Dra. Rivera Ruiz.
Hospital Central De la Defensa Gómez Ulla.

Dra. Bañeros Rojas.
Hospital Central De la Defensa Gómez Ulla.

Key Aspects in Diabetic Retinopathy

Diabetic retinopathy (DR) is a retinal microangiopathy that primarily develops due to chronic hyperglycemia, whether t associated with hypertension. Unfortunately, we can still affirm that diabetic retinopathy is the leading cause of blindness in people younger than 65 in Western countries.

Dietary habits, changes in the population's lifestyle, sedentary behavior, and obesity are some of the reasons leading to an increase in the incidence of diabetic retinopathy and its complications. While other causes of blindness such as cataracts have decreased, in the case of DR, the number of blind people doubled between 1990 and 2015 (1).

After more than 20 years of disease progression, 90% of type 1 diabetes cases and 60% of type 2 cases would have some form of retinopathy, and of these, 5% will require treatment to avoid irreversible blindness.

Given this scenario, the approach to DR should focus on 3 aspects:

1. EARLY DIAGNOSIS OF THE DISEASE

Diagnosis and management in DR are based on identifying at-risk patients before visual acuity loss. This is why all patients should be periodically examined by an ophthalmologist (Evidence Level 1).

The problem with this recommendation would be the burden on health care services, as 70% of people with diabetes do not show signs of diabetic retinopathy.

Due to the scale of the problem, screening programs have been implemented in some countries using non-mydriatic cameras and telemedicine (sensitivity > 80% and specificity > 90%) (2). Thus, the first retinography should be performed 3-5 years after diagnosis in T1DM and at the time of diagnosis in T2DM (1).

Subsequently, screening will be performed every 2-3 years in people with diabetes with a < 10-year history, good control, and no DR; whereas if these criteria are not met, retinography should be annual or for those with mild non-proliferative DR.

This screening program has been successfully implemented in numerous countries by ophthalmologists, such as RETISALUD in the Canary Islands or in the Catalan community, where it is performed by Primary Care physicians. Adding screening macular optical coherence tomography (OCT) to retinography remains debated, given the specificity of the technique which would require expert personnel, but it is increasingly present in diagnosis and treatment.

AI-based screening programs will play a very determinant role in DR, having currently demonstrated high sensitivity and specificity values. Numerous studies have been published using this technology to prioritize follow-up visits, and although they have shown great potential, protocols need to be adjusted to real clinical practices (3).

2. CONTROL AND PREVENTION OF DR

In all stages of DR, endocrinological control has been shown to be the fundamental pillar, with highly relevant criteria being:

- ***Controlling blood glucose levels:***

  Glycated hemoglobin A1c (HbA1c) should be maintained < 7%. People with T1DM who maintain this level reduce the incidence of DR by 76% and progression by 54% according to the Diabetes Control and Complications Trial (DCCT) (4). Intensive glycemic control is associated with a reduction in the risk of DR onset and a reduction in existing DR in both T1DM and T2DM vs conventional therapy. Furthermore, in the DCCT, intensive control was associated with a reduction in the progression of severe NPDR and PDR, the incidence of macular edema, and the need for panretinal photocoagulation (PRP) and focal photocoagulation (4). Paradoxically, very rapid glucose control can cause worsening and macular edema, which is related to a more advanced degree of DR and poorer DM control prior to intensive therapy.

- ***Maintaining blood pressure levels < 130/80.***

  Regarding arterial hypertension (AHT), it also associates with an increased appearance of macular edema and progression, so its control also shows a Grade A evidence. Strict control decreases progression by 34% and vision deterioration by 47% (5).

  Drugs that block the renin-angiotensin system reduce the incidence of DR in patients with type 1 diabetes and induce regression in those with T2DM (6). »

AFTER MORE THAN 20 YEARS OF DISEASE PROGRESSION, 90% OF TYPE DIABETES CASES AND 60% OF TYPE 2 CASES WOULD HAVE SOME FORM OF RETINOPATHY, AND OF THESE, 5% WILL REQUIRE TREATMENT TO AVOID IRREVERSIBLE BLINDNESS

FIGURE 1.

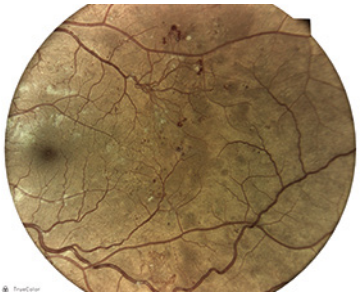

FIGURE 2.

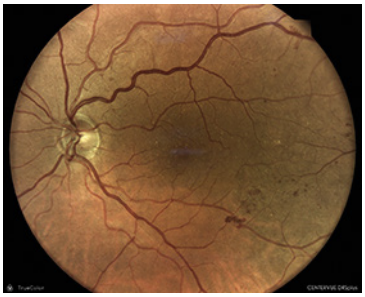

FIGURE 3.

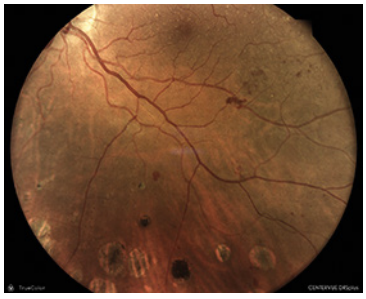

FIGURE 4.

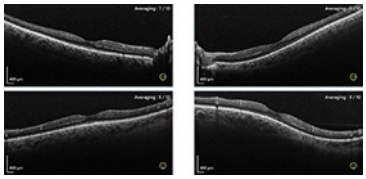

FIGURE 1. Detail of PDR in the left eye. Microaneurysms and hemorrhages are visible in all quadrants and a neovascular tuft dependent on both superior and inferior temporal arcades with proliferation.

FIGURE 2. Moderate NPDR. Aneurysms and some hemorrhages are visible in all 4 quadrants. An area of telangiectasia/IRMA is visible in the inferior temporal vessel in the left eye.

FIGURE 3. Detail of panretinal photocoagulation outside the vascular arcades in moderate NPDR.

FIGURE 4. Detail of macular OCT in the previous patient, where no macular edema is observed.

» • *Having LDL cholesterol levels < 100 mg/dL and triglycerides < 150 mg/dL.*

The use of atorvastatin has not been shown to influence DR progression. However, the use of fenofibrate for triglyceride control did demonstrate an effect on progression and a decrease in patients requiring treatment with photocoagulation (1).

• *Other cardiovascular risk factors.*

- Regarding renal status, urine microalbumin should be controlled.
- Do not smoke.
- Avoid overweight.
- Exercise and follow a healthy diet. Physical exercise is associated with less severe DR.

Close monitoring in adolescent patients. In adolescent patients, the risk of developing complications is high, so pediatricians should intensify their reviews; intensive insulin therapy has been shown to be especially useful in this group (7).

CLASSIFICATION OF DR AND FOLLOW-UP

To establish uniform criteria, the Global Diabetic Retinopathy Project Group (8) published a classification in 2003:

- **Mild non-proliferative DR:** This is the initial stage of the disease. Microaneurysms appear, which are dilatations of the wall of the small retinal blood vessels.

  Requires annual ophthalmological control or retinography.

- **Moderate non-proliferative DR:** Presence of microaneurysms associated with fewer than 20 hemorrhages, hard exudates, and vascular occlusions appearing as whitish spots called soft exudates.

  Requires semi-annual ophthalmological control.

- **Severe non-proliferative DR:** Presence of microaneurysms plus one of the following:
  - > 20 hemorrhages in each of the 4 quadrants.
  - Venous beading in > 2 quadrants.
  - Intraretinal microvascular abnormalities (IRMA) in > 1 quadrants.

  Requires ophthalmological control in a specialized retina unit, follow-up every 3 months.

- Proliferative DR: Presence of new blood vessel growth. These blood vessels grow along the retina and on the vitreous surface, and break easily, causing preretinal or vitreous hemorrhage.

  Monthly follow-up.

The presence of **diabetic macular edema** (DME) can be categorized based on OCT findings, as it is an objective and reliable method, in a simple way according to the International Council of Ophthalmology guideline:

- No macular edema (ME).
- Non-central ME: Retinal thickening that does not involve the central zone (1mm in diameter).
- Central ME: Thickening of the central zone.

3. TREATMENTS

- Non-proliferative DR: Requires strict control of the previously mentioned risk factors.

In the case of the severe or very severe form, PRP is the treatment of choice if the risk of progression is significant.

- Proliferative DR: Currently, treatment with sustained intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) is approved at this stage; however, PRP remains the gold standard due to problems with patient control and follow-up, which if they have only received anti-VEGF can have disastrous consequences (a fact that does not happen with PRP, as it is stable and long-lasting).

- Diabetic macular edema.

It is the most frequent cause of vision loss »

AI-BASED SCREENING PROGRAMS WILL PLAY A VERY DETERMINANT ROLE IN DR, HAVING CURRENTLY DEMONSTRATED HIGH SENSITIVITY AND SPECIFICITY VALUES

» **in a person with diabetes**. It is a complication that can appear in patients with non-proliferative diabetic retinopathy as well as in patients with proliferative diabetic retinopathy. Clinically, it manifests as subacute vision loss and central scotoma.

Diagnosis is based on funduscopy, although increasingly we rely on OCT, as this technique also allows us to quantify the amount of edema and objectively monitor the response to treatment.
The primary treatment for DME is based on intravitreal injections. There are 2 different pharmacological groups: anti-VEGF and corticosteroids. Many patients require a combination of both lines of treatment.

Regarding anti-VEGFs, 4 drugs have been approved for use in DME: ranibizumab, aflibercept, brolucizumab, and faricimab. Bevacizumab is used off-label for economic reasons or when approved drugs are not available or have not been effective.

Regarding intravitreal corticosteroids, dexamethasone implant and fluocinolone acetonide implant can be used. They differ in their duration of action, and both can cause ocular hypertension, glaucoma, or cataract development.

In selected cases, although currently in disuse, Argon focal laser treatment may be applied. D

CONCLUSIONS:

- The increasing incidence of diabetes and its metabolic complications has become a health problem that requires a close and multidisciplinary approach.
- DR screening with early diagnosis is currently the only way to control and prevent the consequences of DR.
- Control of cardiovascular risk factors, with special emphasis on glycated hemoglobin and hypertension, has been shown to improve the risk of DR progression.

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