Non retinal ocular abnormalities of diabetes mellitus

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Contents

Abstract

Diabetes mellitus (DM) is a common health problem characterized by sustained hyperglycemia. Several mechanisms are involved in the ocular abnormalities of diabetic eye disease, as the sorbitol pathway, advanced glycation end products, protein kinase C activation and the microvascular abnormalities.

Diabetic retinopathy is the most common and the most serious complication of diabetic eye disease, but the other ocular structures are also affected.

Lid and conjunctival abnormalities include xanthelasma formation and the microvascular abnormalities with high incidence of dry eye syndrome in diabetics.

Corneal abnormalities include morphological and functional changes of different corneal layers.

Diabetics have a high incidence of iris transluminance and neovascularization which is related to diabetic retinopathy.

There is a high incidence of at least two types of glaucoma in diabetics, open angle and neovascular glaucoma.

Lens abnormalities in diabetes include change in the refractive status and high incidence of cataract formation.

Choroidal abnormalities in diabetics include choroidal degeneration and neovascularization especially after pan retinal laser photocoagulation.

Neuro-ophthalmic abnormalities in diabetes are the following: optic atrophy and neuritis, anterior ischemic optic neuropathy, isolated and combined cranial nerve palsy and pupillary abnormalities.

Diabetic patients have a high incidence of ocular infections especially post operative infections.

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Introduction

Diabetes Mellitus (DM) is a common disorder characterized by sustained hyperglycemia of varying severity secondary to lack or diminished efficacy of endogenous insulin. **(Kanski, 2003).**

Retinopathy is the most common abnormality of diabetic eye disease however; diabetes also can affect other structures in the eye as the lid, the conjunctiva, the cornea, the iris, the lens, the choroid with high incidence of glaucoma, neurological abnormalities and infections. **(Frank, 1992).**

Several pathogenic mechanisms are involved in diabetic eye disease as, the sorbitol pathway, the formation of advanced glycation end products (AGEs), protein kinase C activation and the microvascular abnormalities. **(Brownlee, 2001).**

As regard to the lid, diabetics have a high incidence of xanthelasma. Conjunctival abnormalities were found to be changes in the conjunctival microcirculation. **(Cavallerano, 1992), (Owen et al., 2005).**

Corneal abnormalities in diabetic eye disease include the effect on corneal hydration, morphological abnormalities, damage to corneal nerves and deviated mechanisms of wound healing. **(Chikama et al., 2007).**

Other changes seen in the diabetic eye disease include disorders in tear quantity, quality, conjunctival squamous metaplasia and goblet cell loss. **(Dogru et al., 2001).**

The effect of diabetes on the iris includes abnormality of iris sensory nerve fibres, vacuolation and atrophy of the iris pigment epithelium and neovascularization which is generally associated with proliferative retinopathy. **(Oshima et al., 2006).**

Patients with diabetes have a high risk for at least two forms of glaucoma: primary open-angle glaucoma and neovascular glaucoma. **(Kowluru et al., 2001).**

Diabetes mellitus profoundly affects the function and morphology of the human crystalline lens, the clarity of the lens, its refractive state and its ability to provide accommodation may all be altered by this underlying systemic disease. Cataract is a common cause of visual impairment in diabetics, the hyperglycemic state can affect lens metabolism and plays a role in cataractogenesis in diabetic persons**. (Johns, 1992).**

It was found that, patients with diabetes may suffer from choroidal degeneration with increased risk of choroidal neovascularization, especially, after pan retinal laser photocoagulation. **(Cao et al., 1998).**

Neurological abnormalities are common in diabetics, as, optic nerve diseases including, optic neuritis, atrophy and anterior ischemic optic neuropathy. Cranial nerve palsy may also occur in diabetics as, isolated and combined cranial nerve palsy. Pupillary abnormalities are due to impaired sympathetic and parasympathetic supply of the eye. **(Yee, 1992).**

Diabetics have a high incidence of ocular infections as lid infections, conjunctival infections, and orbital infections with high incidence of endophthalmitis after intraocular surgeries. **(Delmaire et al., 1997)**.

Aim of the work: To review the literature about the non-retinal abnormalities of diabetic eye disease including: the lid, the conjunctiva, the cornea, the iris, the lens, the choroid, neurological abnormalities and the incidence of glaucoma in diabetics.

Pathogenic mechanisms in diabetic eye disease.

The main pathways for glucose metabolism.

1) Glycolysis (Embeden-Meyerhof pathway): it is a very important pathway that operates in almost all tissues of the body under either aerobic or anaerobic conditions. Under aerobic conditions, glycolysis is considered a preparatory step for citric acid cycle (Kreb's cycle). This is best demonstrated in brain and cardiac muscles. Under anaerobic conditions, glycolysis is considered the major pathway for energy production as in case of lack of mitochondria (RBC'S), in case of non-functioning mitochondria due to decreased blood supply as in the cornea and the lens and during severe muscle exercise. **(Frank, 1992).**

2) Citric acid cycle (Kreb's cycle): it occurs under aerobic conditions only and needs glycolysis as a preparatory step. **(Frank, 1992).**

3) The glucuronic acid pathway: it is a quantitatively minor route of glucose metabolism, glucuronic acid formed from glucose has the ability to be conjugated with other compounds as steroids, bilirubin and some drugs making them more water soluble thus facilitating their renal excretion. **(Dyck et al., 1988).**

4) Pentose shunt (pentose phosphate pathway): glucose can be used to form pentose phosphates; it is the only source of pentoses used for nucleic acid synthesis; DNA and RNA. Also it is the major source of nicotin-amide-adenine dinucleotide phosphate (NADPH) used for synthesis of fatty acids and it has a maximum concentration in the lens. **(Brownlee, 2001).**

5) Formation of glycogen and glycoproteines: glucose can be stored in the form of glycogen and react with proteins to form glycoprateins**. (Green et al., 1987)**

6) Polyol pathway (sorbitol pathway): sorbitol is a sugar alcohol, it is a minor dietary constituent and it is very poorly absorbed from the intestine. Under physiological conditions its formation from glucose is of minor importance. **(Green et al., 1987)**

Pathogenic mechanisms of diabetic complications

Several mechanisms had been proposed as having causal importance for the complications of diabetes. But, there is a single, common aetiologic agent that initiates these complications. This agent is hyperglycemia; the effect of glycemic control on diabetic complications had been investigated, and it was found that, aggressive control of hyperglycemia in patients with type I and type II can attenuate the development of chronic complications such as retinopathy and nephropathy. **(Brownlee, 2001).**

A) The polyol pathway.

Under conditions of normoglycemia, most glucose of the lens is metabolized anaerobicaly via the Embeden-Meyerhoh pathway (glycolysis). However, when lenticular glucose levels are high, this pathway is easily saturated shunting excess glucose to aldose reductase. **(Dyck et al., 1988).**

Aldose reductase shows a reducing activity towards glucose only at high glucose levels as in uncontrolled diabetes **(fig, 1)**, and only in cells that lack a glucose pump in their plasma membranes to maintain intracellular glucose concentrations within a relatively narrow physiological range. The sorbitol formed by Aldose reductase intracellularly can not leave the cell by diffusion, since sorbitol and other

sugar alcohols penetrate cell membranes poorly. In diabetics, the production of sorbitol in the lens is enhanced not only by the availability of large quantities of glucose but also by other metabolic abnormalities that actually increase the affinity between aldose reductase and glucose; The concentration of reduced (NADPH), which is the necessary hydrogen donor, is increased in diabetic lenses, favoring sorbitol synthesis. In addition, the activity of sorbitol dehydrogenase is decreased so that sorbitol, once formed, is less likely to be metabolized to fructose. So, the sorbitol formed by Aldose reductase in the lens quickly rises, creating an osmotic force that draws water inside the cells. An intracellular edema increases. Sodium enters and potassium is lost. Glutathione, an important antioxidant, is also lost. **(Frank, 1992)**

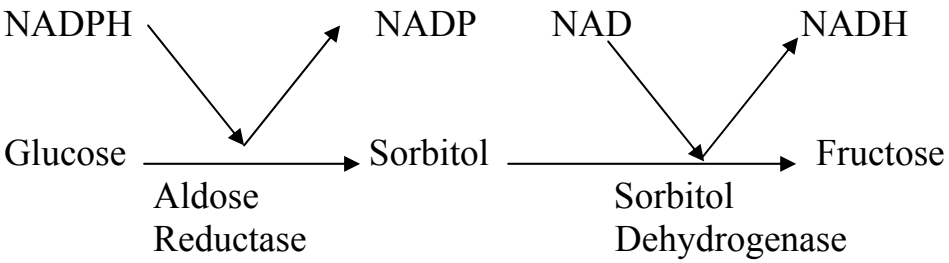

Figure (1): the sorbitol pathway.

(Frank, 1992)

Myo-inositol is a cyclohexane synthesized from and structurally similar to glucose, it is incorporated into cell membrane phospholipids which are essential for plasma membrane sodium-potassium adenosine triphsphatase (Na-K ATPase). High glucose levels in diabetics can lead to depletion of myo-inositol through the following mechanisms: a) hyperglycemia competitively inhibits sodium dependent myo-inositol uptake, as glucose and myo-inositol compete for the same carrier resulting in decreased tissue myo-inositol content. **(Kikawa, 2000).**

b) Also, increased sorbitol levels increase myo-inositol efflux from cells, leading to reduction in tissue myo-inositol content. **(Brownlee, 2001).**

Diminished myo-inositol content in the nerves can impair Na-K ATPase activity in neurons and result in defective neuronal transmission. So decreased myo-inositol content can lead to decreased corneal sensitivity in diabetic patients. **(Green et al., 1987).**

B) The non-enzymatic glycation.

Another major consequence of the hyperglycemia observed in diabetes mellitus is the formation of compounds as a result of the chemical reaction of the glucose with proteins. The importance of this reaction is that;

1) There are several forms of glycosylated hemoglobin, but the most abundant is hemoglobin A1c (Hb A1c). In normal individuals, Hb A1c is about 4 to 6% of the total hemoglobin. During hyperglycemia, the amount of the glycosylated hemoglobin increases. The ability of hemoglobin to release oxygen is regulated by 2, 3 diphosphoglycerate (2, 3 DPG), which combines with hemoglobin, lowering its affinity with oxygen (or raising its ability to release oxygen). HbA1c binds to 2, 3 DPG poorly therefore releases oxygen slowly to tissues. (**Alves et al., 2005).**

2) It was reported that, the non enzymatic glycation of proteins in the extracellular matrix, particularly in basement membranes, leads to formation macromolecules, called advanced glycation end-products (AGEs). AGE proteins differ from early glycation products like glycated hemoglobin. Early glycation products are produced when glucose nonenzymatically attaches to an amino group. The early products are

reversible, and some of them, by a slow process, form irreversible AGE proteins, which continuously accumulate in the extracellular matrix. AGE proteins can link with other adjacent matrix molecules, as well as with extravasated plasma proteins, by attaching to amino groups. **(Frank, 1992).**

3) (AGEs) may alter the functions of extracellular matrix and play a role in basement membrane thickening in diabetic patients. It was reported that, increased levels of AGEs was reported in diabetic and senile cataractous lenses. It was also reported that, accumulation of AGEs in the basement membrane of the corneal epithelium may play a causative role in the corneal epithelial disorders. **(Kikawa, 2000).**

4) Normally, macrophages can remove AGE proteins. The binding of macrophages to AGE proteins causes synthesis and release of proinflamatory cytokines that lead to thrombosis and eventually capillary occlusion and chronically may lead to tissue damage and organ dysfunction**. (Bierhause et al., 2001).**

C) Protein kinase c activation

In diabetic patients, insulin resistance or deficiency leads to increased lipolysis, leading to increased diacylglycerol production which is an intermediate of lipolysis. Diacylglycerol can be also synthesized from glucose due to hyperglycemia in the process of lipogenesis. Increased diacylglycerol production causes increased activation of specific isoforms of protein kinase C which can play a role in diabetic complications. It was revealed that, protein kinase C activation plays a major role in the development of diabetic complications since an inhibitor of protein kinase C activation was reported to be able to correct renal and retinal dysfunction. **(Brownlee, 2001).**

D) Diabetes specific microvascular disease.

Diabetes-specific microvascular disease in the retina, glomerulus and vasa nervorum has similar physiopathological features. Early in the course of diabetes, intracellular hyperglycemia causes abnormalities in blood flow and increased vascular permeability. This reflects decreased activity of vasodilators such as nitric oxide, increased activity of vasoconstrictors such as angiotensin II and endothelin-1, and elaboration of permeability factors such as vascular endothelial growth factor (VEGF). Quantitative and qualitative abnormalities of extracellular matrix contribute to an irreversible increase in vascular permeability. With time, microvascular cell loss occurs, in part as a result of programmed cell death, and there is progressive capillary occlusion due both to extracellular matrix overproduction induced by growth factors such as transforming growth factor-β (TGF-β), and to deposition of extravasated periodic acid-Schiff-positive plasma proteins. **(Alves et al., 2005).**

Hyperglycemia may also decrease production of trophic factors for endothelial and neuronal cells. Together, these changes lead to edema, ischemia and hypoxia-induced neovascularization in the retina, proteinuria and glomerulosclerosis in the kidney, and multifocal axonal degeneration in peripheral nerves. **(Kikkawa, 2000)**

Lid and conjunctival abnormalities in diabetic patients

Xanthelasma:

This condition occurs more frequently in diabetic patients with elevated serum lipid levels, but does not cause a threat to vision. Xanthelasma does not occur due to diabetes precise, but may reflect poor diabetic control. **(Kanski, 2003).**

It is a yellowish, subcutaneous plaque consisting of cholesterol and lipids which are usually located at the medial aspects of the eyelids.

Destruction with carbon dioxide laser or argon laser is preferred to excision for cosmetic reasons. However, recurrences are possible if the disturbance in lipid metabolism persists. **(Cavallerano, 1992).**

Vascular response of the conjunctiva to diabetes:

Diabetes is known to produce change in the morphologic features of the retinal vessels. The effects of diabetes on the vessels of the conjunctiva are less well documented and had been based on subjective rather than objective assessment. In a previous study that documented the morphologic features of the conjunctiva in diabetic patients, the following data were observed:

A strong positive association between the duration of diabetes and the mean vessel width was observed, this increases in vessel width especially found in the large vessels (>80µm in width), the width of conjunctival vessels increase, due to decreased blood flow and velocity in diabetics. Conversely, the duration of diabetes showed a strong inverse association with vessel area which is observed in smaller vessels (<40µm

in width), this decrease in vessel area reflects reduction in vessel density which is consistent with the well-known phenomenon of capillary nonperfusion and drop-out associated with diabetes observed in the retina. Also the effect of type I diabetes was more strong than type II, reflecting the longer duration in those with type I diabetes if compared with type II. **(Owen et al., 2004).**

The relation between conjunctival abnormalities in diabetic patients and the severity of diabetic retinopathy had been studied, and the observations suggested that: there was a correlation between the grade of diabetic retinopathy and the degree of conjunctival vascular abnormalities. But, it is difficult to ascertain whether this association indicates that changes in retinal vessels directly lead to changes in vessels of the conjunctiva or simply that duration of the disease leads to more generalized effect of diabetes on ocular vessels**. (Owen et al., 2005).**

The expression of VEGF, P53 and ICAM-1 in the conjunctiva of diabetic patients:

Vascular endothelial growth factor (VEGF) had been shown to play a crucial role in ocular neovascularization. VEGF, also known as vascular permeability factor (VPF) as it increases vascular permeability, it was also known to play a crucial role in the development of nonproliferative (NPDR) and proliferative (PDR) diabetic retinopathy. High levels of VEGF had been found in the vitreous and in the aqueous humor of diabetic retinopathy (DR) cases, and the level was higher in cases of proliferative than the cases of non proliferative retinopathy, indicating that, regulation of VEGF can control the progression of diabetic retinopathy. **(Nicoliti et al., 2003).**

Inter-cellular adhesion molecule-1 (ICAM-1) had been shown to play an important role in leucocyte adhesion and can result in early