin agonist** (pramlintide) is an injectable therapy that works by slowing gastric emptying, promoting satiety in the brain and inhibiting excessive glucagon secretion. Native amylin is co-secreted by the B-islet cells.

**GLP-1 mimetics/analogs** (liraglutide, exenatide) is an injectable therapy that works by delaying gastric emptying, centrally suppressing appetite, stimulating insulin secretion and suppressing excessive glucagon secretion. Native GLP-1 is secreted by the gut.

- **Insulin** - The many forms of insulin are classified by how fast they start to work and how long their effects last. Rapid-acting insulin, such as lispro, aspart and glulisine, starts working in 15 minutes and lasts 3 hours. A rapid-acting insulin allows the individual to control postprandial hyperglycemia more





effectively. Most patients require some type of multiple or split dosage regimen to maintain adequate blood glucose control.

The basal insulins, glargine and detemir, mimic continuous, endogenous background insulin secreted by the pancreas and have a slow-release, long-acting effect to help control glucose levels throughout the day and night. All insulins may be administered by subcutaneous injection. Only short- or rapid-acting insulins are delivered by continuous subcutaneous insulin pump infusion.

The use of combination oral therapies and oral therapies combined with insulin is increasing. A combination approach enables the individual to obtain the benefit of synergistic actions of the various medications while reducing adverse effects.<sup>208</sup> (C/B)

### **Self-Monitoring Glucose**

Daily self-monitoring of blood glucose by the patient with a glucose monitor is a well-accepted practice. Such monitoring, which is absolutely necessary for intensive management programs, should be encouraged for all persons with diabetes.<sup>78</sup> Continuous glucose monitoring systems (CGMS), which measure interstitial glucose levels, are increasingly being used by insulin-dependent persons with diabetes and have been shown to improve glycemic control in several studies.<sup>229</sup>

<b>TABLE 6</b>				
<b>Diabetes Medication</b>				
<b>Class</b>	<b>Examples</b>	<b>Hypoglycemic potential (Used alone)</b>	<b>Injectable</b>	<b>A1C reduction</b>
Biguanides	Metformin	minimal	No	1.5-2%
Sulfonylurea & glinides	Glyburide Glipizide Glimepiride Nateglinide Repaglinide	Yes	No	1-2%
Alpha-glucosidase inhibitor	Acarbose Miglitol	Minimal	No	0.5-1%
Thiazolidinedione	Rosiglitazone Pioglitazone	Minimal	No	0.6-1.9%
DPP-IV inhibitor	Sitagliptin Linagliptin Saxagliptin	Minimal	No	0.6-0.8%
Bile acid sequestrant	Colesevelam	Minimal	No	0.5-0.6%
Dopamine agonist	Bromocriptine	Minimal	No	0.6-1.0%
SGLT2-inhibitor	Canagliflozin	Minimal	No	0.9-1.1%
GLP-1 agonist/ analog	Exenatide Exenatide LAR Liraglutide	Minimal	Yes	0.8-1.2%
Amylin analog	Pramlintide	Yes (when used with insulin)	Yes	0.6%

## C. MANAGEMENT OF PERSONS WITH VISUAL IMPAIRMENT

Individuals with diabetes are at increased risk of chronic vision loss, subsequent functional impairment, and resultant disability. Common visual impairments associated with diabetic retinopathy include:

- Reduced central visual acuity affecting near, intermediate, and distance visual function
- Central or para-central scotoma from diabetic maculopathy
- Loss of peripheral and mid-central visual field, secondary to retinal ischemia or panretinal laser photocoagulation
- Reduced dark adaptation and increased lag times in seeing in dim light
- Difficulty with glare
- Vision loss resulting from vitreous hemorrhage or preretinal hemorrhage, or traction retinal detachment
- Decreased contrast sensitivity

In addition, important functional sequelae of diabetes-related vision loss can include:

- Inability to self-manage diabetes care, including monitoring of blood glucose
- Difficulty addressing dietary, medical, and other health-related issues
- Difficulty with other health care tasks (such as checking feet and trimming nails)
- Loss of, or restriction in, driver's license and subsequent limitations on independent transportation
- Inability to maintain wellness and comply with preventive health measures

Persons with diabetes-related vision loss should be evaluated to determine their potential to benefit from comprehensive vision rehabilitation. This process provides the only currently available treatment options for those with chronic vision loss. Vision rehabilitation\* can help individuals with vision loss attain maximum function, independence and quality of life.

\*Refer to *AOA Clinical Practice Guideline on Care of the Patient with Visual Impairment*

**ACTION:** Individuals who experience vision loss from diabetes should be provided, or referred for, a comprehensive examination of their visual impairment by a practitioner trained or experienced in vision rehabilitation.

Visual impairment also has physical, psychological, behavioral and social consequences that affect patients, their family, friends and caregivers. Health care providers and stakeholders may be unaware of the overall impact of vision loss on the health and well-being of the patient.

**ACTION:** Persons with diabetes who experience visual difficulties should be counseled on the availability and scope of vision rehabilitation care and encouraged to utilize these services.

The Veterans Affairs model for treatment of vision impairment has demonstrated effectiveness in patients with vision impairment resulting from macular diseases. The Veteran Affairs model involves at least 10 hours of low-vision therapy, including a home visit and assigned homework to encourage practice, for patients with moderate and severe vision loss from macular diseases.<sup>230</sup> (B/B)

Vision-related quality of life is influenced strongly by nonvisual factors, particularly physical and mental health.<sup>231</sup> (C/B) The fear of vision loss associated with diabetic retinopathy can result in a high level of anxiety for any individual with diabetes, and for their family members, regardless of the level of visual impairment.<sup>232,233</sup> Even those without retinopathy or other ocular complications may have personal concerns about diabetes (e.g. problems accepting

the disease, adapting to it and adjusting to emotional and social changes). An early counseling visit may be beneficial for a family with a child who has diabetes.

**ACTION:** Referral for counseling is indicated for any individual experiencing difficulty dealing with vision and/or health issues associated with diabetes or diabetic retinopathy. Educational literature and a list of support agencies and other resources should be made available to these individuals.

## D. SUMMARY

The Institute of Medicine's report *Living Well with Chronic Illness* highlights various chronic illnesses, including diabetes and vision loss. Chronic illnesses have diverse outcomes, including emotional distress, physical impairments and age-related degenerative problems that detract from the quality of life.

While preventive care is best, until therapies are available to prevent or cure diabetic retinopathy and other complications of diabetes, emphasis must be placed on proper diagnosis, careful follow-up, timely treatment and vision rehabilitation for individuals with diabetic eye disease.

These individuals should be encouraged to see their diabetes care providers to work toward achieving good diabetes control. Proper care will result in reduction of personal suffering and a substantial cost savings for the involved individuals, their families and the country as a whole.

All persons with diabetes should be informed of the possibility of developing retinopathy or other non-retinopathy ocular complications, with or without symptoms, and of the associated threat of vision loss. The natural course and treatment of diabetic retinopathy should be discussed with the person and the importance of lifelong eye examinations should be stressed.

In addition, they should be advised of the availability of vision rehabilitation to address functional issues related to vision loss, and provided with referral or treatment for diabetes-related vision loss.

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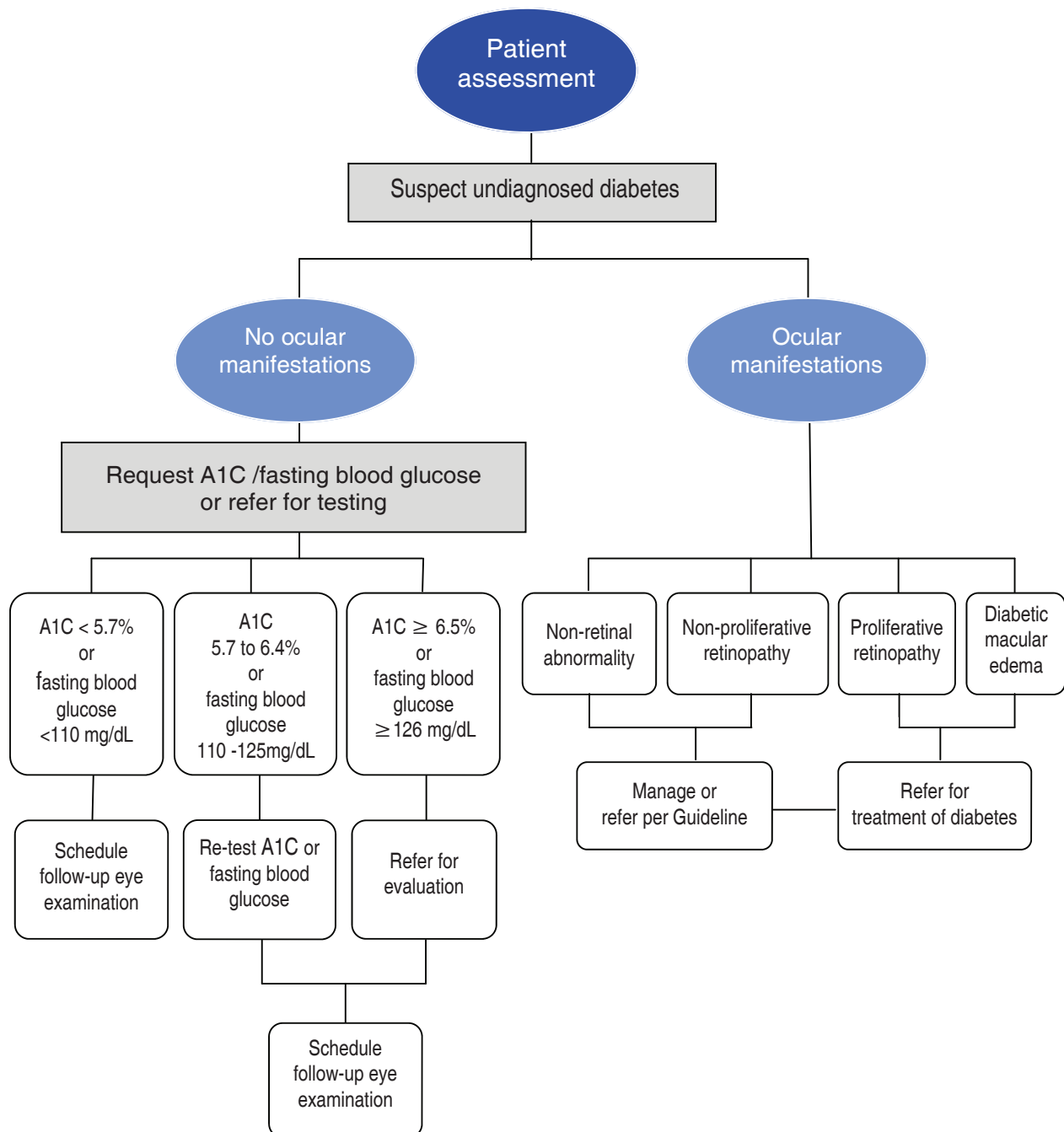


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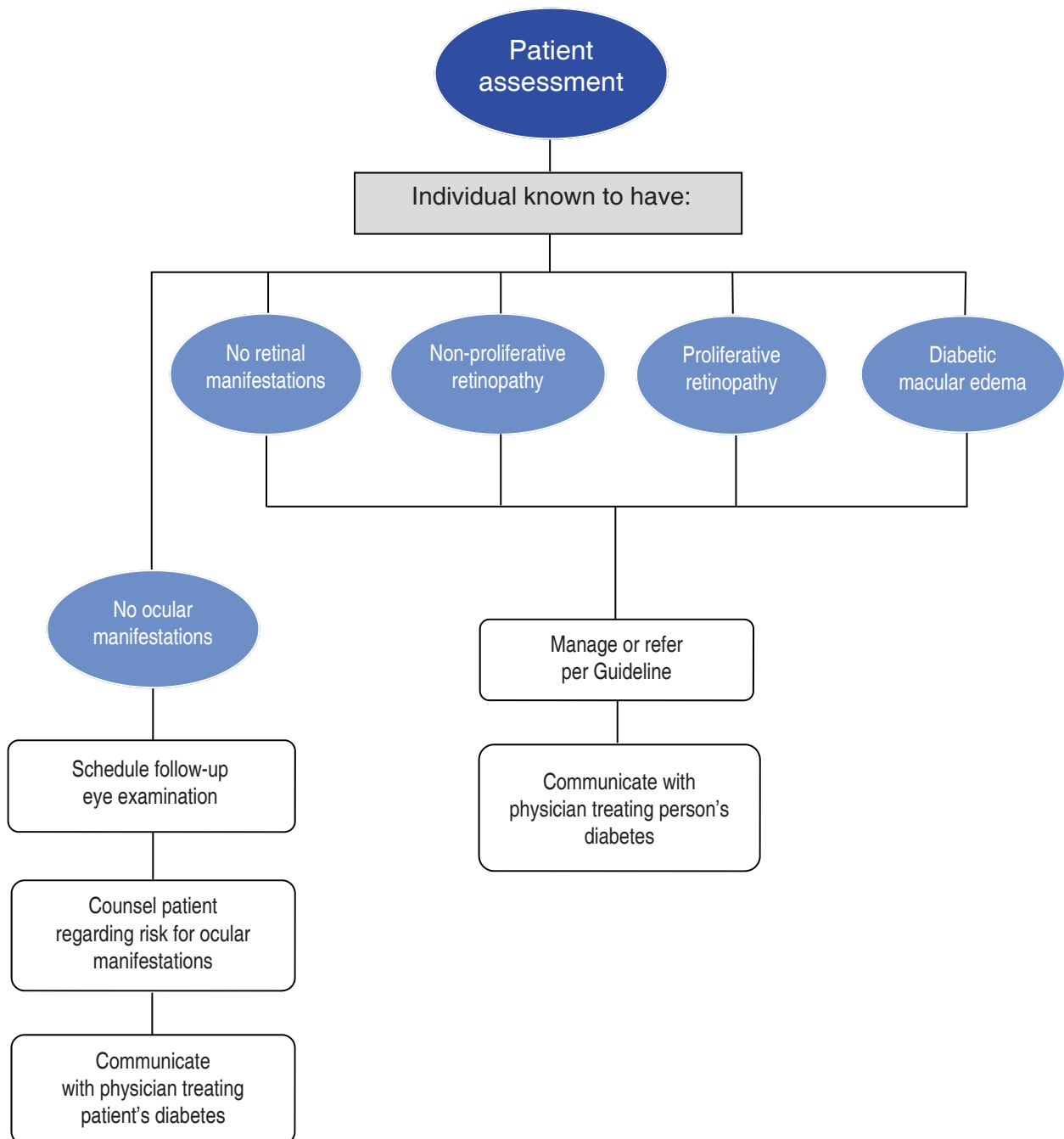
## APPENDIX FIGURE 1

### Optometric Management of the Patient With Undiagnosed Diabetes Mellitus: A Flowchart



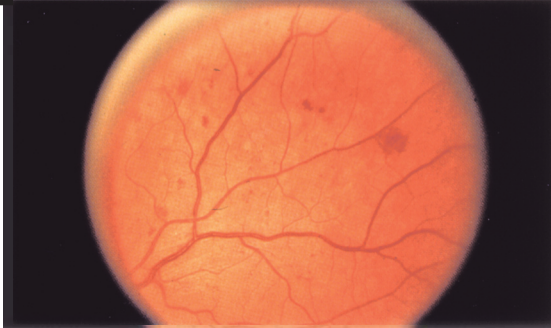
## APPENDIX FIGURE 2

### Optometric Management of the Patient With Diagnosed Diabetes Mellitus: A Flowchart



**APPENDIX FIGURE 3**

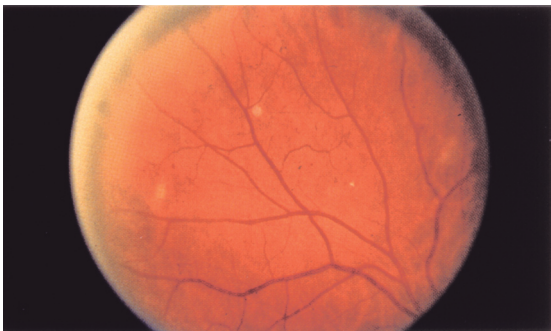
**Early Treatment of Diabetic Retinopathy Study Standard Photographs**



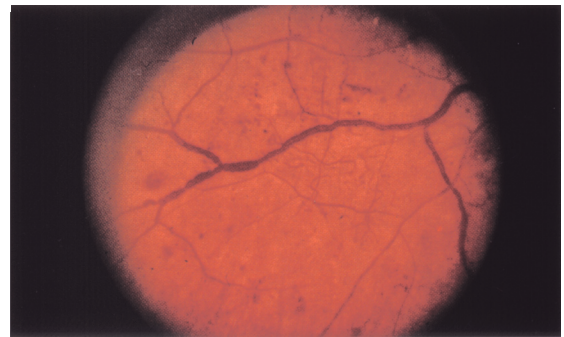
Moderate nonproliferative diabetic retinopathy (standard photograph 2A)



Macular edema



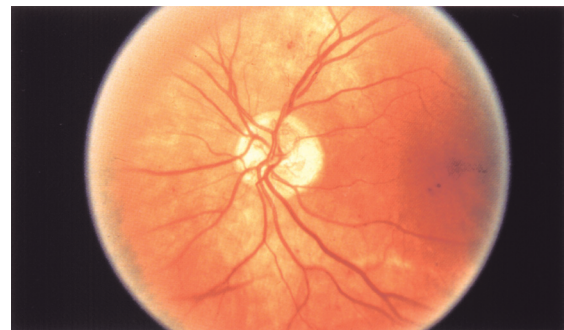
IRMAs (standard photograph 8A)



Venous beading (standard photograph 6B)



NVE (standard photograph 7)



NVD (standard photograph 10A)

Photo references use the Airlie House classification system.

**APPENDIX TABLE 1**  
**Comparison of ETDRS and International Clinical Diabetic Retinopathy**  
**and Macular Edema Severity Scale**

Diabetic Retinopathy	ETDRS	International Scale
No apparent DR		No abnormalities
Mild NPDR	At least one Ma	Ma only
Moderate NPDR	H/Ma > standard photo 2A or soft exudates, VB and IRMA present	More than just Ma, but less than severe NPDR
Severe NPDR	One of the following: <ul style="list-style-type: none"> <li>• H/Ma ≥ standard photo 2A in all 4 quadrants</li> <li>• VB present in at least 2 quadrants</li> <li>• RMA ≥ standard photo 8A in at least 1 quadrant</li> </ul>	No signs of PDR, with any of the following: <ul style="list-style-type: none"> <li>• &gt;20 intraretinal hemorrhages in each of 4 quadrants</li> <li>• Definite VB in ≥ 2 quadrants</li> <li>• Prominent IRMA in ≥ 1 quadrant</li> </ul>
PDR		One or both of the following: Neovascularization, Vitreous/preretinal hemorrhage
Mild PDR	One or more of the following: NVE, FPD or FPE present, NVD and NVE present	
Moderate PDR	One or more of the following: <ul style="list-style-type: none"> <li>• NVE elevated</li> <li>• NVD &lt; standard photo 10A</li> <li>• VH/PRH and NVE &lt; ½ DA</li> <li>• NVD absent</li> </ul>	
High-risk PDR	One or more of the following: <ul style="list-style-type: none"> <li>• NVD ≥ ¼ to 1/3 DA (standard photo 10A)</li> <li>• NVD and VH/PHR</li> <li>• NVE ≥ ½ DA and VH/PRH</li> </ul>	

**APPENDIX TABLE 1 (continued)**

<b>Diabetic Macular Edema</b>	<b>ETDRS</b>	<b>International Scale</b>
DME apparently absent		No apparent retinal thickening or HE in posterior pole
DME apparently present		Some apparent retinal thickening or HE in posterior pole
Mild DME	Retinal thickening within 2 DD of center of the macula	Some retinal thickening or HE in posterior pole, but distant from center of the macula
Moderate DME		Retinal thickening or HE approaching, but not involving, the center of the macula
Severe DME		Retinal thickening or HE involving the center of the macula
CSME	<ul style="list-style-type: none"> <li>• One or more of the following:</li> <li>• Thickening of the retina <math>\leq</math> 500 microns from the center of the macula</li> <li>• HE <math>\leq</math> 500 microns from the center of the macula with thickening of the adjacent retina</li> <li>• A zone or zones of retinal thickening <math>\geq</math> 1 DA in size, any portion of which is <math>\leq</math> 1 DD from the center of the macula</li> </ul>	

**Sources:** Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification. ETDRS Report No. 10. *Ophthalmology* 1991; 98:786-806.

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- DR – Diabetic retinopathy
- NPDR – Non-proliferative diabetic retinopathy
- PDR – Proliferative diabetic retinopathy
- DME – Diabetic macular edema
- CSME – Clinically significant macular edema

*See Abbreviations of Commonly Used Terms on page 74*

## APPENDIX TABLE 2

### Effects of Systemic Medications on the Onset and Progression of Diabetic Retinopathy

#### REVIEWS

<b>Table 1</b>   Effects of currently available systemic medications on diabetic retinopathy					
Systemic agents	Prototypical drugs	Systemic effects	Specific ocular mechanism	References (Author or study)	Implications for diabetes eye-care
<b>Agents for glycemic control</b>					
Insulin	Insulin lispro Insulin glargine Isophane insulin	Regulates carbohydrate, lipid and protein metabolism	Increased VEGF gene expression <sup>36</sup> Alterations in retinal blood flow with improved glycemic control <sup>19</sup>	UKPDS <sup>27,34</sup> DCCT <sup>32</sup> EDIC <sup>30</sup>	Glycemic control with HbA <sub>1c</sub> target of <7% significantly reduces the risk of developing or worsening of DR <sup>27,30,32,34</sup> Risk of early worsening following initiation of intensive control and large reduction in HbA <sub>1c</sub> levels in patients with poorly controlled long-standing DM with moderate NPDR or worse <sup>39</sup> Potentially angiogenic at very high non-physiologic doses <sup>46,47</sup>
Thiazolidinediones	Rosiglitazone Pioglitazone	Improves insulin sensitivity	PPAR $\gamma$ agonist activity <sup>50</sup> Decreased VEGF production <sup>52</sup>	Shen et al. <sup>51</sup> Fong et al. <sup>57</sup>	Delays the onset of PDR <sup>51</sup> May cause DME <sup>56,57</sup>
Biguanides	Metformin	Improves glycemic control Cardioprotective effects	Decreased concentrations of PAI-1 <sup>62</sup> Inhibition of NF $\kappa$ B and TSP-1 <sup>64</sup>	UKPDS <sup>60</sup>	First line oral hypoglycemic agent particularly beneficial in T2DM patients with overweight or obesity and cardiovascular risk factors <sup>59</sup> Clinical implications independent of glycemic control have yet to be fully determined
<b>Agents for lipid control</b>					
Fibrates	Fenofibrate Clofibrate Etofibrate	Improves lipid parameters (increases HDL cholesterol levels, reduces levels of total and LDL cholesterol and triglycerides)	PPAR $\alpha$ agonist activity <sup>70</sup>	FIELD <sup>25</sup> ACCORD Eye <sup>82</sup>	Reduces the need for laser treatment by 31% <sup>25</sup> May reduce the rate of progression in patients with DR <sup>25,76,77</sup> Control of lipid parameters in patients with DME may result in improved visual outcomes <sup>86</sup> Intensive treatment using a combination of fibrates and statins for lipid control may reduce the risk of DR progression by 40% <sup>82</sup>
Statins	Atorvastatin Simvastatin	Improves lipid parameters (reduces total and LDL cholesterol levels)	Potential anti-inflammatory effects through NF $\kappa$ B inhibition <sup>153</sup> Decreased TNF-induced ICAM-1 expression <sup>153</sup>	Steno-2 <sup>79</sup> CARDS <sup>80</sup>	Evidence still insufficient to support primary use to prevent DR progression <sup>78</sup> Control of lipid parameters in patients with DME may result in improved visual outcomes <sup>86</sup>
<b>Agents blood pressure control</b>					
ACE inhibitors	Captopril Enalapril Lisinopril	Blocks the conversion of angiotensin-1 to angiotensin-2	Renin-angiotensin system blockade <sup>83</sup> Vitreous activity of ACE is correlated with VEGF levels <sup>85</sup>	UKPDS <sup>88</sup> EUCLID <sup>89</sup> RASS <sup>91</sup>	Tight blood pressure control reduces the risk for two-step DR progression by 34% and three-line visual loss by 47% <sup>88</sup> Treatment with enalapril in normotensive patients with T1DM reduces the risk for two-step or more progression by 65% <sup>91</sup>
ARB	Candesartan Losartan Telmisartan Losartan	Blocks the activation of angiotensin-2	Renin-angiotensin system blockade <sup>83</sup> PPAR $\gamma$ agonist activity <sup>92</sup>	RASS <sup>91</sup> DIRECT (Prevent 1; Protect 1 and 2) <sup>92,93</sup>	Treatment with losartan in normotensive T1DM patients has been shown to reduce the risk for two-step or more progression by 65% <sup>91</sup> Patients with T2DM and DR may benefit from candesartan treatment as this has been associated with higher rates of DR regression <sup>92</sup>
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-2 receptor blocker; DM, diabetes mellitus; DME, diabetic macula edema; DR, diabetic retinopathy; ICAM-1, intercellular adhesion molecule 1; NF $\kappa$ B, nuclear factor $\kappa$ B; NPDR, nonproliferative diabetic nephropathy; PAI-1, plasminogen activator inhibitor 1; PDR, proliferative diabetic nephropathy; PPAR, peroxisome proliferator-activated receptor; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TNF, tumor necrosis factor; TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor.					



## APPENDIX TABLE 2 (continued)

### Effects of Systemic Medications on the Onset and Progression of Diabetic Retinopathy

#### REVIEWS

<b>Table 2</b>   Effects of currently available systemic medications on diabetic retinopathy					
Systemic agents	Prototypical drugs	Systemic effects	Specific ocular mechanism	References (Author or study)	Implications for diabetes eye-care
<b>Agents for cardiac complications</b>					
Antiplatelet agents	Aspirin	Decreased platelet activation and aggregation Decreased prostaglandin production	Low doses: inhibition of COX-1 and TBXA2 production <sup>104</sup> Intermediate to high doses: inhibition of COX-1, prostaglandin production and NFκB-mediated pathways <sup>102-104</sup>	ETDRS <sup>96</sup> DAMAD <sup>98</sup> TIMAD <sup>105</sup>	Does not worsen DR or predispose to vitreous hemorrhage <sup>96</sup> At intermediate to high doses may theoretically slow the progression of early DR <sup>103,104</sup>
Anticoagulants	Warfarin Heparin	Inhibits synthesis of clotting factors	Inhibits synthesis of clotting factors <sup>106</sup>	Dayani <i>et al.</i> <sup>110,111</sup> Jamula <i>et al.</i> <sup>108</sup> Fu <i>et al.</i> <sup>109</sup>	If maintained at the therapeutic range, it is not a contraindication to ocular surgery <sup>108-111</sup> Does not increase the risk for intraocular hemorrhage <sup>106</sup>
Cardiac glycosides	Digoxin Digitoxin	Anti-arrhythmic agent; Inhibits Na <sup>+</sup> /K <sup>+</sup> -ATPase	Inhibition of KLK expression <sup>118,120</sup> Reduces HIF1α levels <sup>116</sup>	Prassas <i>et al.</i> <sup>118</sup> Phipps <i>et al.</i> <sup>120</sup>	Can potentially inhibit ocular neovascularization and retinal vascular leakage <sup>116</sup> Studies are presently being conducted to determine safety and efficacy
<b>Agents for the treatment of anemia</b>					
Erythropoietin	Erythropoietin	Stimulates increased red blood cell production	VEGF-independent angiogenic factor <sup>124</sup>	Watanabe <i>et al.</i> <sup>124</sup> Tong <i>et al.</i> <sup>125</sup>	Patients requiring treatment with erythropoietin should be monitored closely for the development or worsening of DR particularly in the setting of chronic renal disease and anemia <sup>125</sup>
<b>Anti-inflammatory agents</b>					
Salicylates and COX-2 inhibitors	Salsalate Celecoxib	Inhibits prostaglandin synthesis	Inhibition of COX and prostaglandin production <sup>103</sup> Suppression of NFκB-mediated pathways <sup>128</sup>	Fleischman <i>et al.</i> <sup>128</sup> Chew <i>et al.</i> <sup>129</sup>	Concern on cardiovascular safety with long-term use and higher doses <sup>130</sup> Theoretically may slow the progression of early DR <sup>103,104</sup>
Corticosteroids	Prednisone Triamcinolone	Modulation of inflammatory response	Inhibition of prostaglandin release Inhibition of VEGF gene expression <sup>154</sup>	DRCR.net <sup>131,136,137</sup>	An independent beneficial effect of systemic corticosteroids on the development or progression of DR and/or DME has not been reported and is likely overshadowed by adverse effects
<b>Antiangiogenic agents</b>					
VEGF inhibitors	Bevacizumab Ranibizumab	Inhibits tumor growth and angiogenesis	Inhibition of all VEGF isoforms <sup>155</sup>	Moshfeghi <i>et al.</i> <sup>149</sup> Avery <i>et al.</i> <sup>115</sup> Scott <i>et al.</i> <sup>145</sup> Chun <i>et al.</i> <sup>143</sup> Arevalo <i>et al.</i> <sup>142</sup> DRCR.net <sup>146</sup>	Systemic delivery limited by adverse effects <sup>149</sup> Intravitreal administration has shown benefit in regression of PDR <sup>115</sup> and resolution of DME <sup>142,143,145</sup> Benefit of intravitreal ranibizumab over laser reported <sup>146</sup> Ongoing clinical trials to elucidate optimal use
Abbreviations: COX, cyclooxygenase (also known as prostaglandin G/H synthase); DME, diabetic macula edema; DR, diabetic retinopathy; HIF1α, hypoxia-inducible factor 1α; KLK, kallikrein; NFκB, nuclear factor κB; Na <sup>+</sup> /K <sup>+</sup> -ATPase, sodium/potassium-transporting ATPase; PDR, proliferative diabetic nephropathy; TBXA2, thromboxane A2; VEGF, vascular endothelial growth factor.					

Source: Silva PS, Cavallerano JD, Sun JK, et al. Effect of systemic medications on onset and progression of diabetic retinopathy. *Nat Rev Endocrinol* 2010;9:494-508

## ABBREVIATIONS OF COMMONLY USED TERMS

- A1C - Glycosylated hemoglobin
- ACE - Angiotensin converting enzyme
- ADA - American Diabetes Association
- BMI - Body mass index
- CSME - Clinically significant macular edema
- CVD - Cardiovascular disease
- DA/DCCT - Disc area
- EDIC - Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
- DD - Disc diameter
- DME - Diabetic macular edema
- DR - Diabetic retinopathy
- DRCR.net - Diabetic Retinopathy Clinical Research Network
- DRVS - Diabetic Retinopathy Vitrectomy Study
- DRS - Diabetic Retinopathy Study
- EHR - Electronic health record
- ETDRS - Early Treatment Diabetic Retinopathy Study
- FA - Fluorescein angiography
- FAF - Fundus autofluorescence
- FDA - Food and Drug Administration
- FPD - Fibrous proliferation on or within 1 DD of disc margin
- FPE - Fibrous proliferation elsewhere, not FPD
- FPG - Fasting plasma glucose
- GAD65 - Glutamic acid decarboxylase
- GDM - Gestational diabetes mellitus
- HDL - High-density lipoprotein(s)
- HE - Hard exudates
- HLA - Human leukocyte antigen(s)
- H/Ma - Hemorrhage(s) and/or microaneurysm(s)
- IAAs - Insulin autoantibodies
- ICAs - Islet cell antibodies
- IFG - Impaired fasting glucose
- IGT - Impaired glucose tolerance

- IOP - Intraocular pressure
- IVTA - Intravitreal triamcinolone acetonide
- IRMA - Intraretinal microvascular abnormality
- LDL - Low-density lipoproteins
- Ma - Microaneurysms
- NAION - Non-arteritic anterior ischemic optic neuropathy
- NPDR - Non-proliferative diabetic retinopathy
- NVD - New vessels on or within 1 DD of disc margin
- NVE - New vessels elsewhere in the retina outside of disc and 1 DD from disc margin
- NVG - Neovascular glaucoma
- NVI - New vessels on the iris; rubeosis iridis
- OAG - Open angle glaucoma
- OCT - Optical coherence tomography
- OGTT - Oral glucose tolerance test
- PDR - Proliferative diabetic retinopathy
- PRH - Preretinal hemorrhage
- PRP - Panretinal photocoagulation
- PVD - Posterior vitreous detachment
- TRD - Traction retinal detachment
- UKPDS - United Kingdom Prospective Diabetes Study
- VB - Venous beading
- VCAB - Venous caliber abnormalities
- VEGF -Vascular endothelial growth factor
- VH - Vitreous hemorrhage

## GLOSSARY

### **Clinically significant macular edema (CSME)**

The case where there is retinal thickening at or within 500 microns of the center of the macular and/or hard exudates within 500 microns of the center of the macula associated with retinal thickening of the adjacent area of the retina and/or a zone or zones of retinal thickening 1 disc area in size, any part of which is within 1 disc diameter of the center of the macula.

**Diabetes mellitus** A group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

- **Type 1 diabetes** The result of cell-mediated autoimmune destruction of the beta-cells of the pancreas, formerly referred to as insulin dependent diabetes mellitus (IDDM).
- **Type 2 diabetes** A disease in which individuals can produce insulin but have cellular resistance to it, formerly referred to as non-insulin dependent diabetes mellitus (NIDDM).

**Diabetic cataract** A rapidly forming, sometimes reversible, bilateral cataract associated with diabetes mellitus.

**Diabetic papillopathy** A non-inflammatory edema of the optic nerve head associated with diabetes mellitus.

**Diabetic retinopathy** A highly specific retinal vascular complication of diabetes mellitus, which is broadly classified as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

**High-risk proliferative diabetic retinopathy** New vessels on or within 1 disc diameter of the optic nerve head greater than approximately 1/4 to 1/3 of the disc, or new vessels on or within 1 disc diameter of the optic nerve head less than 1/4 to 1/3 the disc area when accompanied by vitreous and/or preretinal hemorrhage, or new vessels elsewhere in

the retina greater than 1/2 the size of the disc area.

**Hyperglycemia** Presence of high blood glucose levels.

**Insulin** A hormone that allows glucose to enter cells and be converted to energy.

**Intraretinal hemorrhage** A radially striated hemorrhage in the inner layers of the retina, especially in the nerve fiber layer (flame-shaped hemorrhage).

### **Intraretinal microvascular abnormality (IRMA)**

An abnormality that represents either new vessel growth within the retina or pre-existing vessels with endothelial cell proliferation.

**Ketoacidosis** A serious complication of diabetes that occurs when the body burns fat producing very high levels of toxic acids, called ketones, in the bloodstream.

**Legal Blindness** Remaining vision in the better eye after best correction of 20/200 or less, or contraction of the visual fields in the better eye (a) to 10 degrees or less from the point of fixation or (b) so that the widest diameter subtends an angle no greater than 20 degrees.

**Macular edema (ME)** Collection of intraretinal fluid in the macular portion of the retina, with or without lipid exudates, and with or without cystoid changes.

**Microaneurysm (Ma)** As to the eye, a focal retinal capillary dilation.

**Neovascularization** Growth of abnormal new blood vessels.

**Papilledema** Non-inflammatory edema of the optic nerve head from various causes, such as increased intracranial pressure, orbital tumor or blood dyscrasias.

**Postprandial blood glucose** Blood glucose measurement taken 1 to 2 hours after a meal.

**Proliferative diabetic retinopathy (PDR)** A type of retinopathy associated with diabetes mellitus, characterized by proliferation of connective tissue and the formation of new blood vessels in the retina, and by hemorrhages into the vitreous.

**Retinal hypoxia** A deficiency of oxygen supply to the retinal tissue.

**Rubeosis iridis** Non-inflammatory neovascularization of the iris occurring in diabetes mellitus, characterized by numerous, small intertwining blood vessels which anastomose near the sphincter region to give the appearance of a reddish ring near the border of the pupil. The vessels may extend from the root of the iris to the filtration angle to cause peripheral vascular synechiae and secondary glaucoma.

**Severe Visual Impairment** Best-corrected visual acuity of 5/200 or worse.

**Telehealth programs** Refers to remote health care that does not always involve clinical services and may include videoconferencing, transmission of still images, remote monitoring of vital signs, continuing medical education and nursing call centers.

**Venous beading (VB)** A fragmented appearance of the bloodstream in the retinal veins subsequent to retinal artery occlusion.

**Vision rehabilitation** The process of treatment and education that helps individuals who are visually disabled attain maximum function, a sense of well-being, a personally satisfying level of independence and optimum quality of life. Function is maximized by evaluation, diagnosis and treatment including, but not limited to, the prescription of optical, non-optical, electronic and/or other treatments.

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## SUMMARY LISTING OF ACTION STATEMENTS

### Diagnosis of Ocular Complications of Diabetes Mellitus

The ocular examination of an individual suspected of having undiagnosed diabetes should include all aspects of a comprehensive eye examination with supplemental testing, as needed.

Persons without a diagnosis of diabetes who present with signs suggestive of diabetes during the initial examination should be referred to their primary care physician for evaluation, or an A1C test or fasting blood glucose analysis may be ordered.

The ocular examination of a person with diabetes should include all aspects of a comprehensive eye examination with supplemental testing, as indicated, to detect and thoroughly evaluate ocular complications.

Patients should be questioned about the awareness of their personal diabetes ABCs (A1C, blood pressure, cholesterol levels, and their history of smoking).

The initial ocular examination should include, but is not limited to, the following evaluations:

- **Best-corrected visual acuity**
- **Pupillary reflexes**
- **Ocular motility**
- **Refractive status**
- **Confrontation visual field testing or visual field evaluation**
- **Slit lamp biomicroscopy**
- **Tonometry**
- **Dilated retinal examination**

Retinal examinations for diabetic retinopathy should be performed through a dilated pupil.

When vitreous hemorrhage prevents adequate visualization of the retina, prompt referral to an ophthalmologist experienced in the management of diabetic retinal disease should be made for further evaluation.

The individual's primary care physician should be informed of eye examination results following each examination, even when retinopathy is minimal or not present.

As diabetes may go undiagnosed for many years, any individual with type 2 diabetes should have a comprehensive dilated eye examination soon after the diagnosis of diabetes.

Individuals with diabetes should receive at least annual dilated eye examinations. More frequent examination may be needed depending on changes in vision and the severity and progression of the diabetic retinopathy.

Women with pre-existing diabetes who are planning pregnancy or who become pregnant should have a comprehensive eye examination prior to a planned pregnancy or during the first trimester, with follow-up during each trimester of pregnancy.

Examination of persons with non-retinal ocular complications of diabetes should be consistent with current recommendations of care for each condition.

Prompt referral to a vitreo-retinal surgeon is indicated when a vitreous hemorrhage, a retinal detachment, or other evidence of proliferative diabetic retinopathy is present.

## Treatment and Management

Treatment protocols for persons with non-retinal ocular and visual complications should follow current recommendations for care and include education on the subject and recommendations for follow-up visits.

As part of the proper management of diabetes, the optometrist should make referrals for concurrent care when indicated.

### Non-proliferative Diabetic Retinopathy

Panretinal photocoagulation may be considered in patients with severe or very severe non-proliferative diabetic retinopathy (NPDR) or early proliferative diabetic retinopathy (PDR), with a high risk of progression (e.g. pregnancy, poor glycemic control, inability to follow-up, initiation of intensive glycemic control, impending ocular surgery, renal impairment, rapid progression of retinopathy).[Evidence Strength: A, Recommendation: A]

### Proliferative Diabetic Retinopathy

Patients with high-risk proliferative diabetic retinopathy should receive referral to an ophthalmologist experienced in the management of diabetic retinal disease for prompt scatter (panretinal) photocoagulation. [Evidence Strength: A/B, Recommendation A/B]

Eyes in which proliferative diabetic retinopathy has not advanced to the high-risk stage should also be referred for consultation with an ophthalmologist experienced in the management of diabetic retinal disease. [Evidence Strength: A/B, Recommendation A/B]

Following successful treatment with panretinal photocoagulation (PRP), patients should be re-examined every 2 to 4 months. The follow-up interval may be extended based on disease severity and stability.

### Diabetic Macular Edema

Following focal photocoagulation for DME, re-examination should be scheduled in 3 to 4 months.

Patients with center-involved diabetic macular edema (DME) should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for possible treatment.

Individuals with diabetic macular edema (DME), but without clinically significant macular edema (CSME), should be re-examined at 4- to 6-month intervals. Once CSME develops, treatment with focal laser photocoagulation or intravitreal anti-VEGF injection is indicated. [Evidence Strength: A, Recommendation: A]

### Vitrectomy

Eyes with vitreous hemorrhage (VH), traction retinal detachment (TRD), macular traction or an epiretinal membrane should be referred to an ophthalmologist experienced in the management of diabetic retinal disease for evaluation for possible vitrectomy.

### Anti-VEGF Agents

The current standard of care for treatment of center-involved diabetic macular edema (DME), in persons with best corrected visual acuity of 20/32 or worse, is anti-VEGF injections. [Evidence Strength: A, Recommendation: A]

### Patient Education

Persons should be educated about the ocular signs and symptoms of diabetic retinopathy and other non-retinal complications of diabetes, and encouraged to comply with recommendations for follow-up eye examinations and care.

Individuals should be advised of the risks of smoking related to diabetes and encouraged to quit smoking and/or seek smoking cessation assistance.

Individuals should be educated about the long-term benefits of glucose control in saving sight, based on their individual medically appropriate A1C target.

**Management of Systemic Complications and Comorbidities of Diabetes Mellitus**

The glycemic goal for persons with diabetes should be individualized, taking into consideration their risk of hypoglycemia, anticipated life expectancy, duration of disease and co-morbid conditions.

Optometrists should have a rapid-acting carbohydrate (e.g. glucose gel or tablets, sugar-sweetened beverage or fruit juice) in their office for use with diabetes patients who experience acute hypoglycemia during an eye examination.

The majority of persons with diabetes are at risk of coronary heart disease and can benefit from reducing low-density lipoprotein (LDL) cholesterol levels to the currently recommended targets. [Evidence Strength: B, Recommendation: B]

When indicated, overweight individuals should be referred to a qualified health care provider for assistance with weight loss.

Individuals with diabetes should receive nutrition and dietary recommendations preferably provided by a registered dietician who is knowledgeable about diabetes management.

**Management of Persons with Vision Loss/Visual Impairment**

Individuals who experience vision loss from diabetes should be provided, or referred for, a comprehensive examination of their visual impairment by a practitioner trained or experienced in vision rehabilitation.

Persons with diabetes, who experience visual difficulties, should be counseled on the availability and scope of vision rehabilitation care and

encouraged to utilize these services.

Referral for counseling is indicated for any individual experiencing difficulty dealing with vision and/or health issues associated with diabetes or diabetic retinopathy. Educational literature and a list of support agencies and other resources should be made available to these individuals.



## VIII. METHODOLOGY FOR GUIDELINE DEVELOPMENT

This Guideline was developed by the AOA Evidence-Based Optometry Guideline Development Group (GDG). Clinical questions to be addressed in the Guideline were identified and refined during an initial meeting of the GDG and served as the basis for a search of the clinical and research literature.


An English-language literature search for the years 2009-2012 was conducted by two trained researchers. If the search did not produce results, the search parameters were extended to 5 years earlier and subsequently, 10 years earlier. In addition, a review of selected earlier research publications was conducted based on previous versions of this Guideline. The literature search was conducted using the following electronic databases:

- Agency for Healthcare Research and Quality (AHRQ)
- American Academy of Ophthalmology
- [American Diabetes Association](#) professional for the site [Diabetes Pro Standards of Medical Care in Diabetes 2011](#)
- [American Optometric Association](#)
- Cochrane Collection
- Diabetes Prevention Program
- Diabetic Retinopathy Clinical Research Network
- Diabetologia (International)
- Elsevier
- European Association for the Study of Diabetes (EASD) Eye Complications Study Group
- European Association for the Study of Diabetes (EASD, Europe's ADA)
- Eye (Journal)
- Guidelines International Network
- Institute of Medicine Clinical Guideline Welcome Trust
- Mayo Clinic
- Medical Expenditure Panel Survey (MEPS)
- National Guideline Clearinghouse of the Agency for Healthcare Research and Quality (AHRQ)
- National Institute for Clinical Effectiveness (British)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) National Diabetes Information Clearinghouse
- National Library of Medicine Loansome Doc
- NEI National Eye Institute
- Ophthalmologica (International Journal of Ophthalmology)
- PubMed
- World Health Organization

All references meeting the criteria were reviewed to determine their relevance to the clinical questions addressed in the Guideline. They were distributed to two readers who independently reviewed and graded the quality of evidence and the clinical recommendations for each article, based on a previously defined system for grading quality.

A total of 576 papers were identified and filtered for relevance as meeting the key question parameters. Of this number, 298 were categorized as background information and provided to the medical writer. A total of 278 articles were reviewed independently by the two readers and graded on strength of evidence and clinical recommendations. Any gaps in evidence were also noted at this time for future review of this Guideline.

Of the 278 papers read and graded by the GDG, 94 were found to have high-quality of evidence value and/or high grading for clinical recommendations and were included in the Guideline references. One hundred and twenty articles were discarded because they failed to meet the criteria for strength of evidence and/or clinical recommendation for inclusion in the Guideline. The remaining 64 articles were discarded because they did not appropriately address the Guideline questions.



During two articulation meetings of the Evidence-Based Optometry GDG, all evidence was reviewed and clinical recommendations were developed. Grading for the recommendations were based on the quality of the research and the benefits and risks of the procedure or therapy recommended. Where direct scientific evidence to support a recommendation was weak or lacking, a consensus of the Evidence-Based Optometry Subcommittee members was required to approve a recommendation.

At the Draft Reading Meeting of the Evidence-Based Optometry GDG, the Guideline document was reviewed and edited and the final draft was approved by the GDG via conference call. The final draft of the Guideline was then made available for peer and public review for 30 days in order for numerous stakeholders (individuals and organizations) to make comments. All suggested revisions were reviewed and, if accepted by the GDG, incorporated into the Guideline.

Clinical recommendations in this Guideline are evidence-based statements regarding patient care that are supported by the scientific literature or consensus professional opinion when no quality evidence was discovered. The Guideline will be periodically reviewed and updated as new scientific and clinical evidence becomes available.

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