Guidelines for the Management of Diabetic Retinopathy for the Internist

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Abstract: Diabetic retinopathy is classified into three stages based on the stage of progression of the disease—background (simple), preproliferative and proliferative. The earliest stage is called background diabetic retinopathy and is characterized by dot or blot hemorrhages and microaneurysms associated with retinal microvascular lesions which are closely related to hyperglycemia. With the development of retinal capillary obstruction, background diabetic retinopathy progresses to the stage of preproliferative diabetic retinopathy, in which avascular zones can be detected by fluorescein angiography. In proliferative diabetic retinopathy, which develops with further progression of the disease, newly formed blood vessels, vitreous hemorrhage, and retinal detachment produce severe visual loss. Good blood sugar control is essential for preventing the development and progression of diabetic retinopathy; therein lies the important role of the internist. In the stages of preproliferative and proliferative retinopathy, patients should be referred to the ophthalmologist for laser photocoagulation and vitrectomy. Patient education is important to prevent blindness resulting from diabetic retinopathy. Diabetic patients should be aware that diabetic retinopathy may lead to blindness. It must be emphasized that diabetic retinopathy generally causes no visual symptoms in its earlier stages and that, therefore, periodic funduscropy is necessary to detect the changes of retinopathy. In patients who are at a relatively lower risk of becoming blind, funduscropy with the use of polaroid photography could be extremely useful.

Key words: Pathology and stages; Control of blood glucose levels; Patient education for periodic ophthalmologic examination; Frequency of follow-up and stages

Introduction

Medical care of patients with diabetic retinopathy requires the collaboration of the internist and the ophthalmologist. I hope that this article will equip the internists with sufficient basic knowledge of the important issues related to the ophthalmologic treatment of diabetic retino-
Disease Status and the Stage of Disease in Diabetic Retinopathy

The pathophysiology of diabetic retinopathy is explained to facilitate the management and treatment of the disease.

1. Stage before the development of diabetic retinopathy

Diabetic retinopathy is diagnosed when abnormalities are observed on macroscopic examination by a funduscopy. However, microstructural or functional changes have already occurred before macroscopic fundus abnormalities are detected.

(1) Microstructural abnormalities

Diabetic retinopathy is essentially a retinal microvascular disease developing after prolonged hyperglycemia. The walls of small blood vessels are composed of endothelial cells lining the basement membrane and surrounding pericytes. Elevated blood glucose levels promote thrombus on the surface of the endothelial cells and necrosis of the pericytes, resulting in circulatory disturbance of retinal capillary. In addition, thickening and loss of elasticity of the basement membrane occurs, inducing circulatory obstruction (Fig. 1).

(2) Functional abnormalities

Among the microvascular lesions described above, injury to endothelial cells may lead to breakdown of the blood-retinal barrier (BRB). BRB, which is similar to the blood-brain barrier, prevents leakage of high-molecular-weight proteins or lipids into the extravascular space and maintains intraretinal homeostasis. Breakdown of the BRB due to endothelial injury causes extravasation of plasma proteins and lipids. While severe damage to the BRB can be detected by funduscopy, even slight functional deterioration may be detected by vitreous fluorophotometry.

Neuropathy in diabetics sometimes precedes the onset of retinopathy and often involves the retinal nerve cells. In some diabetic patients, abnormal waveforms can be observed on the electroretinogram (ERG) even before diabetic retinopathy is detected.

2. Simple diabetic retinopathy

Chronic hyperglycemia affects the retinal microvessels and facilitates progression of the disease. The earliest manifestation is damage to the retinal vascular walls, which results in microvascular obstruction. Damage to the microvessels triggers the formation of microaneurysms and rupture of the vascular walls, observed as dot or blot hemorrhages in the retina.

Breakdown of the BRB causes the retinal edema and promotes the formation of lipid deposits, mainly consisting of cholesterol derived from the plasma. These yellow-white lesions, called hard exudates, can be identified by funduscopy. When microvessel obstruction produces focal ischemia, pallor and/or edema of the retina develops. These ischemic foci are referred to as soft exudates.

3. Preproliferative diabetic retinopathy

Preproliferative retinopathy is a more severe form of diabetic retinopathy than simple retino-
management of diabetic retinopathy, and often progresses to proliferative diabetic retinopathy. Ischemia due to microvascular occlusion or leakage of plasma constituents stimulates the release of cytokines, particularly vascular endothelial growth factor (VEGF), which acts as an intercellular mediator in various ways.

VEGF facilitates the proliferation of endothelial cells and promotes neovascularization. New vessels are thus prone to form in areas of ischemia or leakage. Preproliferative changes signify the risk of progression to the stage of tissue proliferation, or proliferative diabetic retinopathy.

In the preproliferative stage, the funduscopic findings are characterized by an increased number of soft exudates in association with microvascular occlusions and intraretinal microvascular abnormalities (IRMA), consisting of irregular segmental dilatations or abrupt reduction in vessel branching around occluded vessels. Fluorescein angiography clearly depicts areas of microvascular occlusion as blackouts, since contrast medium does not enter infarcted regions (Fig. 2).

In fluorescein angiography, the patient is administered 5 ml of 10% sodium fluorescein intravenously. Immediately after the injection (in about 10 seconds or less), sequential photographs are taken for up to 10 minutes. These procedures cause a sensation of glare in the eyes of the patient. The dye is hepatotoxic and fluorescein angiography should not be performed in patients with severe hepatic insufficiency. The dye should also not be administered to patients in poor general condition, since anaphylactic shock has been reported in a few cases.

4. Proliferative diabetic retinopathy

With the formation of new blood vessels, diabetic retinopathy shows markedly different pathological features compared to previous two stages. In this stage, lesions are seen extending from the retina to the vitreous. New abnormal vessels form in areas adjacent to occluded vessels and grow out of the retinal surface into the vitreous. These new vessels radiate throughout the vitreous, running along the posterior hyaloid membrane at the border of the vitreous and the retina or infiltrating into the center of the vitreous.

Because of their fragility, newly formed vessels easily rupture with increase in the blood
pressure or traction from the vitreous and bleed into the vitreous (Fig. 3), causing pathological myodesopsia or visual impairment when blood covers the macula. New vessels induce gradual proliferation of connective tissue, mainly consisting of collagen fibers, which proliferates along the surface of the retina as a fibrous proliferative membrane. The proliferative membrane is adherent to the surface of the retina. Contraction of the proliferative membrane causes traction on the retina, resulting in retinal detachment which may result in severe visual loss when the detachment reaches the macula.

If vitreous hemorrhage interferes with fundus examination, echography must be performed to detect retinal detachment and examine the intraocular condition.

Treatment According to the Stages of the Disease

1. Stage before the development of diabetic retinopathy

Even at this stage, it is important to take measures to prevent the development of diabetic retinopathy. Control of blood glucose levels is essential and the internist plays a leading role.

Many cohort studies in the United States and Europe have shown that strict control of blood glucose levels is of critical importance in preventing the development of diabetic retinopathy and it has been recommended that the blood glucose levels be maintained within the normal range as far as possible. In addition, diabetic patients with hypertension should receive effective antihypertensive treatment, since many researchers have indicated that hypertension greatly influences the progression of the disease in type 2 diabetic patients.

Although a number of clinical studies have been conducted with a view to finding a new drug for preventing the development and progression of diabetic retinopathy, at present, no drug effective for this purpose is available. This suggests that many factors are involved in the pathogenesis of diabetic retinopathy and that no single drug can solve all the problems related to the disease.

2. Simple diabetic retinopathy

Damage due to aneurysms, dot/blot hemorrhages, hard exudates, and a small number of soft exudates are pathological condition of simple diabetic retinopathy, and these are reversible under good control of blood glucose levels by the guidance of the internist. Drugs are available for the symptomatic treatment of hemorrhages or exudates, but no medicines, as mentioned before, have been shown to influence the disease course itself.

When retinal edema due to increased capillary permeability extends to the macula, severe visual loss becomes inevitable. While drug therapy may be somewhat useful, the ophthalmologist plays an important role in preventing the progression of macular edema and reducing its severity. At present, laser photocoagulation and vitrectomy are performed at this stage. Photocoagulation should be initiated in time, preferably before the onset of impairment of macular functions.

Vitrectomy may reduce the severity of macular edema. The technique has been increasingly applied to the treatment of macular edema when the condition is too severe to perform laser surgery. However, even when the edema is relieved, visual loss often does not improve in patients with severe macular edema. Some investigators have recommended vitrectomy even in the earlier stages of macular edema, but this is still controversial.

3. Preproliferative diabetic retinopathy

In this stage, treatment is focused on the prevention of neovascularization. As new vessels develop in areas of retinal vessel occlusion, laser photocoagulation on the occluded area has been shown to be useful for the prevention of neovascularization. This is a bloodless operation and can be performed on an outpatient
basis. The usefulness of this intervention has been demonstrated in several clinical trials and its success rate in the prevention of severe diabetic retinopathy and blindness has been reported to be 70 to 90%.10)

At this stage, conservative medical treatment instead of laser surgery may increase the risk of blindness and impair the chances of improvement of the disease.

4. **Proliferative diabetic retinopathy**

Even at this stage, if neovascularization is mild or moderate, laser therapy may be effective. However, when vitreous hemorrhage or retinal detachment is detected, vitrectomy is recommended. Vitrectomy requires special surgical skill and expensive equipments.

Recently, the success rate of vitrectomy has improved with technical advances and the development of elaborate devices, but the operation is still challenging and the success rate is not high enough around 80%. Several studies have demonstrated a better outcome when vitrectomy is performed at the stage of mild retinal dysfunction and have recommended early vitrectomy.

**Guide to the Management of Diabetic Retinopathy for the Internist**

1. **Blood glucose levels control is the key**

   Treatment of diabetic retinopathy is based on good control of blood glucose levels. It is essential to maintain good control of blood glucose levels without interruption and to never leave hyperglycemia untreated. The first step in the management of diabetic retinopathy by the internist is to make the patient aware of how serious the complications could be.

2. **Subjective symptoms are not reliable indicators for the detection of diabetic retinopathy**

   The patients do not complain any symptoms until diabetic retinopathy progresses to the advanced stage. When vitreous hemorrhage, retinal detachment and severe macular edema occur, the patient may develop visual loss. Macular edema commences even at the earlier stage of simple diabetic retinopathy, and the morbidity of macular edema becomes worse and the condition becomes more severe as the retinopathy progresses.

   Vitreous hemorrhage often provokes pathological myodesopsia or blurred vision, while retinal detachment may induce visual loss or visual field defects. However, by the time the patient develops these symptoms, the disease has become far advanced and the risk of blindness is substantially high at this stage. Diabetic patients should thus be encouraged to undergo periodic ophthalmologic examination, even if they have no visual symptoms.

3. **Follow-up with polaroid photography**

   Fundus photographs provide a permanent record for later evaluation and can be studied by the same ophthalmologist or other specialists. Polaroid photography offers the additional benefits of instantaneous development and printing on the spot, and the patient does not have to wait for the results till the next visit. For the internist, fundus photographs obtained immediately are very useful for clearly explaining the current status of the disease to the patient. However, this simple technique also has the following disadvantages:

   The image quality of polaroid photographs is grainy and sometimes there are inconsistencies in printing. Thus, tiny lesions in the earlier stages or subtle vascular changes are often not clearly detected.

   The angles at which fundus photographs can be taken are limited, and only areas of the posterior pole at 45 degrees can be photographed. Lesions in the earlier stages of diabetic retinopathy are mainly noted on the nasal side of the optic disc, and photographs limited to areas surrounding the macula often miss severe lesions in other areas.

   Accordingly, polaroid photography is acceptable for excluding the disease in low-risk groups.
with good control of blood glucose levels in whom no fundus abnormalities have been detected by complete funduscopy in the previous one or two years. 11)

However, if any minor hemorrhage or lesions are detected, the patient should be referred to the ophthalmologist for a thorough fundus examination.

4. Frequency of the follow-up of funduscopic examination according to the stage of the disease

Diabetic retinopathy may progress differently according to the stages. The frequency of funduscopic follow-ups should be determined according to the stage of the disease in individual cases (Table 1). The internist should fully understand the status of the disease in each patient and refer the patient to the ophthalmologist when necessary, so as to offer timely intervention and prevent blindness.

Conclusion

This article describes the different stages of progression of diabetic retinopathy, and provides guidelines to the internist for the management of the disease. I hope that these descriptions will equip the internist with the basic knowledge for the treatment of patients with diabetic retinopathy.

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**Reference document:**