CHAPTER 5

GLAUCOMA in diabetes

Glaucoma is a progressive optic disease that is mainly caused by high pressure in the eyes and is characterized by gradual death of retinal ganglion cells (RGC). Glaucoma, which is a leading cause of irreversible blindness worldwide, has generated a major public health problem. Primary open angle glaucoma (POAG) is the most common type of glaucoma in diabetic individuals, with nearly 70 million affected worldwide. Therefore, potential risk factors for POAG need to be identified so that interventions to reduce its incidence can be developed.

The pathogenesis of POAG is still not well understood, so far. Some researches suggested damage to the microvasculature network and/or reduced nutritional supply to the RGC axons due to interference of blood regulation in the optic nerve head area. This nutritional deficiency can lead to degeneration of RGCs and initiate glaucomatous impairment.

Therefore, any vascular-related systemic disease, such as diabetes, which directly or indirectly disrupts nutritional supply to RGCs, may result in development of POAG.

Diabetes has been deemed as a risk factor for POAG by some reports, however, epidemiologic studies of the relationship between diabetes and POAG are still controversial.

Some studies have revealed that the incidence of glaucoma markedly increased by 36% in patients with diabetes compared with individuals with no diabetes Several hypotheses on biological links between diabetes mellitus and glaucoma have been proposed by various authors. Firstly, it was postulated that diabetes would lead to impairment of micrangium and vascular autoregulation. These vascular injuries would reduce blood flow to the retina and optic nerve, resulting in reduced nutrient and oxygen supply to the RGC axons and increased expression of hypoxia-inducible factor-1 in the retinal cells in response to

elevated IOP. Ultimately these changes were likely to induce the degeneration of the RGCs and initiation of glaucomatous impairment. Secondly, there was a large amount of evidence that the hyperglycemia and lipid anomalies induced by diabetes could increase the risk of neuronal injury indicating that the RGCs were more likely to be destroyed in the patients with diabetes.

Third, the hyperglycemia of aqueous humour in the eyes of diabetes patients would stimulate the synthesis and accumulation of fibronectin in the trabecular meshwork to promote depletion of trabecular meshwork cells, which could impair the outflow system of the aqueous humour and finally result in POAG.

Both diabetes and glaucoma seem to share some common risk factors and pathophysiologic similarities with studies also reporting that the presence of diabetes and elevated fasting glucose levels in an individual are associated with elevated intraocular pressure – which is the primary risk factor for glaucomatous optic neuropathy.

The burden of diabetes on the health care system has manifested in many different ways. Diabetic patients require more outpatient visits, chronic medications, and are at risk for a number of systemic microvascular complications that result in end organ damage and associated complications: renal disease, cardiovascular disease, amputations, vision loss, and premature death. Vision loss from diabetic retinopathy (DR),in particular,represents one of the most devastating complications on quality of life and is the leading cause of blindness in todays working age.

Mechanical stress from elevated IOP is thought to occur primarily at the level of the lamina cribrosa – the point at which the optic nerve fibres penetrate the posterior sclera. The optic nerve fibres arise form the axons of the RGCs, but IOP-induced mechanical stress causes posterior bowing and thinning of the lamina, which disrupts axonal transport. As a result, the RGCs undergo apoptotic cell death in conjunction with loss of neuroretinal rim tissue of the optic disc and corresponding enlargement of the optic cup.

Glaucoma Risk Factors and Correlation with Diabetes

Common Pathophysiologic Mechanisms in Glaucoma and 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. Also, 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 scientists 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 remodelling 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 humour 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, which is 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. With regard to the eye and glaucoma, insulin and insulin-like growth factor have been shown to play a role in RGC survival. Also, 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 2diabetes, 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.

Neurodegeneration and Ganglion Cell Apoptosis:

RGC apoptosis and retinal nerve fibre layer (RNFL) thinning are characteristic structural findings seen in glaucoma that have also been described in diabetic retinopathy. In conjunction with RNFL loss, excavation or cupping at the level of the optic nerve head is the pathognomonic finding that is most commonly associated with glaucoma. However, a similar appearance of the optic nerve head may also be seen in the presence of anterior ischemic optic neuropathy, which occurs more frequently in diabetic patients in some studies, or after laser photocoagulation treatment for proliferative diabetic retinopathy. Structural optic nerve abnormalities have also been reported in an experimental

rat model of diabetes, which also showed corresponding RGC dysfunction as measured by electroretinogram. Such similarities can present challenges in distinguishing glaucomatous from non-glaucomatous optic neuropathy, especially in the presence of both conditions.

Though diabetic retinopathy is generally considered primarily a microvascular complication of diabetes, it is now known that neurodegeneration is also a significant component in its pathophysiology and may even precede the microvascular changes that are typically seen in diabetic eye disease. In a recent study by Sohn and colleagues, progressive loss of both the nerve fibre layer and RGC/inner plexiform layer was observed using optical coherence tomography (OCT) in 45 patients with no or minimal diabetic retinopathy. In the same study, they also demonstrated progressive inner retinal thinning and RGC loss in a streptozotocin- induced mouse model of type 1 diabetes on both OCT and immunohistochemistry. These findings are consistent with earlier work from the same investigators, who reported selective thinning limited to the inner retina in type 1 diabetic patients. Cross-sectional human studies from other groups comparing RNFL thickness in healthy subjects and patients with preclinical diabetic retinopathy have also demonstrated mean and superior quadrant RNFL thickness to be reduced in diabetic patients when measured by OCT. As a result, neurodegeneration in diabetic eye disease appears to occur in the same location of the neural retina as glaucomatous optic neuropathy.

Also, neurodegeneration in both glaucoma and diabetic eye disease is believed to be relatively nonselective, affecting all RGC types. In general, RGCs can be classified based on their functional features and projections from the optic nerve head to layers of the lateral geniculate nucleus. Studies in experimental primate models of glaucoma have shown that RGC loss of all types occurs by apoptosis with greater loss occurring as a direct function of IOP. Specifically, loss of neurons in the magnocellular and parvocellular pathways has been demonstrated in glaucoma, which has also been reported in a histologic study of human retinas with diabetic retinopathy by Meyer-Rusenberg and

colleagues as well.

Functional Abnormalities in Glaucoma and Diabetes:

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.

Metabolic Syndrome and Insulin Resistance in Glaucoma and Diabetes:

Metabolic syndrome is a cluster of clinical risk factors, including hypertension and dyslipidemia, which is a significant predictor of diabetes. Insulin resistance is thought to be involved in the pathophysiology of metabolic syndrome and as a result, the components of metabolic syndrome are comprised of significant systemic risk factors for either elevated IOP or glaucoma.In a study examining individual components of metabolic syndrome, Newman- Casey and colleagues found that hyperlipidemia alone in the absence of diabetes or glaucoma was not a risk factor for open angle glaucoma. However, both diabetes mellitus and systemichypertension, either alone or in combination, were associated with an increased hazard of open angle glaucoma.

With regard to insulin resistance, a recent study comparing IOP changes in diabetic and non- diabetic individuals found reported that hyperglycemia during oral glucose tolerance testing has a

positive correlation with IOP. Similarly, data from the Korean National Health and Nutrition Examination Survey also reported higher mean IOP to be positively correlated with estimated insulin resistance in addition to the presence of diabetes mellitus, hypertension, metabolic syndrome, and lipid abnormalities. In a study of normal tension glaucoma patients and components of metabolic syndrome, Kim and colleagues found hypertension and impaired glucose tolerance were associated with a significantly higher prevalence of normal tension glaucoma. However, a slightly lower prevalence of glaucoma was seen among participants with metabolic syndrome in the Singapore Malay Eye Study and neither pre- diabetes or metabolic syndrome were consistently associated with glaucoma in a cross- sectional study of subjects from the 2005–2008 National Health and Nutrition Examination Survey . Recently, a study using healthcare claims data reported a dose-dependent reduction in POAG risk among diabetic persons using metformin, the first-line medication used to treat patients with type 2 diabetes mellitus and improve insulin sensitivity. In addition, those subjects with a higher HBA1c had an increased risk of glaucoma, suggesting that glycemic control and insulin sensitivity may contribute to glaucoma risk. Many of the risk factors associated with diabetes may also be contributory to glaucoma as well, when considered together,Both diabetes and glaucoma are major ophthalmological 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 as discussed above. 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 demands further consideration as we continue to learn more about the association between these two blinding conditions.

Since glaucoma is now considered as a major diabetes side effect and a leading cause of blindness, diabetes doctors and ophthalmologists advise an eye examination periodically based upon the risk of a person to get glaucoma.

While glaucoma is generally suspected in a normal eye examination, certain diagnostic tests are prescribed in order to confirm the diagnosis of glaucoma. These tests include:

Diagnostic tests for glaucoma

- Tonometry – This test is done to determine the intraocular pressure
- Ophthalmoscopy – This test is done to examine (damage to) the optic nerve
- Gonioscopy- This test measures whether the angle where the iris meets the cornea is wide, open, or narrow
- Pachymetry – This test is done to measure the corneal thickness
- Perimetry- This test is done to measure the field of vision
- Slit-lamp examination
- Optical coherence tomography
- Dilated fundus examination with 78D/90D
- Laser scan of the retina (Laser tomography)

Based upon the results of these tests, the treatment options for glaucoma is evaluated and the appropriate treatment is given by the ophthalmologist in conjunction with a diabetes doctor.

Treatment

The main goal for glaucoma treatment is slowing the disease progression and preservation of quality of life. Reduction of intraocular pressure to desired target pressure is the only proven method to treat glaucoma. The target intraocular pressure should be achieved with the fewest medications and minimum adverse effects. Several different classes of pressure-lowering medications are available:

Class of Medication	Example	Usual Dosages	Mechanism of Action
Prostaglandin analogues (prostamide)	Latanoprost, travoprost, tafluprost, unoprostone, bimatoprost	1/d At night	Increase in uveoscleral outflow of aqueous humor
β-Adrenergic blockers	Timolol, levobunolol, carteolol, metipranolol, betaxolol	1/d In the morning	Reduction of aqueous humor production
α-Adrenergic agonists	Brimonidine, apraclonidine	3/d (Sometimes 2/d)	Initial reduction of aqueous humor production with subsequent effect of increase in outflow
Carbonic anhydrase inhibitors	Dorzolamide, brinzolamide, acetazolamide (oral)	3/d (Sometimes 2/d)	Reduction of aqueous humor production
Cholinergic agonists	Pilocarpine, carbachol	Usually 4/d, but may vary	Increase in aqueous humor outflow

Image: showing various topical anti-glaucoma medications with their mechanism of action.

When medical treatment does not achieve adequate intraocular pressure reduction with acceptable adverse effects, laser or surgeries are indicated.

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