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### Optimizing Outcomes in Diabetic Retinopathy: Improving Screening, Referral, and Treatment

Narrator:

Welcome to CME on ReachMD. This segment, *Optimizing Outcomes in Diabetic Retinopathy: Improving Screening, Referral and Treatment*, is jointly sponsored by the University of Cincinnati and Core Medical Education and supported by an educational grant from Genentech, Incorporated. The target audience for this educational activity includes physicians and other healthcare professionals who manage patients with diabetic Retinopathy.

Your host is Dr. Matt Birnholz, and our guest today is Dr. Rishi P. Singh. Dr. Singh is the staff surgeon at Cole Eye Institute and Associate Professor of Ophthalmology at the Lerner College of Medicine at the Cleveland Clinic in Cleveland, Ohio.

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Dr. Birnholz:

Diabetes is a growing epidemic in the United States, affecting an estimated 29 million individuals, including an estimated 8 million who are undiagnosed. More than one-third of US adults aged 20 years or older have prediabetes. Ocular complications are common with this systemic disorder, and it has been shown that diabetes is the leading cause of new-onset blindness among working age adults in the United States. Individuals with diabetes are more likely to develop glaucoma and cataracts at a younger age than are those without diabetes.

Diabetic retinopathy develops in the retina in nearly all patients with long-term type 1 diabetes and greater than 60% of those with long-term type 2 diabetes. According to the American Academy of Ophthalmology, diabetic retinopathy affects approximately 4 million people older than 40 years, and vision-threatening diabetic retinopathy affects approximately 900,000 people. By 2020, these figures are projected to increase to 6 million people with diabetic retinopathy, including 1.3 million with vision-threatening diabetic retinopathy. The past 40 years have witnessed great advances in therapeutic options for diabetic retinopathy, but despite a number of effective treatments, diabetic eye disease is still one of the leading causes of vision loss in the United States, in part because many patients are not identified as needing therapy.

In addition to counseling patients on the importance of glucose control has on maintaining vision, clinicians should emphasize the need for regular vision tests among patients with diabetes, including dilated eye exams. Early detection offers the best long-term visual outcomes and is even more important with new treatments approved for the management of patient with diabetic retinopathy. With these new treatments we enter an era of a potential for visual improvement after therapy.

This is CME on ReachMD. I am Dr. Matt Birnholz. My guest, Dr. Rishi Singh, and I will be focusing on diabetic retinopathy and the need for earlier detection, better counseling methods and enhanced management strategies. And a reminder to our listening audience that an online tool kit supplement is also available for clinicians to download as a specialized resource, and that's available at [ReachMD.com/CME](http://ReachMD.com/CME).

So, without further ado, welcome to our program, Dr. Singh.

Dr. Singh:

Thank you. Thank you for having me.

Dr. Birnholz:

Great to have you with us. So, to start, what can you tell us about the current prevalence of diabetic retinopathy?

Dr. Singh:

Diabetic retinopathy is increasing as diabetes has been increasing. It's one of the four leading causes of new blindness in the United States, actually the leading cause of blindness among working-age adults, so patients the age of 20 to 74, and therefore has some of the largest socioeconomic impacts of any eye disease currently. With the working-age population, patients aren't able to necessarily attend their jobs and tend to their normal day-to-day business opportunities and therefore struggle to make up the ability to keep their vision as well as keep their careers and their productive lives going. And the interesting thing has been the increase in diabetes, which is also increased with obesity in the US population because there's been - a significant increase in diabetic retinopathy, which is the endstage form of diabetic eye disease, and that has increased to 89% from 2000 to 2010.

Dr. Birnholz:

Eight-nine percent, it's a pretty staggering statistic. Why don't we review the pathophysiology of diabetic retinopathy and how this disease affects the eye specifically?

Dr. Singh:

Sure. Dr. Singh:

So, diabetes can affect multiple parts of the eye, and it actually can affect both the front or the back of the eye. We know that patients with diabetes have an increased risk of cataracts, which is a coloration or change in the lens in a patient with diabetes, and that can blur vision over time. Patients with diabetes can also develop glaucoma, which is an increase in intraocular pressure of the eye. But probably the more significant ways of treating patients or patients who develop ocular complications is actually diabetic retinopathy and diabetic macular edema. Diabetic retinopathy is the proliferation of blood vessels and the closure of blood vessels in response to diabetes from glycosylation end-products, and diabetic macular edema is from the breakdown of the blood-retinal barrier, which is the leading cause of vision loss in patients with diabetes.

Chronic hyperglycemia from diabetes causes a significant amount of both microvascular damage and metabolic responses. The microvascular damage is mediated mostly by chronic subclinical inflammation, which leads to retinal capillary leukostasis, endothelial cell damage and capillary closure, and this ultimately leads to ischemia and loss of vision in those patients. The metabolic response is important because it leads to glycosylation end-products, reactive oxygen species, and activation of protein kinase C, and this in turn leads to the release of vascular endothelial growth factor. This vascular endothelial growth factor has been identified in ocular tissues of diabetic patients and was the first implementation that this was an important factor in this disease state of these patients. VEGF is important for vascular permeability and vascular stability, and increased levels of VEGF can also cause breakdown of the inner blood-retinal barrier, capillary leakage and, finally, the leakage of fluid into the retina known as macular edema, or the closure of capillary blood vessels and then new blood vessel formulation, which is known as proliferative diabetic retinopathy.

Dr. Birnholz:

And I imagine there is some confusion around the classification of diabetic retinopathy among some clinicians. Can you review that really quickly?

Dr. Singh:

Yes, sure. So, clinicians classify diabetic retinopathy in multiple different ways. First, there is a scale of nonproliferative diabetic retinopathy and proliferative diabetic retinopathy, and within these major classifications are subcategories as well, such as mild, moderate and severe in nonproliferative diabetic retinopathy, and this is a continuum from the more common, less severe, nonproliferative diabetic retinopathy to the less common, more severe, proliferative diabetic retinopathy. Also, to remember, diabetic macular edema, which is the leading cause of vision loss in patients with diabetic retinopathy, can occur at any level within this spectrum. It can occur early in the disease state when you have early microvascular changes, or it can occur very late in the disease state when you have proliferative changes in proliferative diabetes and therefore needs to be monitored and managed at each of these stages.

Dr. Birnholz:

Why don't we turn to screening? Dr. Singh, what are the current guidelines for diabetic retinopathy screening?

Dr. Singh:

Sure. So, the American Diabetes Association and the American Academy of Ophthalmology have gotten together and sort of reviewed these guidelines for screening, and that includes an annual exam with a dilated eye examination, so that's an examination where they perform... put drops in your eyes and dilate your pupils so they can look at the back of the eye into the periphery of the retina and

causes a little bit of blurred vision at distance for about 3 to 4 hours. They recommend in type 1 diabetics or juvenile-onset diabetics that you have an examination within 3 to 5 years of diagnosis and then yearly follow-up thereafter. In the adult-onset patient or the type 2 diabetic, you have at the time of diagnosis and then yearly thereafter. And then, finally, those patients who are -- a growing number or percentage of patients -- who are pregnant and have diabetes, that they recommend those patients have an examination prior to conception if possible, early within the first trimester. If there's any amount of nonproliferative disease, they recommend it to be done every trimester and, more significantly or more frequently, if they have more severe diabetic eye disease, but essentially, you go for trimester visits in those who have some amount of diabetic retinopathy, and then eventually after birth you have another examination about 2 to 3 months after delivery of the baby.

One of the key issues for patients and providers to understand is there are different types of eye exams they need. They are referred to sometimes as a dilated eye examination, a retinal exam or diabetes eye exam. They all consist of the same thing, eyedrops in the eyes for a period of 2 or 3 hours where it blurs the vision in order for us to see the retinal, mid and far periphery. The real issue that we have noticed from the majority of studies, thus far, is that many patients aren't getting sufficient care to prevent visual impairment. In recent cross-sectional analyses, only 46% of patients who are above the age of 40 were actually getting their annual eye examination or visit within a 12-month period. In addition, the number of eye examinations have really just been lacking their annual percentages. Commercial payers, Medicaid and Medicare, have all reported their rates of annual eye exams which approach about 50 or 60% depending on what you look through in those groups. Now, that's a significant improvement over 2008 but still leaves a lot of room for growth.

Dr. Birnholz:

And just to carry forward our theme here for reviewing in the first half of our interview, I'd like to go over some of the established risk factors for diabetic retinopathy for our audience. Can you go over those for us?

Dr. Singh:

Sure. So, there's a variety of established risk factors for the progression of diabetic retinopathy, and the pillars of this are really hyperglycemia, which is a key modifiable factor, hypertension and hyperlipidemia, and there have been a variety of studies that have shown this. With the level of retinopathy or the increase in hemoglobin A1c and the duration of diabetes, the longer the duration and the higher the hemoglobin A1c can have a much more significant impact on the progression to both proliferative and severe nonproliferative diabetic retinopathy. That can almost double based on 1 percentage point of hemoglobin A1c. So, those patients who are meeting the American Diabetes Association guidelines, have an A1c of less than 7, have a very low rate of progression over time from 4 to 6 to 8 years. However, those patients who have a hemoglobin A1c of greater than 7.5 or even 8, who are not meeting ADA guidelines, can have almost a doubling of their rates of retinopathy over time because of the poor control of their hyperglycemic state.

Probably the more important study that has looked at this recently was the ACCORD study, and this was 2,800 patients, and subjects were randomized to intensive or standard glycemic treatment and also dyslipidemia treatment and systolic blood pressure control, and the study really found a significant reduction in both the progression rates in those patients who underwent intensive glycemic and lipidemic control, and so, that was a really strong recommendation that both of these factors systemically when controlled right can really reduce the progression of retinopathy progression over time.

Dr. Birnholz:

Well, for those who are just tuning in, you're listening to CME on ReachMD, and I am Dr. Matt Birnholz. My guest is Dr. Rishi Singh, and we're talking about diabetic retinopathy and some of the advances both in earlier detection and treatment.

So, on that note, Dr. Singh, why don't we turn over to the treatment side and look at the latest interventions for diabetic retinopathy and diabetic macular edema respectively. What can you tell us?

Dr. Singh:

Well, we've gone through a huge revolution in treatment of this disease state. When I first started in the field, there were very few treatments to offer. We were essentially using a laser for both treatment of diabetic retinopathy and diabetic macular edema, and this was back in the 1990s, and what it allowed for was the treatment of both diabetic edema and proliferative disease with laser photocoagulation, and we were lasering eyes that had neovascularization to prevent the ischemic drive from peripheral nonperfusion, as well as treating central edema by putting in laser scars, which essentially would artificially scar the retina down and prevent future swelling or progression of the diabetic macular edema we were seeing. In fact, we also lasered microaneurysms as a way to close off the leakage that would occur through the capillaries into the retina in those patients. And what we found for the majority of cases was that there was quite a significant reduction in vision loss over time, a 50% reduction, in fact, in those who got focal laser treatment versus control patients who were just observed at the time in the 1990s. So, while it was an effective therapy, it only, unfortunately,

caused visual stabilization and not necessarily improvement.

We have now moved on in the past few years from 2004 onward amongst the interventions for diabetic macular edema and diabetic retinopathy has been these growth factor inhibitor drugs such as vascular endothelial growth factor inhibitor drugs, and these have been pioneered in both the RISE and RIDE studies looking at ranibizumab, as well as the VIVID and VISTA studies, which looked at the intravitreal injection of aflibercept for the treatment of diabetic retinopathy and diabetic macular edema. Also, in comparison to that, there have been some other newer studies as well both looking at intravitreal steroids, first the dexamethasone intravitreal implant, which was approved in late 2009, as well as the fluocinolone intravitreal implant, which is also known as the Iluvien implant, which was released in 2010, and has received market approval for the treatment of diabetic macular edema. And this ushers in a treatment period of visual improvement versus previous laser treatments which were about visual stabilization.

Dr. Birnholz:

Let's talk about the differentiation between the local versus systemic treatment methods that have come along. How do these types of approaches affect treatment outcomes in your experience thus far?

Dr. Singh:

Well, there's been, I think, a variety of different effects from these treatments. So, the local treatments such as anti-VEGF agents are important because they control retinopathy and diabetic edema locally. Systemically, even if the patient is poorly controlled systemically, what we have at least found is these local agents work really quite well. And there used to be this moniker that when a patient first showed up in the ophthalmologist's office that if they had really bad diabetic eye disease, that they would first refer them back to the primary care physician for better, or an endocrinologist, for better systemic control before initiating therapy. The vast majority of studies have shown that's not necessary.

We also know that we've looked at quartiles of hemoglobin A1c and their impact as far as the treatment outcomes go, and what we found from those studies was that, essentially, there was no such improvement or no change in the improvement seen in patients with different hemoglobin A1c quartiles. For those patients who have the highest quartile, 8.6 to 12.6, they had an equivalent improvement in visual acuity than those who had a hemoglobin A1c of 4.2 to 6.6 within the post-hoc analysis performed.

Let's look at some of the results in more detail. Anti-VEGF therapy has been shown in multiple studies to improve retinopathy scores. One of the interesting findings about this has been that anti-VEGF drugs can actually reduce the 2-step and 3-step improvements in retinopathy scoring from baseline, as well as the fact that in the different drugs they have about a 30 to 35 to 40% rate of improving 2-step retinopathy scoring from baseline; and therefore, in the patient with very, very severe disease, for example, the severe nonproliferative disease, it has almost a 71% rate of improving 2-step retinopathy scores. And this is a unique treatment in that it reduces the progression and causes regression of retinopathy that was not achieved prior with our laser treatments and other drugs we had tried in the past. One of the key clinical questions that comes up during conversations with other internal medicine providers and endocrinologists is: Do systemic outcomes affect the treatment outcomes with these newer anti-VEGF agents? If you're not already aware, many of these anti-VEGF agents, including ranibizumab and aflibercept, have been shown to improve visual acuity over time with patients achieving between a 10- to 15-letter improvement in visual acuity on the eye chart from receiving these intravitreal or intraocular injections of these anti-VEGF agents over a 2-year period.

Dr. Birnholz: And you alluded to this before regarding comparing anti-VEGF and some more panretinal laser treatments. Can you just cover that again a little bit more detailed as to how the two compare in the treatment of diabetic retinopathy?

Dr. Singh:

Yes. So, we used to use panretinal laser as our mainstay for the treatment of proliferative disease, and this was a great treatment. Unfortunately, what it did cause was peripheral vision losses. It was reducing the ischemic drive of the retina to produce VEGF by giving panretinal laser to ablate the retinal periphery. And, in fact, nowadays what we found in treating patients with anti-VEGF agents is we can have an improvement in retinopathy and regression by simply giving the intravitreal or intraocular drug. PROTOCOL S was a study that looked at this. This was a study conducted by the DRCRnet, and they looked at the treatment with ranibizumab versus panretinal laser for patients with proliferative diabetes, and what they found was even though the value of visual acuity gain was only 2 letters greater in those patients who had ranibizumab treatment versus panretinal laser, there was a large area under the curve for those patients who received ranibizumab over time. And, in fact, those patients who received ranibizumab went on less to developing neovascular glaucoma and some of the other endstage complications from diabetes as a result of getting their anti-VEGF treatments.

Dr. Birnholz:

Now, one of my last questions to you, Dr. Singh, I want to turn to a practical side, and that has to do with how we incorporate team-based care models for managing these particular patients and how that might further enhance patient outcomes. What about teams-

based models for care here?

Dr. Singh:

You know, that's a great question. I have, as an ophthalmologist, worked in concert with our endocrinologist, our primary care physician and also podiatrists and nephrologists to manage these diabetic patients. When we see diabetic eye disease, we refer or tell that patient that they have that eye disease and let their physicians know as well, because the goal is then to determine what their risk stratification is for their other microvascular and macrovascular complications, and it's really a multidisciplinary team that approaches these patients. Their primary care helps a lot by realistically talking about their long-term goals. The ophthalmologists help with the short-term and comprehensive eye examinations. And, obviously, endocrinology helps modify and help with very complicated patients who have maintained other treatments and not done well on other treatments and get them better on diabetic control. And we utilize this team approach for all of our diabetic patients at this point. It's an effective way of really preventing vision loss and also preventing the severe complications from diabetes in those patients.

Dr. Birnholz:

Well, Dr. Singh, we've covered a lot of points here regarding diabetic retinopathy, the earlier detection, pathophysiology, some of the treatment directions, but before we wrap up, are there any important points you want to summarize or reiterate on this subject for our audience?

Dr. Singh:

Yes, so I would say that we are in a new era of treatment for these patients with diabetes. Before, you were assured if you were a diabetic patient to developing severe eye disease to the point where you would not be able to see and, potentially, some of the previous treatments weren't necessarily going to help with regressing retinopathy. The growth in new treatments available for patients for diabetes and diabetic macular edema is significant. Anti-VEGF therapy is probably the cornerstone of these therapies that we use for patients and has improved vision and improved retinopathy outcomes in these patients in many, many studies. We moved from a period of vision preservation to vision improvement, and I think if any of us are going to develop diabetes in the next couple years, we should be quite satisfied that the treatments we have available will prevent many of these patients from going severely blind or blind all together from these disease states. And with the recent approval of anti-VEGF therapies for other indications such as diabetic retinopathy, we have really some significant methods of treating to address it.

Dr. Birnholz:

With that I very much want to thank my guest, Dr. Rishi Singh, for discussing advanced concepts in diabetic retinopathy, detection and management with me.

Dr. Singh, it was great having you on the program.

Dr. Singh:

Thank you for having me.

Narrator:

Additional resources are available to complement this program.

An online toolkit supplement for clinicians is available at [reachmd.com/cme](https://reachmd.com/cme). These resources are fully downloadable and include:

- From the National Eye Institute at the NIH, a diabetic retinopathy fact sheet and the diabetes and healthy eyes toolkit
- The American Academy of Ophthalmology's latest treatment guidelines on diabetic retinopathy
- A key publication for participants wishing to go into greater depth of some of the clinical trials discussed in our program
- And lastly, a listing of key websites and resources for patients and their caregivers

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