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Ocular Disease, Knowledge, and Technology Applications in Patients with Diabetes

Jennifer Threatt, BS¹, Jennifer Faye Williamson, BS², Kyle Huynh, BS^{2,3}, and Richard M. Davis, MD²

¹East Carolina University

²University of North Carolina at Chapel Hill

³School of Medicine and Health Sciences, George Washington University

Abstract

An estimated 25.8 million children and adults in the United States, approximately 8.3% of the population, have diabetes. Diabetes prevalence varies by race and ethnicity. African Americans have the highest prevalence (12.6%), followed closely by Hispanics (11.8%), Asian Americans (8.4%), and Whites (7.1%). The purpose of this article is to discuss the ocular complications of diabetes, the cultural and racial differences in diabetes knowledge, and the role of telemedicine as a means to reach the undeserved who are at risk of complications. Information on the pathophysiology of ocular disease in patients with diabetes and the role of telemedicine in diabetes care was derived from a literature review. National Institutes of Health (NIH) on-line resources were queried to present data on the racial and cultural understandings of diabetes and diabetes-related complications. The microvascular ocular complications of diabetes are discussed for retinopathy, cataracts, glaucoma and ocular surface disease. Racial and cultural differences in knowledge of recommended self-care practices are presented. These differences in part, may explain health disparities and the increased risk of diabetes and its complications in rural minority communities. Finally, advances in telemedicine technology are discussed that show improvements in metabolic control and cardiovascular risk in adults with type 2 diabetes. Improving provider and patient understanding of diabetes complications may improve management and self care practices that are important for diabetes control. Telemedicine may improve access to diabetes specialists and may improve self-management education and diabetes control particularly in rural and underserved communities.

Keywords

Diabetes; Self-Management; Telemedicine

The Diabetes Epidemic

An estimated 25.8 million children and adults in the United States, approximately 8.3% of the population, have diabetes. Of the 25.8 million, 7 million people are suspected to be undiagnosed with an additional 79 million people living with pre-diabetes.¹ Diabetes prevalence varies across ethnicities and communities. African Americans have the highest prevalence (12.6%), followed closely by Hispanics (11.8%), Asian Americans (8.4%), and

Corresponding Author: Richard M Davis, MD, UNC Eye, 5151 Bioinformatics CB #7040, Chapel Hill, NC 27599-7040; Phone: 919-843-0295; Fax: 919-966-1908; richdavis@unc.edu.

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Whites (7.1%).¹ This paper discusses three related areas of importance with respect to diabetes control, 1) microvascular complications represented by ocular disease, 2) diabetes knowledge, and 3) the role of telemedicine as a means to reach undeserved populations at risk of complications.

Diabetic retinopathy is the leading cause of new cases of blindness among adults aged 20–74 years in the US.² Moreover, the odds of vision-threatening diabetic retinopathy are significantly higher among non-Hispanic Blacks compared to non-Hispanic Whites.³ Despite the increased attention on diabetes and its complications, there is lack of understanding among those with diabetes regards to treatment adherence and complications. This article will discuss the various ocular manifestations of diabetes, the attitudes and perceptions of those with diabetes, and the current movement toward telecommunications as a method to increase access to improve education and diabetes-related knowledge, and preventive care and treatment in diabetes and ocular health.

Within the medical literature, it is well known that uncontrolled type 1 or type 2 diabetes and the resultant microvascular complications may have a detrimental effect on vision. Therefore, routine dilated eye examinations are recommended to identify and manage vision-threatening diabetic retinal disease. Patients with type 1 diabetes mellitus are advised to have an initial comprehensive eye exam, including dilation, by an eye care provider between 3–5 years following disease onset. Since the onset of disease and duration are often unknown in type 2 diabetics, it is recommended that these patients have a complete examination at, or close to, time of diagnosis with regular follow-up examination annually.⁴ Despite the recommendations, studies show that only about half of diabetic patients complete their recommended annual eye examination.⁵ Those with uncontrolled diabetes, whether type 1 or 2, who do not adhere to clinical practice recommendations are at a much greater risk for presenting with later stages of diabetic retinopathy and other rare diabetic ocular complications, including: glaucoma, cataract, and dry eye disease.

Pathology of Diabetic Ocular Disease

Retinopathy

Diabetic retinopathy is the leading cause of blindness among adults aged 20 to 74 in the United States. The prevalence of diabetic retinopathy is especially high, with more than 90% of type 1 and at least 60% of type 2 diabetics having some degree of retinopathy 20 years after diagnosis.⁶ Both type 1 and type 2 diabetes are associated with retinal microvascular changes. Longstanding hyperglycemia contributes to vascular endothelial dysfunction, resulting in degeneration of endothelial and pericyte cells. These changes give rise to microaneurysms, intraretinal hemorrhages, and retinal ischemia, also referred to as cotton wool spots.⁶ This stage of diabetic retinopathy is classified as non-proliferative diabetic retinopathy (NPDR). With advanced retinopathy and prolonged vascular injury, retinal ischemia becomes an identifiable feature. On dilated fundoscopy, ischemia presents as venous beading, intra-retinal microvascular abnormalities, and progressive hemorrhages.⁶

With advance stages of retinopathy, compensatory chemical mediators, primarily vascular endothelial growth factor (VEGF), induce growth of new blood vessels on the inner retina that are architecturally weak and lacking in tight junctions. This stage is called proliferative diabetic retinopathy (PDR) and can affect the optic disc or elsewhere on the retina.⁶ With neovascularization as seen in PDR, the blood vessels have a propensity to hemorrhage, resulting in the phenotypic presentation of floaters and even vision loss.⁶ Without intervention, the neovascularization process accompanied by compensatory fibrotic tissue changes result in retinal traction and can cause a retinal tear or detachment.⁶

In addition to non-specific retinal changes, the macula can also be affected. Macular edema, a feature of uncontrolled diabetes, is a leading cause of preventable vision loss in diabetics and can occur at any stage of diabetic retinopathy. Damaged retinal blood vessels are permeable and prone to plasma and lipid efflux. This results in fluid accumulation in the inner layer of the retina and is seen as yellow, hard exudate under direct visual examination. Macular edema is often asymptomatic, but may present as blurred vision.⁶

The Diabetes Control and Complications Trial (DCCT) conducted in 1993 was significant in specifying glycemic control as the risk factor that most influenced the predisposition to develop diabetic retinopathy.⁷ The study evaluated 1441 patients with either no retinopathy or mild retinopathy at baseline, who were randomly assigned to the intensive therapy group or to the conventional therapy group. Over the course of the 6.5-year study, the intensive group maintained a hemoglobin A1c of less than 7%, while the conventional therapy group maintained a HbA1c near 9%. Ultimately the DCCT trial demonstrated that strict glycemic control was highly effective in primary prevention of retinopathy, reducing the risk of new retinopathy by 76% in the intensive therapy group compared to the conventional therapy group. Strict glycemic control was also shown to slow the rate of progression of retinopathy in those who had mild to moderate NPDR at baseline. With glycemic control as a key factor in slowing the onset and/or progression of diabetic retinopathy, other studies sought to better elucidate the mechanism relating hyperglycemia and the development of retinopathy.

Research has found a possible link within the aldose reductase (polyol) pathway (Figure 1). The pathway is active in conditions of hyperglycemia and in tissues (e.g., retina) that do not require insulin as a mediator for glucose sequestration into cells. In the absence of insulin, glucose is diverted from the default oxidative pathway and is reduced to sorbitol, a sugar alcohol, by aldose reductase. Sorbitol is then converted to fructose by sorbitol dehydrogenase.⁸ Sorbitol and fructose are not permeable across cell lipid membranes and are osmotically active in influencing cell fluid volume.⁹ In diabetic patients with poorly controlled hyperglycemia, there is an increase in sorbitol and fructose formation and a subsequent trapping within the cells of the retina, such as endothelial cells and pericyte cells, resulting in hypertonicity leading to osmotic stress.⁸

In explaining the microvascular complications of retinopathy, non-enzymatic glycation of proteins is believed to be involved. In non-enzymatic glycation, glucose becomes attached to free amino acid groups of proteins, causing a modification of the protein structure and forming advanced glycation end products (AGEs). Specific cells, such as macrophages, have receptors for AGEs allowing them to accumulate in tissues and produce a variety of structural changes. The structural changes from AGEs can explain the retinopathy complications of microaneurysms and thickened basement membranes.⁸

Glaucoma

The underlying mechanism that leads to PDR may be similar for neovascular glaucoma. Neovascular glaucoma results from tissue ischemia mediated by VEGF production.¹⁰ VEGF acts on healthy endothelial cells of viable capillaries to stimulate formation of new, but fragile vessels.¹⁰ As more retina becomes ischemic the VEGF diffuses anteriorly within the globe to the proximal area of available capillaries. Such locations include, but are not limited to, the posterior iris where capillaries bud off growing along the posterior iris, through the pupil, and into the drainage angle.¹⁰ Once neovascularization occurs in the angle, there is a physical impedance of natural aqueous outflow, leading to acute closed-angle glaucoma and resultant increase in intraocular pressure.¹⁰ If not immediately recognized and managed, this may lead to permanent vision loss.

Diabetes has also been suspected as a risk factor for Primary Open Angle Glaucoma (POAG), the more common form of glaucoma.¹¹ POAG is an optic neuropathy characterized by progressive peripheral vision loss, eventually affecting central vision. It is associated with elevated intraocular pressure and the optic nerve has a characteristic “cupping” or hollowed-out appearance associated with retinal nerve fiber ganglion cell loss. Known risk factors include: age, African American race, family history, corneal thickness, and elevated intraocular pressure. In 2003, a meta-analysis of published studies showed that diabetes was a significant risk factor in patients with POAG.¹¹ The underlying biomechanical mechanism is poorly understood. Possible theories include increased susceptibility of optic nerve fibers leading to visual field defects because of the effect of diabetes on small vessels.¹¹

Cataract

Premature cataract development is another major cause of visual impairment in patients with diabetes.¹² The propensity for cataract formation is 20 years earlier when compared to patients without diabetes.¹³ Cataract is an opacification of the lens system and can occur symmetrically or asymmetrically. Cataract causes a detrimental impact on optic refractive power and the amount of light penetrance onto the retina; thus, causing blurring, glaring, and a shift in the color-spectrum that can be appreciated by patients. Cataracts are categorized depending on their location within the lens: nuclear, cortical or subcapsular.

It is currently hypothesized that three different mechanisms are involved in the formation of diabetic cataracts: (1) aldose reductase pathway, (2) oxidative damage, and (3) glycation of proteins.^{12,13} Similar to the mechanism of osmotic imbalance seen in diabetic retinopathy, there is substantial evidence showing involvement of the aldose reductase pathway as the primary mechanism in the formation of diabetic cataracts via osmotic changes and oxidative damage. In normoglycemic patients, it is approximated that only 5% of glucose enters the aldose reductase pathway.¹³ In hyperglycemic conditions, there is a six-fold increase in the amount of glucose entering the aldose reductase pathway, leading to sorbitol synthesis and accumulation within the lens system. This accumulation of sorbitol within the lens, similar to the macula, causes osmotic shifts accelerating lens swelling and premature cataract development.¹³

In addition to the osmotic damage, over activity of the aldose reductase pathway depletes the co-factor NADPH, an essential energy carrier within cells. NADPH is necessary for the downstream reactions of glutathione reductase. If NADPH is not present in sufficient quantities as a co-factor for glutathione reductase, cellular antioxidant capacity is affected. Studies show a loss of reduced glutathione in diabetic cataractous lenses compared with non-diabetic lenses.¹³

Lastly, hyperglycemia contributes to diabetic cataracts via glycation of proteins, altering their biological behavior. Glycation of the lens, a process noted both in aging adults and diabetics, leads to aggregation, cross-linking and insolubilization of the lens proteins. This results in cloudiness, most often occurring in the cortex and posterior subcapsular portions of the lens.¹²

Dry Eye Disease

The last ocular manifestation of diabetes to be discussed is ocular surface disease or Dry Eye Disease (DED). DED, one of the most common reasons people present to an eye care specialist, is a condition of insufficient tears and an altered ocular surface.¹⁴ The symptoms of dry eye can be numerous, including: red eyes, burning, irritation, gritty sensation, blurred vision, and excessive tearing. Similar to cataract, dry eye symptoms can present as a natural

course of aging. Other risk factors include: age, female gender, systemic disease, contact lens wear, medications, and specific nutritional deficiencies (e.g. vitamin A).¹⁴

Studies confirm that diabetic patients complain of dry eye symptoms more often than their non-diabetic counterparts.^{15, 16} Based on usage of ocular lubricating drops, the prevalence of DED was found to be significantly higher in patients with diabetes.¹³ In addition, there is an observed decrease in tear production by 37% as measured by the Schirmer test in patients with insulin dependent diabetes mellitus compared to patients without diabetes.¹⁶

The proposed mechanism of dry eye in diabetes is prolonged hyperglycemia resulting in corneal neuropathy. Corneal neuropathy triggers downstream effects that destabilize the tear film and causes ocular metaplasia. Corneal sensitivity, a manifestation of corneal neuropathy, and tear function were found to be significantly decreased in diabetic patients compared to patients without diabetes. The reduction in corneal sensitivity did not relate to duration of disease or the status of retinopathy, but did correlate with degree of diabetic control.¹⁷ Tear film instability and rapid tear break up time (TBUT) are likely a result of conjunctival goblet cell loss as noted on cytologic analysis in diabetic patients. Goblet cells produce mucin, which functions to stabilize the tear film and minimize evaporative tear loss.¹⁷ Goblet cell loss is also a good indicator of squamous cell metaplasia, also noted on cytologic analysis in diabetic patients presenting with dry eye symptoms. The exact mechanism of ocular surface disease is unclear, but squamous cell metaplasia is believed to be associated with keratinization of the conjunctival epithelial cells¹⁷ that may result in symptoms of DED.

Limiting factors in Patient Understanding of Diabetes and Ocular Health

While medical personnel may understand the ocular complications of diabetes, knowledge of diabetes and related complications among people with diabetes is less clear. Furthermore, lack of knowledge by patients with diabetes may represent a barrier to appropriate and important preventive examinations. To better understand the knowledge, attitudes and perceptions of patients with diabetes, the National Eye Health Education Program (NEHEP) and the National Eye Institute (NEI) collaborated to assess individuals with diabetes and their knowledge of the disease. Focus groups were organized in five major cities, including: Washington, D.C., Houston, TX, Atlanta, GA, Cleveland, OH and Miami, FL. The focus groups were then divided by ethnicity to include African Americans, Hispanics/Latinos-Spanish speaking, Hispanics/Latinos-English speaking, and Whites. All participants had the diagnosis of diabetes and were within the age range of 17 to 70.

Among African Americans, there was a good understanding of diabetes in a global context, but lacked knowledge in how diabetes specifically affects the eye. Despite this, the subjects generally knew the importance of having their eyes checked yearly. The participants blamed their lack of knowledge on a lack of available resources linking diabetes and eye disease. In the Hispanic/Latino-Spanish speaking group, the majority of their diabetes education came from their health insurance company. This group raised concerns regarding their medical provider's cultural competency as a barrier to acquiring knowledge.

Among the Hispanic/Latino- English speaking group, few participants had heard of diabetic eye disease and few could correlate diabetes with eye disease. Although vision was ranked highly in contributing to quality of life, many admitted to only seeing an eye care specialist when they experienced a problem. The main limitation to visiting an eye care specialist was cost of the visit, exam, and glasses. Within the White group, very few were familiar with the term "diabetic eye disease" although most acknowledged that blood sugar levels affect vision. Participants voiced a dislike of having their eyes dilated and some voiced a concern that they felt eye care professionals pushed "pills, treatments, or eyeglasses" to increase their

income instead of what was best for the patient. Denial of the diagnosis of diabetes was unique to the White group.

Among all focus groups, there was an understanding of the importance of seeing an eye doctor and maintaining tight glucose control, but there was a lack of knowledge of how diabetes can affect vision. Despite frequent follow-ups with the primary care provider (PCP) for glucose monitoring and identifying the PCP as the most trusted source for information, most information on diabetes came from the Internet. All participants desired more information on the correlation between glucose control and eye disease. There was also a repeated concern of cost to visit an eye care professional. The implications of this formative research are that providers must be aware of the barriers to diabetes control, which include knowledge, preferences on how medical information is ascertained, cost of care, and denial of disease status. Knowledge, attitudes, and preferences may have powerful influences on the adoption of healthy behaviors that modify diabetes control.

Current standard of care recommend annual eye examinations for patients with diabetes, yet only 50% obtain yearly eye exams.⁵ During the annual examination, the eye care provider first examines the anterior aspects of the eye using a slit-lamp biomicroscopy. The patient's eyes are then dilated and ophthalmoscopy is performed to allow for direct examination of the retina. With appropriate patient follow-up, annual examinations for patients with diabetes prevent vision-threatening retinopathy.¹⁸ Early detection of retinopathy is important to facilitate timely administration of treatment strategies to prevent vision loss. A dilated fundus exam helps to examine the retina for the presence of either clinically significant macular edema (CSME), or severe NPDR or PDR. The Early Treatment Diabetic Retinopathy study found that in patients with CSME, early treatment with focal laser photocoagulation reduces the risk of moderate visual loss by 50%.¹⁹

Unfortunately, travel, cost, time, and pupil dilatation are reasons mentioned by participants in the formative study which limit adherence to this practice. Of more concern is that as the diabetic population increases, the workforce may not meet the demand to screen all diabetics.

Current Role of Telemedicine

Telemedicine (telecommunication for diagnostic and therapeutic intervention) is proving itself as a useful tool in the future of medicine, particularly in rural communities with limited access to specialists. For example, one study using teleophthalmology to detect diabetic retinopathy in Canada showed that telemedicine benefits rural communities by decreasing time to treatment, allowing patients to be followed remotely, and prevented unnecessary referrals.²⁰ Other studies evaluating the benefits of telemedicine within rural communities found that telemedicine improves the local communities perception of healthcare, therefore decreases the desire or need for local patients to travel outside of their community; this simultaneously reduces financial costs by avoiding travel for consulting patients.^{21, 22}

In combination, the use of telemedicine and digital retinal photography have been shown to facilitate timely retinal examinations, create an efficient model of care, and address workforce shortages, particularly in rural communities with limited access to specialists.²³ The advancement of digital retinal photography has facilitated rapid acquisition and interpretation of fundus images, as well as quantitative analysis of data for longitudinal documentation of retinopathy progression. Retinal imaging can be performed using digital retinal photographs with (mydriatic) or without (nonmydriatic) dilating the pupil. The digital photographs may be interpreted either by trained readers within the office or forwarded to a reading center for interpretation ("store and forward").⁶ Studies examining the sensitivity

and specificity of both the mydriatic and nonmydriatic cameras favorably compare them to conventional ophthalmoscopy screening.²⁴

The potential of this technology for efficient delivery of remote retinal assessments may prevent vision loss. Countries that have implemented national screening programs, such as the National Plan for Screening in the United Kingdom and the OPHDIAT program in France, have had impressive outcomes. The OPHDIAT was a telemedicine network designed to facilitate time-saving access to regular annual evaluation of patients with diabetes. The study was comprised of 11 screening centers equipped with non-mydriatic cameras in which fundus photographs were taken by technicians. The photos were electronically linked to a telemedicine reference center for remote interpretation by ophthalmologists who graded the images. Over the 28-month evaluation period, 15,307 screening examinations were performed, detecting diabetic retinopathy in 3,350 of patients (23.4%).²⁵ The study ultimately proved that rates of diabetic retinopathy screening improved from 50% prior to utilization of digital retinal imaging to more than 70% after implementation of OPHDIAT.²⁶ The use of non-mydriatic cameras and telecommunication are being implemented in endocrinology, family medicine, and internal medicine clinics across the United States, improving both patient and provider satisfaction. Despite these promising advances, remote retinal imaging is not a replacement for a comprehensive eye exam by an eye care provider.

While telemedicine and retinal imaging programs have a demonstrable benefit to remote delivery of evidence-based diabetes self-management education, improving the adoption of self-care practices for at-risk patients with diabetes is more challenging. The role of telemedicine may be an effective means to foster adherence to evidence-based clinical practice guidelines as disseminated by the American Diabetes Association.²⁷

The Future of Telemedicine

A study conducted in rural South Carolina was the first of its kind to conduct a clinical trial to evaluate a remote comprehensive diabetes self-management education (DSME) intervention that including a remote retinal assessment. The study was set in an underserved and rural community, which was primarily African American. To improve adherence to American Diabetes Association (ADA) guidelines, a registered dietitian and a nurse certified diabetes educator conducted the DSME intervention. The remote DSME intervention was implemented as a method to overcome the barriers of access and transportation for adults with diabetes living in rural South Carolina. Interactive videoconferencing, telephone (cellular and land line), fax line, and telehealth-enabled retinal cameras were technologies employed.²³

One hundred sixty-five patients were recruited from CareSouth Carolina, LLC (Hartsville, SC), a federally qualified health center. The participants were randomized into the Diabetes TeleCare intervention group or the usual care group, 85 and 80 participants respectively. Inclusion criteria included hemoglobin A1c over 7%, age ≥ 35 years of age, visit within the last year to the community health center, a clinical diagnosis of diabetes, and willingness and ability to participate in a 1-year clinical trial. Over the 12-month DSME intervention trial, 13 sessions for subjects in the intervention group were held: 3 individual and 10 group sessions. Three of the 13 groups sessions were conducted in person, all others were conducted by interactive videoconferencing by the self-management education team.²³

Additionally, the intervention participants were offered retinal imaging in the primary-care setting when they were due for their annual eye exam. A licensed practical nurse (LPN) was trained to pharmacologically dilate the pupils, use a retinal camera, and electronically store and send retinal images to a remote reading center for interpretation by an ophthalmologist.

Referrals for retinal abnormalities or ungradeable images were scheduled with the nearest ophthalmologist.²³

The primary study outcome was glycated hemoglobin (GHb) with the secondary outcomes LDL cholesterol, albumin-to-creatinine ratio, blood pressure, body mass index (BMI), and waist circumference. This data was collected on all patients at baseline, 6 months, 12 months, and 24 months. Results at 6, 12, and 24 months showed significant improvement of GHb in the intervention group compared with the usual care group. There was also significant improvement in LDL cholesterol in the intervention group compared with the usual care group from baseline to 12 months. There was no difference in the other secondary outcomes, including systolic and diastolic blood pressure, BMI, waist circumference, or albumin-to-creatinine ratio. Also noted at the 12-month visit, 81.2% of the intervention group participants had received an annual eye exam compared to 38.8% in of the usual care group.²³

Concluding remarks

The microvascular complications of diabetes may effect several ocular structures including the cornea, lens, and retina as well as ocular function such as vision and intraocular pressure. The role of telemedicine to facilitate, prevent, and treat diabetes and ocular diseases is evolving. Telemedicine may efficiently and effectively improve diabetes knowledge, provide remote health services that promote early recognition of retinopathy, as well as the adoption of self-care practices such as medication adherence, self-monitoring of blood glucose, healthy diet, and physical activity. Telemedicine technologies may help to bridge the knowledge gap between patient and health care providers on the importance of strict glycemic control and the health complications and associated burden that may occur without preventive health services. Telemedicine may improve access to diabetes specialists that fosters self-management education and diabetes control particularly in minority and underserved.

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Figure 1.