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Medical Treatment of Retinopathy of Type-2 Diabetes

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Abstract
The medical treatment of retinopathy in type-2 diabetes should be considered as a major component in the overall management of diabetic retinal disease. It is clear that specific and timely interventions, such as glycemic and blood pressure control, are the basis for good management of diabetic retinopathy. The American Diabetes Association has developed specific recommendations concerning diabetic retinopathy for the primary care physician and diabetologist. The ophthalmologist must be aware of these recommendations and establish efficient communication channels with the colleagues who follow their patients and the progression of diabetes closely. The challenge for the ophthalmologist is to make sure that, when signs of retinopathy are detected, information regarding the status of the retina, prognostic factors and the rate of progression must be given to the primary care physician and diabetologist. Under these circumstances, excellent glycemic control, aggressive management of blood pressure and normalization of lipids are all needed, and the goals to be achieved must be shared between the ophthalmologist and the primary care physician or diabetologist. Appropriate medical management of diabetic retinopathy is fundamental to reduce the risk of blindness. This goal can only be achieved if the ophthalmologist is fully aware of the role of medical management and establishes an efficient flow of communication with the primary care physician or diabetologist, particularly for the diabetic patients whose eyes show signs of risk for rapid progression of their retinopathy.

Diabetic retinopathy (DR) remains the leading cause of visual disability and blindness among professionally active adults in economically developed societies. This is of even greater concern now that a sharp increase in diabetes mellitus is expected in the next decade.

Laser photocoagulation remains the only tested method for treating DR. However, laser photocoagulation is advised only for patients with advanced retinal disease, either high-risk proliferative retinopathy or clinically significant macular edema. Vitrectomy has also been shown to be beneficial in even more advanced stages of retinopathy. These statements summarize the guidelines of 'preferred practice pattern' issued by the American Academy of Ophthalmology [1].

It is clear that the ophthalmologist views the accepted treatment of DR to include mainly surgical and ablative procedures. In general, these forms of treatment are given independent of the diabetes disease itself and metabolic status. However, recent developments in the medical management of diabetes have indicated that it may play a

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major role in preventing the macro- and microvascular complications of diabetes. The appropriate management of diabetes is particularly useful and effective in the earliest stages of retinal disease, when the disease process may still be reversible and before visual loss is already present.

Therapeutic Strategies for Diabetic Retinopathy

Medical therapy may be targeted to control DR at three levels: The first level should be directed at achieving near physiological levels of glycemia as soon as the diagnosis of diabetes mellitus is made. This approach is particularly effective if applied when retinopathy is in its initial stages [2].

The second and third levels are still at the developmental stage [3]. Their potential, however, is tremendous and the ophthalmologist must be aware of this and the rapid development.

The second level includes drugs aimed at controlling the biochemical events occurring in the retina as a result of the excessive availability of glucose: good candidates include aldose reductase inhibitors [4], inhibitors of protein kinase C activation [5] and inhibitors of advanced glycation end-products [6]. Evidence, mostly experimental but also clinical, is accumulating of their potentially favorable effects on the stabilization of the early stages of diabetic retinal disease.

Finally, the third level at which medical therapy may be targeted in order to halt the progression of diabetic retinal disease is at the lesion site, both at the neuronal and vascular levels. Treatment of the initial sites of cytotoxic and vasogenic retinal edema may be considered an appropriate goal, because there are now techniques available to monitor these initial retinal changes clinically [7, 8].

Cytotoxic edema may be addressed using neuroprotective agents such as calcium channel blockers, antioxidants and glutamate receptor antagonists. The field of neuroprotective drugs is very active and drugs specifically developed for retinal neuroprotection are expected to become available in the near future.

Vasogenic retinal edema is directly associated with breakdown of the blood-retinal barrier (BRB) [9]. Medical therapy of vasogenic retinal edema may be targeted to act directly on BRB function using corticoids, lazaroids or acetazolamide, but these drugs must be used with caution in the management of diabetes mellitus. Correction of the breakdown of the BRB in diabetes is a desirable goal and drugs acting as nitric oxide inhibitors or histamine H_1-receptor antagonists have been shown to have a stabilizing effect on the BRB alteration occurring in diabetes [6, 10]. The studies available, however, have been mostly experimental and are not yet for a variety of reasons, transferable to clinical practice. Another group of drugs that should be considered includes drugs like calcium dobesilate which has shown a vasoprotective effect in pilot clinical trials and have an established record of safety [11].

Finally, antihypertensive therapy should be considered at least when there is recurring vasogenic retinal edema with clear breakdown of the BRB. Angiotensin-converting enzyme inhibitors, like lisinopril, have been shown to act favorably on the evolution of the retinopathy [12]. Calcium-channel blockers should also be considered because of their multiple effect: antihypertensive, neuroprotective, and correction of ATP synthesis.

In the near future, medical therapy for DR will probably involve the association of drugs acting at all three levels. Therapy for DR should therefore include medications necessary for the best euglycemic control (insulin or oral antidiabetic drugs), a second drug given to correct the altered metabolism of the retina associated with excess glucose availability (aldose reductase or protein kinase C inhibitors, or antioxidants) and, finally, a third drug acting as a neuroprotective or vasoprotective agent. The choice of this third drug may be made based on clinical examinations showing the predominance of either cytotoxic or vasogenic edema of the inner retina.

The major concern, however, will be safety. Medical therapy of DR may be initiated immediately after the diagnosis of diabetes, and certainly before there is visual loss and the retinal lesions are irreversible. Therefore, it is long-term therapy. Side effects should be minimal and the medication must have a good benefit to risk ratio to be accepted.

At present it must be realized that medical management for DR is largely that of prevention. Controlled clinical trials have demonstrated that aggressive glycemic control reduces the risk of retinopathy. As a consequence, current recommendations for glycemic control are to aim for a fasting plasma glucose of <110 mg/dl and HbA_{1C} of $<7\%$ (normal range about 3.0–6.0%). Controlled clinical trials have also shown that aggressive blood pressure control reduces the risk of retinopathy. As a consequence, current recommendations for blood pressure control are to aim for a systolic blood pressure of <130 mm Hg and a diastolic blood pressure of <85 mm Hg in adults with diabetes.

Glycemic Control

Analyses from a number of epidemiologic studies and randomized controlled clinical trials suggest a significant relationship between glycemia and retinopathy. In these studies, integrated glycemic control is measured by glycosylated hemoglobin – either HbA_{1C} or HbA_1 (which includes HbA_{1C} as well as HbA_{1a} and HbA_{1b}) or total glycosylated hemoglobin. At both 4- and 10-year follow-up in the Wisconsin Epidemiologic Study of Diabetic Retinopathy [13, 14], there was a statically significant relationship between baseline HbA_1 and the incidence of retinopathy, progression of retinopathy by two or more steps on a modified scale developed by the Early Treatment Diabetic Retinopathy Study (ETDRS), and progression to proliferative DR (PDR).

The Diabetes Control and Complications Trial (DCCT) [15], a randomized, multicenter, controlled clinical trial, demonstrated that intensive treatment of type-1 diabetes with the goal of meticulous glycemic control decreased the frequency and severity of retinopathy, nephropathy, and neuropathy.

The intensive-therapy group achieved a median HbA_{1C} of 7.2% versus 9.1% in the conventional group. This separation in median glycemic values between the 2 groups was maintained for 4–9 years, with mean duration of follow-up 6.5 years for a total of approximately 9,300 patient-years of observation.

Within each treatment group, the mean HbA_{1C} during the trial was the dominant predictor of retinopathy progression. The most important risk factors for early worsening were higher levels of HbA_{1C} at screening and rapid reduction in HbA_{1C} in the first 6 months.

A study from Kumamoto University in Japan involved 110 non-obese patients with type-2 diabetes [16]. Of these, 102 subjects completed the 6-year study which was designed to be similar to the DCCT except for the inclusion of subjects with type-2 diabetes. Over the 6 years of follow-up, glycemic outcomes and risk reductions were almost identical to those found in the DCCT. The intensive-therapy group achieved a mean HbA_{1C} over the 6 years of the study of 7.1% versus a value in the conventional-therapy group of 9.4%. Progression to severe nonproliferative DR (NPDR) or to PDR was reduced by 40%, as well as the need for laser photocoagulation in the intensive-therapy group.

Finally, the United Kingdom Prospective Diabetes Study (UKPDS) [17, 18], a randomized, multicenter, controlled clinical trial, demonstrated that an intensive-treatment policy in type-2 diabetes with the goal of meticulous glycemic control decreased diabetic complications including retinopathy. A total of 5,102 subjects with newly diagnosed type-2 diabetes were enrolled. Retinopathy was assessed by four-field fundus photography performed at baseline and every 3 years. The intensive-treatment group achieved a median HbA_{1C} of 7.0 versus 7.9% in the conventional-treatment group. Patients assigned to intensive treatment had a significant 25% risk reduction in microvascular endpoints compared with conventional treatment, most of which was due to fewer cases of retinal photocoagulation for which there was a significant 29% risk reduction.

The current glycemic recommendations of the American Diabetes Association (ADA) appear in their 'Standards of Medical Care for Patients with Diabetes Mellitus' [19]. The goal is, ideally, for a fasting plasma glucose of <110 mg/dl and a HbA_{1C} of $<7\%$ (normal range about 3.0–6.0%). The ADA uses the term 'action suggested' to define another category which might also be defined as 'unacceptable glycemic control', that is a fasting plasma glucose of >140 mg/dl and a HbA_{1C} of $>8\%$.

Contemporary diabetes management is based on the concept of 'targeted glycemic control'. Therapy, based on glycemic goals, utilizes progressive, stepwise additions of whatever treatment modality is necessary to achieve glycemic goals. Medical nutritional therapy and promotion of physical activity are fundamental and needed for all patients, as well as basic diabetes education.

Intensive insulin therapy is mandatory in type-1 diabetes. This is accomplished, as in the DCCT, with insulin administered either as a continuous subcutaneous infusion with a pump or by multiple daily injections; frequent self-monitoring of blood glucose, and meticulous attention to balancing the insulin dose, food intake, and energy expenditure.

In type-2 diabetes progressive pharmacologic therapy is required, the specific choice is based on disease severity and glycemic targets, and should include insulin secretagogues (e.g. sulfonylureas and repaglinide) which stimulate insulin production.

Insulin sensitizers (e.g. biguanides and thiazolidinediones) which enhance muscle glucose uptake and decrease hepatic glucose production, α-glucosidase inhibitors which retard carbohydrate absorption, and, finally, when necessary replacement of insulin deficiency with insulin or insulin analogs.

Blood Pressure Control

For long time epidemiologic studies have suggested a relationship between blood pressure elevation and progression of retinopathy.

The Hypertension in Diabetes Study (HDS) was embedded in the UKPDS by using a factorial design [20, 21]. The HDS was conducted in 20 centers with 1,148 patients who had type-2 diabetes and coexisting hypertension. The design was a randomized controlled trial comparing 'tight' blood pressure control aiming for a blood pressure of <150/85 mm Hg with the use of an angiotensin-converting enzyme inhibitor (captopril) or a β-blocker (atenolol) as the main treatment, and 'less-tight' control aiming for a blood pressure of <180/105 mm Hg. Median follow-up was 8.4 years. The tight control group achieved a mean blood pressure of 144/82 versus 154/87 mm Hg in the less-tight control group ($p < 0.0001$). Patients assigned to the tight control group had a significant 37% risk reduction in microvascular end points compared with the less-tight control group.

Blood pressure lowering with captopril or atenolol was similarly effective in reducing the incidence of diabetic complications. There was no evidence that either drug had any specific beneficial or deleterious effect, suggesting that blood pressure reduction in itself may be more important.

In patients with diabetes, current blood pressure recommendations of the ADA appear in their 'Standards of Medical Care for Patients with Diabetes Mellitus' and in a consensus statement on 'Treatment of Hypertension in Diabetes'. Similar recommendations are contained in 'The 6th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure' and elsewhere [22].

The primary goal of therapy for (non-pregnant) adults (>18 years of age) with diabetes is to decrease blood pressure to, and maintain it at, <130 mm Hg systolic and <85 mm Hg diastolic. For patients with an isolated systolic hypertension of >180 mm Hg, the initial goal of treatment is a reduction of 20 mm Hg. If these goals are achieved and well tolerated, further lowering to <140 mm Hg may be appropriate.

The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus, a randomized, multicenter, controlled clinical trial, was conducted in 354 patients with type-1 diabetes aged 20–59 years in 15 European centers [12]. Patients were not hypertensive and were either normoalbuminuric (85%) or microalbuminuric (15%). Patients were randomized at baseline and followed up for 24 months. Lisinopril decreased retinopathy progression by two or more grades (73% risk reduction, $p < 0.05$) and progression to PDR (82% risk reduction, $p < 0.03$). In this study, patients with better glycemic control had the most benefit from ACE inhibitors, suggesting that the combination may be the best therapeutic approach.

Dyslipidemic Control

Diabetic dyslipidemia, particularly in patients with poor glycemic control, is characterized by increased levels of total cholesterol, low-density lipoproteins (LDLs), and triglycerides and by decreased levels of high-density lipoproteins (HDLs). Data from the ETDRS showed that elevated total serum cholesterol and LDL cholesterol is associated with a significant increase in the presence of retinal lipid exudates [23]. ETDRS patients with total cholesterol levels of >240 mg/dl were twice as likely to have retinal lipid exudates than were those patients with serum cholesterol levels of <200 mg/dl.

Data from the ETDRS suggest that treatment of hyperlipidemia may help stabilize the retinal status and possibility visual acuity. However, there are no data to suggest that visual acuity can be improved by the treatment of hyperlipidemia. Moreover, whether such treatment has a long-term beneficial effect on visual outcome is unknown.

Experimental Medical Therapies

Platelet Inhibitors

Diabetes is associated with increased platelet aggregability. As a consequence, there have been a number of investigations of various platelet-aggregation inhibitors, including aspirin, dipyridamole, and ticlopidine.

The ETDRS included a double-masked, placebo-controlled comparison of the effect of aspirin versus placebo on the progression of DR and the incidence of vitreous hemorrhage. There was no significant difference between aspirin and placebo [24]. The ADA, however, recommends considering aspirin therapy as a primary prevention strategy in high-risk men and women with type-1 or type-2 diabetes.

Aspirin alone and aspirin plus dipyridamole were evaluated in a double-masked, placebo-controlled European clinical trial, the Dipyridamole and Aspirin Microangiopathy of Diabetes Study [25]. The effect of these drugs

was quantified by macular microaneurysm counts in 475 patients with NPDR assigned randomly to aspirin alone, aspirin plus dipyridamole, or placebo. The mean yearly increase in microaneurysm count was less for the 2 treatment groups (aspirin alone and aspirin plus dipyridamole) than for the placebo group. This was true for patients with type-1 or type-2 diabetes. The clinical significance of this finding remains uncertain.

In France, the Ticlopidine Microangiopathy of Diabetes Study Group evaluated another platelet-aggregation inhibitor, ticlopidine, on the progression of microaneurysm counts in patients with diabetes and NPDR [26]. Microaneurysm counts were obtained from fluorescein angiography and included the macula as well as four peripheral fundus fields. For insulin-treated patients, ticlopidine was associated with a 7-fold decrease in microaneurysm count during 3 years of follow-up when compared to placebo.

Aldose Reductase Inhibitors

Aldose reductase inhibitors have been shown to prevent diabetes-like retinal vascular changes in some animal models. The Sorbinil Retinopathy Trial, a prospective, randomized clinical trial, tested this hypothesis by comparing the aldose reductase inhibitor sorbinil (250 mg/day) to placebo [27]. A total of 497 patients entered the study and follow-up examinations ranged from 12 to 56 months. Retinopathy was assessed by standardized fundus photography. There was no significant difference in retinopathy progression between the treatment and control groups. There are no aldose reductase inhibitors currently on the market. Several remain in clinical development.

Agents to Improve Capillary Fragility

Calcium dobesilate was developed to improve capillary fragility and decrease capillary leakage. A number of studies have examined its effect on DR. A number of small studies have indicated some promise [11], but the rationale of its action remains unclear.

Histamine Receptor Antagonists

In animal models with experimental diabetes, there is increased retinal histamine production. Histamine reduces the expression of tight-junction proteins in retinal endothelial cells, and histamine H_1- and H_2-receptor antagonists reduce retinal vascular permeability. This is the basis of a potential role of histamine in diabetic macular edema. In a double-blind, placebo-controlled 6-month pilot study of 14 patients with type-1 diabetes, combined astemizole and ranitidine therapy significantly reduced BRB permeability as measured by vitreous fluorometry [10]. This finding led to a double-blind, placebo-controlled study, the Astemizole Retinopathy Trial, which is being conducted to examine the effects of the histamine receptor antagonist, astemizole, in patients with macular edema.

Inhibitors of Protein Kinase C

Hypoxic retinal tissue produces vascular endothelial cell growth factor which stimulates endothelial cell mitosis. Experimentally, inhibitors of protein kinase C block endothelial tube formation in vitro and intraocular neovascularization caused by retinal ischemia [28, 29]. Two double-blind, placebo-controlled clinical trials are currently being conducted to test the effects of an orally effective β-isoform-selective inhibitor of protein kinase C: one in patients with diabetic macular edema and the other in patients with DR.

References

1 Fong DS, Ferris FL: Practical management of diabetic retinopathy. Focal Points, American Academy of Ophthalmology, March 2003, Section 3.

2 Skyler JS: Diabetic complications: the importance of glucose control. Endocrinol Metab Clin North Am 1996;25:243–254.

3 Cunha-Vaz JG, Lobo C: Medical therapy of diabetic retinopathy. Exp Ophthalmol 1998; 24:1–5.

4 Kinoshita JH: Aldose reductase in the diabetic eye: XLII Edward Johnson memorial lecture. Am J Ophthalmol 1986;102:685–692.

5 Aiello LP, Bursell SE, Clermont A, Duh E, Ishii H, Takagi C, Mori F, Ciulla TA, Ways K, Jirousek M, Smith LE, King GL: Vascular endothelial growth factor-induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective beta-isoform-selective inhibitor. Diabetes 1997;46:1473–1480.

6 Corbett JA, Tilton RG, Chang K, Hasan KS, Ido Y, Wang JL, Sweitland MA, Lancaster JR, Williamson JR, McDaniel M: Aminoguadine, a novel inhibitor of nitric oxide formation, prevents vascular dysfunction. Diabetes 1992;41: 552–556.

7 Lobo C, Bernardes R, Faria de Abreu JR, Cunha-Vaz JG: One year follow-up of blood retinal barrier and retinal thickness alterations in diabetes type 2 subjects with mild nonproliferative retinopathy. Arch Opthalmol 2001; 119:1469–1474.

8 Hee MR, Puliafito CA, Duker JS: Topography of diabetic macular edema with optical coherence tomography. Ophthalmology 1998;105: 360–370.

9 Cunha-Vaz, J.G.: Diabetic macular edema. Eur J Ophthalmol 1998;8:127–130.

10 Gardner TW, Eller AW, Friberg TR, et al: Antihistamines reduce blood-retinal barrier permeability in type I (insulin-dependent) diabetic patients with nonproliferative retinopathy: A pilot study. Retina 1995;15:134–140.
11 Leite, E. Mota, M.C., Faria de Abreu, J.R., Cunha-Vaz, J.G.: Effect of calcium dobesilate on the BRB in early stages of diabetic retinopathy. Int Ophthalmol 1990;14:81–88.
12 Chatuverdi N, Sjolie AK, Stephenson JM, Abrahamian H, Keipes M, Castellarin A, Rogulja-Pepeonik Z, Fuller JH: Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes: EUCLID Study Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus. Lancet 1998;351:28–31.
13 Klein R, Klein BE, Moss SE, Davis MD, DeMets DL: Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. JAMA 1988;260:2864–2871.
14 Klein R, Klein BE, Moss SE, Cruikshanks KJ: Relationship of hyperglycemia to the long-term incidence and progression of diabetic retinopathy. Arch Intern Med 1994;154:2169–2178.
15 Diabetes Control and Complications Trial Research Group: The effect of intensive treatment on of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986.
16 Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Schichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–117.
17 UK Prospective Diabetes Study Group: Intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) Lancet 1998;21(suppl 1):S23–S31.
18 UK Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865.
19 American Diabetes Association: Standards of medical care for patients with diabetes mellitus. Diabetes Care 1998;21(suppl 1):S23–S31.
20 UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703:713.
21 UK Prospective Study Group: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 39. BMJ 1998;317:713–720.
22 The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997;157:2413–2446.
23 Chew EY, Klein ML, Ferris FL III, Remaley NA, Murphy RP, Chantry K, Hoogwerf BJ, Miller D: Association of elevated serum lipid levels with retinal hard exudates in diabetic retinopathy. ETDRS Report Number 22. Arch Ophthalmol 1996;114:1079–1084.
24 Early Treatment Diabetic Retinopathy Study Research Group: Effects of aspirin treatment on diabetic retinopathy. ETDRS Report Number 8. Ophthalmology 1991;98:757–765.
25 DAMAD Study Group: Effect of aspirin alone and aspirin plus dipyridamole in early diabetic retinopathy: A multicenter randomized controlled clinical trial. Diabetes 1989;38:491–498.
26 TIMAD Study Group: Ticlopidine treatment reduces the progression of nonproliferative diabetic retinopathy. Arch Ophthalmol 1990;108:1577–1583.
27 Sorbinil Retinopathy Trial Research Group: A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy. Arch Ophthalmol 1990;108:1234–1244.
28 Ishii H, Jirousek MR, Koya D, Takagi C, Xia P, Clermont A, Bursell SE, Kern TS, Ballas LM, Heath WF, Stramm LE, Feener EP, King GL: Amelioration of vascular dysfunctions in diabetic rats by an oral PKC beta inhibitor. Science 1996;272:728–731.
29 Danis RP, Bingaman DP, Jirousek M, Yang Y: Inhibition of intraocular neovascularization caused by retinal ischemia in pigs by PKC beta inhibition with LY333531. Invest Ophthalmol Vis Sci 1998;39:171–179.