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ISSN: 2096-3246
Volume 54, Issue 02, December, 2022
Special Issue

"ANALYTICAL STUDY ON GLAUCOMA IN DIABETIC PATIENTS"

S. Yaminipriya
Dhanalakshmi Srinivasan College of Engineering, Coimbatore, Tamil Nadu, India

Priyanka Dixit
Babu Banarasi Das University, Lucknow (U.P.) India

Abstract:
Diabetes mellitus represents a growing international public health issue with a near quadrupling in its worldwide prevalence since 1980. Though it has many known microvascular complications, vision loss from diabetic retinopathy is one of the most devastating for affected individuals. In addition, there is increasing evidence to suggest that diabetic patients have a greater risk for glaucoma as well. Though the pathophysiology of glaucoma is not completely understood, both diabetes and glaucoma appear to share some common risk factors and pathophysiologic similarities with studies also reporting that the presence of diabetes and elevated fasting glucose levels are associated with elevated intraocular pressure – the primary risk factor for glaucomatous optic neuropathy. While no study has completely addressed the possibility of detection bias, most recent epidemiologic evidence suggests that diabetic populations are likely enriched with glaucoma patients. As the association between diabetes and glaucoma becomes better-defined, routine evaluation for glaucoma in diabetic patients, particularly in the telemedicine setting, may become a reasonable consideration to reduce the risk of vision loss in these patients.
Keywords: Glaucoma, Diabetes Mellitus, Diabetic Retinopathy

1. Introduction:

Glaucoma is the name for a group of eye conditions in which the optic nerve is damaged at the point where it leaves the eye. This nerve carries information from the light sensitive layer in your eye, the retina, to the brain where it is perceived as a picture.

Your eye needs a certain amount of pressure to keep the eyeball in shape so that it can work properly. In some people, the damage is caused by raised eye pressure. Others may have an eye pressure within normal limits but damage occurs because there is a weakness in the optic nerve. In most cases both factors are involved but to a varying extent.

Eye pressure is largely independent of blood pressure.

2. Diabetic Eye Disease

Non-proliferative diabetic retinopathy, previously called background retinopathy, is the earliest stage of diabetic eye disease. Microscopic changes occur in the blood vessels of the eye in non-proliferative disease; however, the changes typically do not produce symptoms and are not visible to the naked eye. Non-proliferative disease progresses from mild to moderate to severe.

Non-proliferative diabetic retinopathy is initially characterised by microaneurysms (microscopic blood-filled bulges in the artery walls) which may burst and leak into the retina. Tiny spots or dots of blood may accumulate in the retina, but they usually do not produce noticeable symptoms in the early stages of the disease. As the disease progresses, hard exudates (accumulations of fluid that has leaked from blood vessels), abnormalities in the growth of microscopic blood vessels in the retina, and bleeding from the veins that feed the retina may occur.

While non-proliferative diabetic retinopathy is not itself a sight-threatening condition, it can trigger macular oedema or macular ischaemia, which are other forms of diabetic retinopathy that may cause rapid vision loss at any stage of non-proliferative disease. In addition, the vascular changes that occur in non-proliferative retinopathy lead to retinal ischaemia (lack of blood flow to the retina) and trigger progression to sight-threatening proliferative disease. As the severity of non-proliferative retinopathy increases, the risk of developing sight-threatening proliferative diabetic retinopathy also increases.

2.1 Proliferative diabetic retinopathy

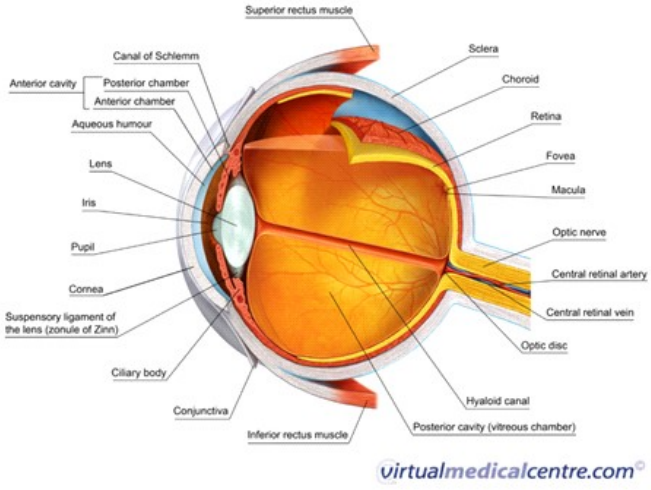
Proliferative diabetic retinopathy is characterised by neovascularisation – that is, the growth of abnormal new blood vessels in the retina. The vessels are weak and may burst and bleed into the retina or vitreous fluid (fluid surrounding the retina), causing vision loss.

2.2 Diabetic macular oedema

At all stages of non-proliferative diabetic retinopathy, there is also a risk of macular oedema, a sight-threatening condition that occurs as a consequence of the vascular changes of diabetic retinopathy. Macular oedema is the most common cause of diabetes-associated vision loss. It occurs when abnormal new blood vessels burst and bleed into the macula (the area of the eye that enables clear, sharp vision), disrupting vision.

2.3 Ischaemic maculopathy

Ischaemic maculopathy is an untreatable form of diabetic retinopathy characterised by the loss of capillaries (tiny blood vessels) that provide blood flow to the macula.



3. Statistics

By a pooled analysis of population-based studies estimates that the total number of people with DR worldwide is approximately 93 million and of these, 28 million (30.1%) have vision-threatening DR. In general, DR is believed to be more common in patients with type 1 diabetes compared to type 2 diabetes. According to this report, the age-standardized prevalence of DR in type 1 diabetic patients was 77.31%, whereas 25.16% of type 2 diabetic patients had DR. The higher rate of DR seen in type 1 diabetic patients is believed to be a result of the increased diabetes duration, hemoglobin A1c levels, and blood pressure typically observed in these patients

As in other organ systems affected by diabetes, microvascular abnormalities are central to the development of DR. Though the exact mechanism by which hyperglycemia causes DR is not completely understood, several factors have been implicated: sorbitol accumulation, oxidative stress, accumulation of advanced glycation end products (AGEs), protein kinase C (PKC) activation, and angiogenic factors.

The biochemical processes associated with chronic hyperglycemia ultimately lead to vascular abnormalities that result in endothelial and metabolic dysfunction both at the level of the eye as well as other organ systems. Loss of retinal pericytes, capillary basement membrane thickening, and vascular endothelial cell dysfunction are some of the early changes that have been described in DR. Impaired retinal vascular autoregulation is seen in part, due to pericyte loss, and disruptions in vascular permeability represent key features that are central to the development of both DR and diabetic macular edema. In addition, increased leukocyte adhesion and retinal leukostasis are believed to play a role in capillary nonperfusion.

4. Glaucoma Risk Factors and Correlation With Diabetes

Several common mechanisms have been postulated to contribute to the possible link between glaucoma and diabetic retinopathy. Diabetes and hyperglycemia is associated with glycation of lipids and abnormalities of lipid metabolism which may increase oxidative stress and promote cellular apoptosis – the same mechanism by which RGC loss occurs in glaucoma.

Vascular dysregulation has been described in both diabetic eye disease and glaucoma, and upregulation of nitric oxide, a potent vasodilator, has been reported in both conditions. Nitric oxide is a known regulator of not only vascular tone, but also apoptosis. In addition, reactive nitrogen species have been shown to contribute to inflammatory responses via oxidative stress and optic nerve degeneration as well. The contributory role of PKC in the pathophysiology of diabetic retinopathy has also been established and there is evidence to suggest that elevated PKC may also be associated with abnormalities of matrix metalloprotease in the trabecular meshwork causing impaired aqueous outflow and elevated IOP. In addition, overexpression of matrix metallprotease-9 has been associated with structural optic nerve head changes in diabetic patients, thus providing another potential link between diabetes and glaucoma.

Other pathways by which investigators have linked diabetes and glaucoma include glial cell dysfunction and impairment of retrograde axonal transport. Glial cells, such as astrocytes, are non-neuronal cells that support and protect neurons in the central nervous system, including the retina and optic nerve. Dysfunction of these cells has been demonstrated in animal models of diabetes and glaucoma and is believed to contribute to neuroinflammatory pathways of apoptosis. In addition, it has been postulated that alterations in connective tissue remodeling due to diabetes may affect both the lamina cribrosa and the trabecular meshwork, thereby potentially increasing susceptibility to glaucoma through biomechanical changes at the optic nerve and impairment of aqueous humor outflow affecting IOP homeostasis.

Diminished neurotrophic factor delivery secondary to abnormalities in axonal transport has been demonstrated in both diabetic peripheral neuropathy and the optic nerve in glaucoma. Alterations in neurotrophic factor expression, such as insulin-like growth factor and neurotrophin-3, are also seen in the presence of elevated intraocular pressure, the primary risk factor for glaucomatous optic neuropathy. In particular, insulin-like growth factor is necessary for proper glucose metabolism in the central nervous system and resistance to insulin may be a contributor to neurodegenerative processes as a result. With regard to the eye and glaucoma, insulin and insulin-like growth factor have been shown to play a role in RGC survival. In addition, insulin has been reported to affect IOP with lower IOP being associated with insulin-induced hypoglycemia while increased IOP has been associated with insulin resistance. Clinically, a large retrospective cohort of diabetic patients with open angle glaucoma reported that metformin, a first-line agent used to treat insulin-resistance in type 2 diabetes, is associated with a decreased risk of developing open angle glaucoma even after accounting for variations in glycemic control. In addition, genetic polymorphisms related to pancreatic beta-cell function in type 2 diabetes mellitus were associated with increased risk of POAG and provide further support for these findings.

From a functional standpoint, it is well-established that RGC loss in glaucoma is associated with visual field deterioration and loss. Several animal and human electrophysiologic studies have reported a variety of abnormalities in the presence of both diabetic retinopathy and glaucoma compared to normal eyes. A recent study of visual field profiles for POAG from the Nurses' Health Study found that early peripheral, as opposed to paracentral, visual field loss was more common in POAG patients with diabetes mellitus. While the diagnosis of diabetes in this study was based on patient self-report and did not exclude diabetic patients with retinal laser photocoagulation (which can also produce peripheral visual field loss), chart review in a subset of these subjects demonstrated that self-report was a valid method for accurate classification of diabetes among health professionals. Nevertheless, these findings suggest that there may be important phenotypic differences in glaucoma patients depending on diabetes status. Similarly, Kim et al. have also reported differences in the location and rate of deterioration of visual field defects in glaucoma patients based on diabetes status.

4.1 Cardiovascular Risk Factors in Glaucoma and Diabetes

Hypertension and hyperlipidemia have long been considered significant contributory risk factors for the development and progression of DR, and assessment and management of both

hypertension and dyslipidemia in diabetic persons are considered the standard of care by the American Diabetes Association [166–174]. However, the contributory role of cardiovascular disease in the development or progression of glaucoma is less clear.

A positive correlation between systemic hypertension and glaucoma has been reported in the Blue Mountain Eye Study, the Rotterdam Study, and the Egna-Neumarkt Study. However, the Barbados Eye Study and the Early Manifest Glaucoma Trial did not find a correlation between systemic hypertension and incidence or progression of glaucoma, although the Early Manifest Glaucoma Trial did find that a history of cardiovascular disease was a significant predictor of glaucoma progression. The Los Angeles Latino Eye Study reported somewhat conflicting results when they reported that both low diastolic and high systolic and mean arterial blood pressures were associated with a higher prevalence of open angle glaucoma even after controlling for IOP. The authors of the study postulate that low diastolic blood pressure can lead to decreased ocular perfusion pressures, which is consistent with the vascular hypothesis of glaucomatous optic neuropathy, whereas changes associated with chronic systemic hypertension, such as arteriosclerosis, can also decrease ocular perfusion. A recent meta-analysis of 16 studies found that individuals with systemic hypertension had a pooled odds ratio of 1.2 for the development of glaucoma compared to normotensive individuals. Several studies have, however, shown a positive correlation between IOP and systemic hypertension, particularly elevated systolic blood pressure. Though the Barbados Eye Study did not find a correlation between hypertension and incident glaucoma, elevated systolic blood pressure, diabetes history, and age were positively associated with elevated IOP. While elevated IOP is a risk factor for glaucoma, evidence from the population-based studies above would suggest that these changes in IOP may not always increase the risk of incident glaucoma.

The relationship between glaucoma and dyslipidemia has not been studied as extensively as its relationship with hypertension or diabetes. As in the case of systemic hypertension, there are published reports that dyslipidemia may be associated with increases in IOP. However, the Beijing Eye Study found that despite a positive correlation between dyslipidemia and IOP, there was no association with glaucoma. Kang and colleagues also found no relationship between risk of POAG and total cholesterol, but consumption of a high ratio of n-3 to n-6 polyunsaturated fat was associated with an increased risk of POAG. Likewise, Ko and colleagues found an association between self-reported diabetes and glaucoma in the National Health and Nutrition Examination Survey, but this association was not significant after adjustment for triglyceride levels.

Both diabetes and glaucoma represent significant public health issues in the aging population. Several epidemiologic studies suggest that diabetic individuals are at increased risk for the development of glaucoma and there may be pathophysiologic similarities to support an association between these two conditions. Given the potential to utilize early detection and treatment efforts to significantly reduce vision loss from both glaucoma and diabetic retinopathy in at-risk individuals, the possible role of routine glaucoma evaluation in diabetic persons warrants further consideration as we continue to learn more about the association between these two blinding conditions.

Conclusion

Both diabetes and glaucoma represent significant public health issues in the aging population. Several epidemiologic studies suggest that diabetic individuals are at increased risk for the development of glaucoma and there may be pathophysiologic similarities to support an association between these two conditions. Given the potential to utilize early detection and treatment efforts to significantly reduce vision loss from both glaucoma and diabetic retinopathy in at-risk individuals, the possible role of routine glaucoma evaluation in diabetic persons warrants further consideration as we continue to learn more about the association between these two blinding conditions.

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