

### Transcript Details

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### See What Matters in Diabetic Macular Edema (DME)

#### Dr. Adiguzel

Hello and thank you for joining us. I'm Eser Adiguzel and I'm here with my colleague Randy Wong, and we're here to see what matters in diabetic macular edema, or DME, specifically the multifactorial challenges of DME.

#### Dr. Wong

This presentation will not include discussion of any specific treatment and will remain focused on disease state. This nonpromotional program is for scientific and educational purposes only and is not an accredited continuing medical education program. The presenters, Eser and I, are both Novartis employees.

#### Dr. Adiguzel

First, we'll begin with an overview of DME.

#### Dr. Wong

Diabetes is a growing worldwide epidemic affecting the working age population. The working age population is defined as those workers age 20 to 79. In 2019 it's estimated that there were over 463 million patients with diabetes, and that number is expected to grow to over 700 million by the year 2045. And if you look below those numbers, that is the associated economic impact.

#### Dr. Adiguzel

Diabetes is associated with several macrovascular and microvascular complications. So, for macrovascular complications, some of those are stroke at an incidence of 18 per 1,000 patients, cardiovascular disease, with an incidence of 26 per 1,000 patients, as well as lower limb amputation at an incidence around 1%. Some of the microvascular complications that we might see with diabetic patients are retinopathy at an incidence of 4.6%, as well as neuropathy with a prevalence of around 7.7%.

#### Dr. Wong

Now a common complication of diabetes is diabetic macular edema. Of the 463 million people age 29 to 79 years old living with diabetes, many will develop diabetic retinopathy at about a rate of 27%. Of those 27%, a smaller subset will develop diabetic macular edema, and that's what we're here to talk about today.

#### Dr. Adiguzel

So, DME is a chronic vision threatening condition that may result in blurred vision and blindness. It's one of the major causes of vision loss in the working age population, again, those patients that are 20 to 79 years. Typical patient characteristics with DME include hypertension, poor glycemic control, as well as having had diabetes for over 15 years.

#### Dr. Wong

So, you can say that vision loss is a major complication of diabetes through diabetic retinopathy. Loss of vision affects the normal daily activities, such as reading, driving, walking around the house, anything that impacts the ability to function independently. Visual impairment leads to considerable social and emotional strain, particularly in people who are also living with diabetes. Vision loss has been linked with falls and injury, and worsened status in domains, such as employment and education.

#### Dr. Adiguzel

Now we'll start to discuss the pathophysiology and clinical features of DME.

#### Dr. Wong

Let's look closer at this slide. DME is the downstream result of hyperglycemia, induced oxidative stress, which leads to

neurodegeneration, vascular pathology, and inflammation. And if we look at those three processes, which are orange in this schematic, neurodegeneration, vascular pathology, and inflammation, look how VEGF interplays between vascular pathology and inflammation. This will be pertinent later on in the discussion. It's these three processes that we believe lead to the alteration of the blood retinal barrier and increased vascular permeability, which is the definition of diabetic macular edema.

**Dr. Adiguzel**

So, macular edema, which is characterized by fluid accumulation in the retinal layers, results from the breakdown of the blood retinal barrier. Normally, the interstitial spaces of the retina remain dry. However, in DME, increased VEGF levels contribute to vascular permeability and result in fluid leakage into the retina.

**Dr. Wong**

Fluid accumulation results in retinal thickening and disruption of the retinal architecture. Fluid in the intraretinal space is the most common type of retinal fluid seen in patients with DME, while fluid in the subretinal space is only seen in a minority of patients, as depicted in the graphic.

Let's look at the right side of this slide. As a result of fluid accumulation, retinal thickening and disruption to the retinal structure compromises visual function in patients with DME. Let's look at the left side, where there's a fluorescein angiogram showing lots of macular edema. If we look on the right side, we see a classic OCT showing both intraretinal fluid and subretinal fluid.

**Dr. Adiguzel**

So, structural and functional changes are associated with DME. Let's go over a few of them. First and foremost, there is retinal swelling or thickening, there's breakdown of the blood retina barrier or the BRB. There is blood vessel leakage, as well as cystoid macular edema. There is serous retinal detachment, vitreomacular traction, and hard intraretinal exudates. So, Randy, why don't you walk us through some of these features as seen on the OCT and the fluorescein angiogram.

**Dr. Wong**

Sure. Let's look at the OCT, which is at the top, and this is typical retinal thickening that you see in patients with diabetic macular edema. You can see where the RPE layer is, and the choroid, those are normal. Below is a fluorescein angiogram and it shows normal choroidal perfusion, it shows normal retinal vessels, those are those big riverlike conduits that you see, and those bright spots are microaneurysms, and those dark spots are intraretinal hemorrhage, and those are characteristic of patients with diabetic retinopathy.

**Dr. Wong**

Now, as a retina specialist, we use many imaging tools to diagnose or monitor patients with diabetes mellitus. And let's look at this slide a little bit closer. Some of the tools that we use are fundus autofluorescence, it's also known as fundus photography, spectral domain OCT is very useful, but I think the mainstay is OCT, which is third on the right. It's quick, it's reproducible, it's noninvasive. And then the mainstay has always been fluorescein angiography.

**Dr. Adiguzel**

Now we'll get into some of the challenges in DME.

**Dr. Wong**

The patient journey involves screening, diagnosis, and monitoring. And this is required of every patient with diabetes. Screening involves complete ophthalmic examination to include visual acuity testing, with refraction, or a pinhole. Retinal examination may include direct or indirect ophthalmoscopy, as well as a good slit lamp exam.

Diagnosis of diabetic macular edema may include fundus photography, fluorescein angiography, or OCT. Critical to this process is monitoring. Now, monitoring varies from patient to patient and depends upon really how much disease is present. The goal of monitoring is to maintain or improve vision, the goal of monitoring is to maintain or improve quality of life. And all this is dependent upon one thing, and that's compliance of the patient.

**Dr. Adiguzel**

So, timely referral, screening, and management, are important for preventing vision loss. Screening, early detection, and appropriate management, as recommended in clinical practice guidelines, can prevent cases of severe vision loss and blindness in patients with DR or DME. Vision loss itself can be prevented with a broad-based system level approach, such as some of the items outlined here. Increasing public knowledge by using targeted healthcare education, by well implemented community or national level screening programs, timely referral for patients with more severe levels, as well as appropriate treatment for advanced diseases such as DME.

**Dr. Wong**

Management of DME involves control of risk factors and use of ocular treatments. To prevent retinopathy and its progression, it's really

important to manage risk factors, such as blood glucose, blood pressure, and serum lipids. Our available ocular treatments in 2021 include laser treatment, anti-VEGF therapies, and steroids.

**Dr. Adiguzel**

Now approaches to DME have evolved over the past decades to move towards improving vision. Prior to the 1980s we had no treatment, and these patients unfortunately experienced vision loss. From the 1980s onwards, we had laser photo coagulation, which the main purpose was to stabilize the vision the patients had. From 2000 onwards, with steroids, and 2010 onwards anti-VEGF therapy, both of which could be used to improve vision. In this day and age, 2020 and beyond, we're really looking towards ongoing research to help optimize treatments.

**Dr. Wong**

Challenges for DME are multifactorial. We have to consider the disease burden, patient comorbidities, the huge issue of noncompliance, increased healthcare resource utilization, which we'll see in a couple slides, and the degree at which poor vision is the driving force for all of this. Key obstacles to overcome in the management of DME are to reduce challenges while maintaining sustained visual function in patients.

**Dr. Adiguzel**

So, disease associated comorbidities really contribute to disease burden for patients with DME. If we look at this slide, we can see on the left-hand side, all of the different types of medical experts these patients may have seen in the past six months, and on the right-hand side, the average number of times they've seen them in these six months, ranging anywhere from one to almost seven times.

**Dr. Wong**

That's a lot of doctors and a lot of visits in only six months.

As we've alluded to, patients with DME have higher healthcare resource utilization compared to non-DME patients with diabetes. Let's just look on the Y axis on the left. Look at the number, or the total healthcare visit days, the outpatient visit days, inpatient visit days, number of trips to the ER, the number of times they have to go to an eyecare specialist, and unique medications.

**Dr. Adiguzel**

So, patient compliance with clinic visits is low for DME compared to wet AMD. So, on this slide, we can see on the left-hand side for the US, and on the right for Europe, with wet AMD patients represented in gray, and DME patients seen in blue. And what we can see here is that there's a higher no-show rate for patients with DME that may be attributed due to this high monitoring burden, due to the multiple comorbidities associated with diabetes.

**Dr. Wong**

Comorbidities and lost time contributed to patient noncompliance with care for DME, and when polled, 209 patients had these reasons for being noncompliant, and these are listed on the left. We've got longer waiting times in the clinic, we've got other medical or physical conditions, some patients just forgot to come. They're unable to leave work responsibilities, life may get in their way for others, they may not have an escort, or way of transportation to get to the office. Some patients were unhappy with the care they received in the previous clinic visits. And of course, there's the financial costs.

**Dr. Adiguzel**

As well, noncompliance has been seen to lead to a greater than 10 times rate of significant vision loss in patients with DME. On the right-hand side of the slide, you can see that with an average follow up time of almost 30 months, patients have approximately 25 visits. And on the left-hand side, you can see a graph representing the change in letters of vision gained by the number of therapy breakoffs in DME vision with the number of breakoffs increasing as you move from left to right.

This shows that as the number of breakoffs increase, the vision loss increases as well. And approximately 15% of patients who are noncompliant versus approximately 1% who are compliant, have been shown to have greater than a 15-letter loss in their first year of therapy.

**Dr. Wong**

So, as we've seen, challenges for DME are multifactorial. There's the disease burden and patient comorbidities. We talk about how diabetes affects macrovascular and microvascular organ systems. The issue of noncompliance is huge. We saw on the slides how many office visits, and how many different healthcare providers, are involved in the care of a patient with diabetic macular edema. There's the increased healthcare resource utilization, and in combination, these are the burdens, or the hurdles our patients face to prevent poor vision.

I'm Randy Wong for Novartis, along with Eser Adiguzel, thank you very much for joining us today, we hope to see you soon.