Diabetic Retinopathy

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INTRODUCTION:

Diabetic retinopathy and other diabetic eye changes represent an important public health problem. Of all the complications of diabetes, diabetic retinopathy is the most disabling and one of the leading cause of blindness in the world. It has been estimated that in United States alone the loss of income and public welfare expenses due to diabetic retinopathy are about 75 million dollars annually. Clinical trials have shown that timely photocoagulation can reduce visual loss and blindness caused by diabetic retinopathy. These findings suggest the need for identification and referral to opthalmologist of diabetic patients at risk of visual loss.

NATURAL HISTORY:

The sequence of anatomical changes in the retina leading to blindness in diabetes is fairly well defined. The earliest observable opthalmoscopic sign of diabetic retinopathy is the appearance of the retinal microaneurysm. These small circular red dots, varying in the size about 20 to 200 µm., are outpouchings of the retinal capillaries. They usually appear in areas of retinal capillary closure and disappear at an average rate of about 3.3 per cent per month. In insulin-taking diabetic patients, the first microaneurysm usually does not appear until at least 3 years after diagnosis; by 20 or more years, they are found in nearly 100 per cent of patients (1). Davis et al have reported a prevalence of about 69% after 6 years of IDDM, this figure approached 100% after 14 years of diabetes and actually reached 100% at 18 years (2). Most investigators have found that retinopathy develops sooner after the diagnosis of maturity onset diabetes than after the diagnosis of the juvenile-onset type (3). Microaneurysms may be found in the eyes of non-diabetic persons with other conditions, such as carotid artery disease or severe hypertension.

By themselves, retinal microaneurysms usually are not a threat to the vision. They may begin to leak lipoprotein material, however, resulting in the appearence of hard exudates. These are yellow, variable in size, and sharply defined, they may present in a scattered, aggregated, or ring-like configurations. They may last for years, often collecting in the posterior part of the retina, leading to macular thickening. An entity called "clinically significant macular edema" may cause a decrease in visual acquity. It has been defined as the presence of any one of the following:

1. Thickening of the retina, located 500 µm or less from the centre of the macula.
2. Hard exudates with thickening of the adjacent retina, 500 µm or less from the centre of the macula.
3. Zone of retinal thickening, one disc area or larger in size, located one disc diameter or less from the centre of the macula.

Development of retinal ischemia, caused by closure of retinal capillaries and arterioles, also may occur. This may result in the appearence of whitish or greyish areas called cotton-wool spots or soft exudates. Intraretinal microvascular abnormalities (IRMA) are found in areas of capillary nonperfusion. These dilated capillaries develop as a compensatory response to the retinal hypoxia. Further retinal ischemia and hypoxia is associated with the appearance of venous beading and duplication, and large, dark intraretinal hemorrhages. A combination of venous beading, IRMAs, intraretinal hemorrhages, and cotton-wool spots have been labeled as the "preproliferative" stage of diabetic retinopathy because their appearence suggests the impending growth of abnormal new retinal blood vessels.

The proliferative stage of diabetic retinopathy (PDR) begins with the appearence of abnormal retinal blood vessels, usually found on or near the optic nerve-head or in the vicinity of retinal veins. These new vessels initially appear as fine tufts on the surface of the retina and their growth is confined to the outermost layer of the vitreous. Because they are permeable, they may bleed into the vitreous, especially as a result of vitreous contraction. Vitreous contractions occurs when there is increased intraretinal pressure as occurs in coughing, jumping and bending forward. Fibrous tissue often is associated with the development of new retinal blood vessels. If this fibrovascular tissue contracts, traction or dragging of the sensory retina, especially in the area of the macula may result, leading to a disturbance in vision. Further contraction can cause a tractional retinal detachment.

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Late in the course of retinopathy, if abnormal retinal blood vessels regress and there has been no significant hemorrhage or retinal traction, fibrous tissue may remain as the only sign of proliferative retinopathy. Fukuda (4) et al have clinically classified diabetic retinopathy from benign to malignant as follows:

Level 0 : No retinopathy
Level 1 : Microaneurysms only (AI)
Level 2 : Microaneurysms and retinal Hemorrhage (All)
Level 3 : Preproliferative retinopathy, (Soft exudates, increased capillary occlusion and intraretinal microvascular abnormalities-IRMAs) (BI)
Level 4 : Neovascularization elsewhere (BII)
Level 5 : Neovascularization of disc (BIII)
Level 6 : Vitreous hemorrhage or proliferative tissue (B IV V)

Fukudas classification of retinopathy coincides with the severity of retinopathy.

PATHOGENESIS:

Diabetic retinopathy is thought to be a consequence of hyperglycemia. This assumption is supported by a number of empiric observations:

1. The frequency and severity of retinopathy, which increases with the duration of diabetes.
2. The production of retinopathy in experimental diabetes animal models.
3. The presence of retinopathy in patients with secondary diabetes.

It is not known for how long or at what level high blood glucose would lead to retinopathy. Hyperglycemia has been hypothesized to affect the retinal circulation and induce ischemia and hypoxia through a number of pathologic mechanisms. These include increased platelet aggregation, increased red blood cell rigidity and aggregation, thickening of retinal capillary walls, decreased oxygen release from red blood cell secondary to biochemical changes, such as elevated levels of glycosylated hemoglobin, and reduced cellular levels of 2, 3-diphosphoglycerate (1).

There is a general agreement that the earliest anatomical change in the retina of patients with diabetes is selective loss of retinal capillary pericytes (mural cells). These cells are thought to control blood flow through the retinal vasculature and may also contribute to the stability of the vessel wall. Non-enzymatic glycosylation of retinal matrix which may occur in diabetes as a result of increased glucose concentration in the plasma may play a role in the pericytic death (1). Pericytes grow slower when cultured in high glucose, a phenomenon possibly contributing to the loss of pericytes from retinal capillaries in diabetes. It has been also shown that high plasma glucose affects production of collagen more than that of proteoglycan. High glucose also modulates the effects of ascorbic acid on collagen but not proteoglycan. These changes may contribute to the abnormalities of pericyte growth in diabetic retinopathy (6).

Abnormalities of both ascorbic acid (an antioxidant) and free radical metabolism have been reported in diabetes. Disturbances in the ascorbic acid metabolism may be linked to the development of diabetic microangiopathy. Even if free radical mechanisms are involved in diabetes, some of the markers of activity like plasma thiobarbituric acid reactivity (TBA) and red blood cell glutathione concentration (GSH) are kept within normal limits possibly by consumption of ascorbic acid during free radical scavenging (7). Vit C is shown to lower non-enzymatic glycation of serum proteins in vitro and in vivo. Use of Vit C has been proposed in adjuvant therapy and prevention of late complications of diabetes (8).

Vitreous degeneration plays a role in the progression of proliferative diabetic retinopathy. It has been shown that there is non-enzymatic glycosylation and abnormal crosslinking of collagen in vitreous of diabetic humans (5). Such abnormalities in vitreous collagen biochemistry probably induce vitreous degeneration and contribute to the proliferative diabetic retinopathy (PDR).

Hyperglycemia leads to increased cellular uptake of glucose in tissues that are not dependent on insulin, such as the lens, nerves and kidney. As a result, in these tissues the flux of glucose and glucose derived products through a variety of metabolic pathways is increased, often with deleterious effects. The activity of these pathways, of which the sorbitol or polyol pathway is the best characterized, is affected by insulin, anoxia, a variety of drugs, and probably the diabetic state. The sorbitol pathway is operative in a number of tissues, including the lens, intramural pericytes of retinal capillaries, and Schwann cells. The rate limiting enzyme in the sorbitol pathway, aldose reductase, has a very low affinity for glucose, and thus appreciable sorbitol production occurs only in the presence of high blood glucose (9).

Non-enzymatic glycosylation is of greater importance in the development of diabetic complication. It is a process by which glucose attaches to the amino acids

of a protein without the catalytic involvement of a specific enzyme. This process can involve proteins in cells that are not dependent on insulin, cell-membrane proteins, and circulating and extracellular structural proteins. Glycosylated hemoglobin was the first product of this type of reaction that was recognized and characterized but many other glycosylated proteins have since been identified, they include antithrombin-III, fibrinogen, fibrin, enzymes such as cathepsin B, and a large number of structural proteins such as crystallins, collagen, and myelin. A variety of processes can be altered by nonenzymatic glycosylation. Many glycosylated proteins, including components of basement membranes, are less succeptible to proteolysis and this is one of the several factors contributing to the thickening of basement membranes. Endocytosis by capillary endothelial cells is affected by nonenzymatic glycosylation, unmodified albumin, for example, is normally not ingested, whereas glycosylated albumin is taken up avidly by these cells and may affect endothelial cell function (9).

Secretion of proteases by capillary endothelial cells is an early event in angiogenesis. Activation of Protein Kinase C (PKC) has been observed in vitro and diabetic animals (10).

Genetic factors have been studied in an attempt to explain why some diabetic patient develop severe retinopathy while others do not. Attention has been focused on histocompatibility antigens (HLA). In one study, patients with more severe retinopathy were found to have a higher frequency of HLA-DR4 (11). Specific RNAs have been detected in human retinal microvessels either by the titration assay or in situ hybridization, thus providing the means of quantitating diabetes-induced changes in gene expression (12).

Microvascular advanced glycosylation product accumulation precedes the full development of diabetic retinopathy. It has been shown that aminoguanidine inhibits advanced glycosylation product accumulation in diabetic retinal vessels (13).

EPIDEMIOLOGY AND RISK FACTORS

Population based epidemiologic studies recently have been conducted or are under way in an effort to obtain data about systemic, genetic, and ocular factors associated with the incidence or progression of diabetic retinopathy to proliferative disease. This is of importance in:

1. Efforts to change the course or prevent the development of retinopathy.
2. Better understanding of the underlying biological mechanisms.
3. Characterization of "high risk" patient.
4. Prediction of future health service needs and health care delivery.

In developed countries, diabetic retinopathy ranks number one amongst the various causes of age-related blindness like glaucoma and macular degeneration. It has been estimated that 300,000 people are at risk of blindness from diabetic retinopathy in the United States (14). Data from U.S. Model Reporting Area (MRA) suggests that diabetic retinopathy may be responsible for about 10% of new blindness at all ages and for about 20% of new blindness between the ages of 45 and 74. In addition, 85 persons per 100,000 population are registered as legally blind from diabetic retinopathy (15).

In India which is a country at an interim stage of development, blindness rate due to diabetic eye diseases is on the increase, because of an increase in the average span of life, better standards of living and better care of the diabetic. According to the survey conducted by the Department of Ophthalmology at the PGI, retinopathy was present in 42.9% cases, out of which 15.2% cases had vision-threatening retinopathy. Amongst diabetics in India, IDDM accounts only for 2% of diabetics. NIDDM is 10 time more common than IDDM. Retinopathy in NIDDM cases was 16 times more prevalent than IDDM (16).
Study of the Pima Indians, a group with prevalence of diabetes greater than 40% (diabetes mostly of NIDDM type) showed no relationship between age at diagnosis and frequency of retinopathy (17). A restrospective study of Joslin clinic patients showed the prevalence of retinopathy to be related to age only if diabetes had been present for less than 10 years (18).

Duration of diabetes consistently has been shown to be related to the presence and severity of diabetic retinopathy. The prevalence of PDR was found to vary from zero percent in younger onset persons with fewer than 5 year, to 56 per cent in persons with 20 or more years of disease.

Blood glucose levels as measured by glycosylated hemoglobin (HbA_{1c}) is a main determinant of progression of diabetic retinopathy and incipient diabetic nephropathy. Most clinical studies suggest that patient with good glycemic control are less likely to develop severe diabetic retinopathy. Good glycemic control should be maintained from the beginning of the diagnosis of diabetes as, mechanisms leading to retinopathy are initiated early in the course of poorly controlled diabetes and may be difficult to

arrest after the appearance of the first few retinal microaneurysms.

Although different studies suggest a causal relationship of poor glycemic control to the development of retinopathy, it is also possible that hyperglycemia and the development of retinopathy are independent manifestations of severe diabetes. The final proof of the causal relationship rests with controlled clinical trials.

Poor glycemic control with the raised apolipoprotein B/A-I ratio and/or obesity is characteristic of NIDDM with retinopathy (19). The relationship between obesity and the progression of diabetic retinopathy have been rarely studied. It has been shown that severe weight reduction during a period of worse control is associated with progression of retinopathy.

Microalbuminuria and high normal blood pressure predicts development of diabetic retinopathy in IDDM hence urinary albumin excretion should be monitored in patients with IDDM to detect those who should be considered at the risk of developing nephropathy and retinopathy (20).

The rates of each complications of diabetes vary widely from one population to another and the distribution and type of complication differ considerably among the population. Malay have the highest prevalence of both background end sight-threatening retinopathy, Malay race appears to be a risk factor for the development of diabetic retinopathy (21).

Among diabetic pregnant woman, retinopathy has shown a steady increase, because there are now more young diabetic patients with diabetes of long duration. Beta-thromboglobulin (B-TG) concentration is elevated during pregnancy, especially in diabetic pregnancy. Diabetic retinopathy during pregnancy is related to increased release of plasma B-TG from platelets during pregnancy (22).

DIAGNOSIS AND SCREENING:

Diabetic retinopathy is diagnosed by a fundoscope. In order to screen diabetic retinopathy in general population standard camera with mydriasis and polaroid film can be useful. Although non- mydriatric camera can improve detection of serious diabetic retinopathy in the community, poor photographic quality, particularly in the elderly, may limit its use in screening unselected diabetic patients.

Educating diabetic patients with regard to the need to have annual eye examination and the significance of the disease may improve the rate of screening and lead to less visual loss.

TREATMENT:

Treatment of diabetic retinopathy is a very difficult task and should be carried out jointly by a diabetologist and ophthalmologist. There are two modes of treatment available: Medical and Surgical.

MEDICAL MANAGEMENT:

This consists of maintenance of good glycemic control as early as possible, after the diagnosis of diabetes for reasons mentioned earlier.

There are various drugs tried in the treatment of diabetic retinopathy and prevention of its further progression.

Aspirin is being studied because of its ability to interrupt the process of abnormal platelet aggregation, which is pressumed to play a role in retinal capillary closure. It has been reported that long term inhibition of platelet function by ticlopidine was effective in the prevention and improvement of diabetic retinopathy.

Hypersorbitol accumulation may be an important factor in diabetic retinopathy (23). In view of this fact aldose reductase inhibitors like Tolrestat and Statil are being evaluated in the treatment and prevention of diabetic retinopathy.

Recombinant Alpha Interferon (AI) has been shown to stabilize and reverse the neovascularization of proliferative diabetic retinopathy. AI inhibits angiogenesis in vitro and has been successfully used to treat vascular tumours including Kaposi's Sarcoma and pulmonary hemangioendotheliosis (24).

SURGICAL MANAGEMENT:

Surgical management for diabetic retinopathy consists of photocoagulation and vitrectomy.
Provided careful follow-up can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate non-proliferative retinopathy (25). When retinopathy is more severe, scatter photo-coagulation should be considered and usually should not be delayed if the eye has reached the high risk proliferative stage.

Vitrectomy is indicated when there is retinal or vitreous hemorrhage and this causes acute loss of vision. Chronic vitreous hemorrhage may lead to fibrosis and detachment of retina.

REHABILITATION:

The visually impaired diabetic patient faces problems in rnonitoring glucose levels, identifying the type of insulins, determining the amount of insulin in the vial, measuring dose, and locating insulin injection site. Fortunately, a number of low-vision aids are available. A team approach, including psychologists, orientation and mobility instructors, social workers and rehabilitation teachers, usually are needed to develop a successful program for dealing with the visually impaired diabetic patients. The blind or those facing blindness must cope with guilt, anger, anxiety, loss of self-esteem, and multiple other difficulties in social adjustment. Helping the diabetic patient to accept partial or complete visual loss is an important step in planning arrangements and in developing coping stategies.

REFERENCES

1. Klein R. Recent Developments in the Understanding and Management of Diabetic Retinopathy; MCNA. 88; 72;1415.
2. Davis M D, MacCormick AJA, Haris WAC, Haug GA. Diabetic Retinopathy-Prevalence and Importance XXII. Concilium Opthalmologium Paris, ACTA. 1976; (Supplement I): Paris: 165.
3. Aiello LM, Rand RI, Briones JC et al. Diabetic Retinopathy in Joslin Clinic Patient with Adult Onset diabetes Opthalmol (Rochester, MN) 1981; 619:88.
4. Fukuda M. Clinical Classification of Diabetic Retinopathy. Diabetes 1991 ; 40 (Supplement I): 207 A.
5. Sebag J, Reiser K, Buckingham B et al. Effects of Diabetes on Human Vitreous Collagen Biochemistry. Diabetes 1991; 40 (Supplement I): 301A.
6. Fisher E, Mclennan S, Yue DK, Turtle JR. The Effects of Glucose and Ascorbic Acid on Proteoglycan and Collagen Production by pericytes. Diabetes 1991 ; 40 (Supplement 1): 209A.
7. Sinclair AJ, Lunec J, Barnett AH. Ascorbic Acid Metabolism and Free Radical activity in Diabetic Retinopathy. Diabetes 1991; 40 (Supplement 1): 209A.
8. Stolba P, Straskova J, Hatle K et al. Vitamin C Lowers Non-enzymatic Glycation of Serum Proteins and Collagens in Vitro and in Vivo. Diabetes 1991; 40 (Supplement I): 202A.
9. Marimee T J. Diabetic Retinopathy-A Synthesis of Perspectives. NEJM. Apr 5, 1990; 322 (14): 978.
10. Stramm L, Marder P Johnston C, Ober P, Heath W. Modulation of Retinal Capillary Endothelial Cell Protease Activity by Protein Kinase C. Diabetes, 1991 ; 40 (Supplement I): 208A.
11. Dornon TL, Ting A, McPerson CK et al. Genetic succeptibility to the development of retinopathy in insulin dependent diabetes. Diabetes 1982; 31 : 226.
12. Cagliero E, Grant MB, Lorenzi M. Measurement of Gene Expression in Human Diabetic Reginal Microvessels. Diabetes 1991; 40 (Supplement I): 9A.
13. Hammes HP, Federlin K, Brownless M. Aminoguanidine treatment inhibits advanced glycosylation product accumilation in diabetic retinal vessels. Diabetes 1991 ; 40: 303A.
14. National Advisory Eye Council; Vision Research, a National Plan, 1978-1982, 1977 DHEW Publ. (NIH): 78.
15. Kahn HA, Moorchead HB. Statistics on blindness in Model Reporting Area (MRS), 1969-70, DHEW Publ (NIH): 73.
16. Jain IS. Vision Threatening Diabetic Retinopathy. Ind. J. Opthal. Jan-Mar 88; 36 (1): 3.
17. Dorf A, Ballantine E, Benett PH, Miller m, Reginopathy in Pima Indians. Relationship to glucose levels, duration of diabetes, and age at examination in a population with a high prevalence of diabetes mellitus. Diabetes 1976; 25: 554.
18. Kahn HA, Bradley RF. Prevalence of Diabetic Retinopathy Age, Sex and duration of diabetes. Br. J. Opthalmol. 1975; 59: 345.
19. Senmaru H, Ohohashi K, Park H et al. Association of Serum Apolipoprotein with Diabetic Retinopathy in NIDDM. Diabetes 1991 ; 40 (Supplement l): 336A.
20. Freire MBS, Bonorno PP, Pareira AB, Zanelca MT. Microalbuminuria and High Normal Blood Pressure Predicts Development of Diabetic Retinopathy in Insulin Dependent Diabetic Patients. Diabetes 1991 ; 40 (Supplement I): 335A.
21. Khoo DHC, Hart P, Chew SJ et al. Prevalence of Diabetic Retinopathy amongst different racial groups in Singapore. Diabetes 1991; 40(Supplement I): 331A.
22. Honda M, Omeri Y, Nakabayashi M et al. Increase in Plasma Level of Beta-Thromboglobulin in Pregnant Diabetics with Retinopathy. Diabetes 1991 ; 40 (Supplement I): 420A.
23. Akazawa Y, Asayama K, Oishi M, Tsujii S, Tashiro S. Relationship between Platelet function and Diabetic Retinopathy. Diabetes 1991 ; 40 (Supplement I): 335A.
24. Skowsky R, Siddiqui T, Hodgetts D et al. Recombinant Alpha Interferon (AI) will stabilize and Reverse the Neovascularization of Proliferative Diabetic Retinopathy (PDR). Diabetes 1991; 40 (Supplement I): 33A.
25. ETDRS Research Group, Early Photocoagulation for Diabetic Retinopathy. Diabetes 1991 ; 41 (Supplement I): 330A.