

# Diabetes and POAG

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Although the clinical picture of glaucoma is well described, the exact mechanism leading to this specific type of damage to the optic nerve head (ONH) is not yet clear.

- ▶ It is generally accepted that the mechanism of damage in glaucoma is almost certainly *multifactorial*.
- ▶ But while elevated intraocular pressure (IOP) remains the risk factor most commonly associated with glaucomatous optic neuropathy (GON), numerous other variables involved in the development and progression of glaucoma have been identified.

- ▶ Vascular risk factors in particular have been extensively studied.
- ▶ These include systemic blood pressure alterations, diabetes, reduced ocular blood flow (OBF), and vasospasm.

- ▶ Conventionally, two theories have been presented for the pathogenesis of glaucoma, pressure and vascular:

1. **Pressure theory**, introduced by *Muller*, supposes that GON is a direct consequence of elevated IOP, damaging the lamina cribrosa and neural axons.

2. **Vascular theory**, suggested by *von Jaeger*, considers GON as a consequence of insufficient blood supply to the ONH due to either elevated IOP or to other risk factors reducing OBF.

- ▶ Both theories have been vigorously studied and defended by various research groups for over a century.

## Potential Mechanisms of Ocular Blood Flow Reduction in Glaucoma Patients



- ▶ Theoretically, there are three components contributing to ocular blood flow reduction in glaucoma patients:
  - (1) Increased local resistance to flow
  - (2) Decreased ocular perfusion pressure (OPP)
  - (3) Increased blood viscosity.

- ▶ Several indications point to the role of both **increased local resistance to flow** and **decreased ocular perfusion pressure** in the development and progression of glaucoma:

## Local resistance to blood flow

- ▶ Increased resistance to blood flow is manifested as reduced vascular diameter and is affected by either structural changes due to anatomic variations in the vessels, vasculitis, or mechanical obstruction of the lumen (via thrombosis or arteriosclerosis) or functional changes such as abnormal or defective autoregulation of blood flow.

## Local resistance to blood flow

- ▶ Reduced vascular diameter can also be due to reversible spasm of the smooth muscle cells in the vessel wall.

## Ocular Perfusion Pressure

- ▶ Ocular perfusion pressure=

**Mean arterial blood pressure**

**Minus**

**Venous blood pressure**

in a specific vascular bed.

- ▶ Normally, venous pressure is slightly higher than IOP and for practical purposes IOP is a good indicator of the venous pressure.

## Ocular Perfusion Pressure

- ▶ Therefore, OPP can be considered as the difference between mean arterial blood pressure and IOP (where mean arterial blood pressure = diastolic blood pressure +  $\{1/3\}$  [systolic blood pressure – diastolic blood pressure]).
- ▶ Reduced ocular perfusion pressure might be attributed to either increased IOP or decreased systemic blood pressure or to both.

## Ocular Perfusion Pressure

- ▶ During the past four decades an increasing amount of evidence was found to support each of the above theories hypothesized to play a crucial role in the pathogenesis of glaucomatous optic neuropathy.

- ▶ *Autoregulation* refers to the capacity of an organ or tissue to regulate its blood supply in accordance with its functional or metabolic needs.
- ▶ With intact autoregulation, changes in ocular perfusion pressure or metabolic demands are associated with local constriction or dilatation of the terminal arterioles, which causes vascular resistance to increase or decrease, thereby maintaining a constant supply of oxygen and nutrients to the tissues.

## Ocular Effects of Diabetes



- ▶ Diabetes mellitus is associated with abnormalities of the general circulation including:

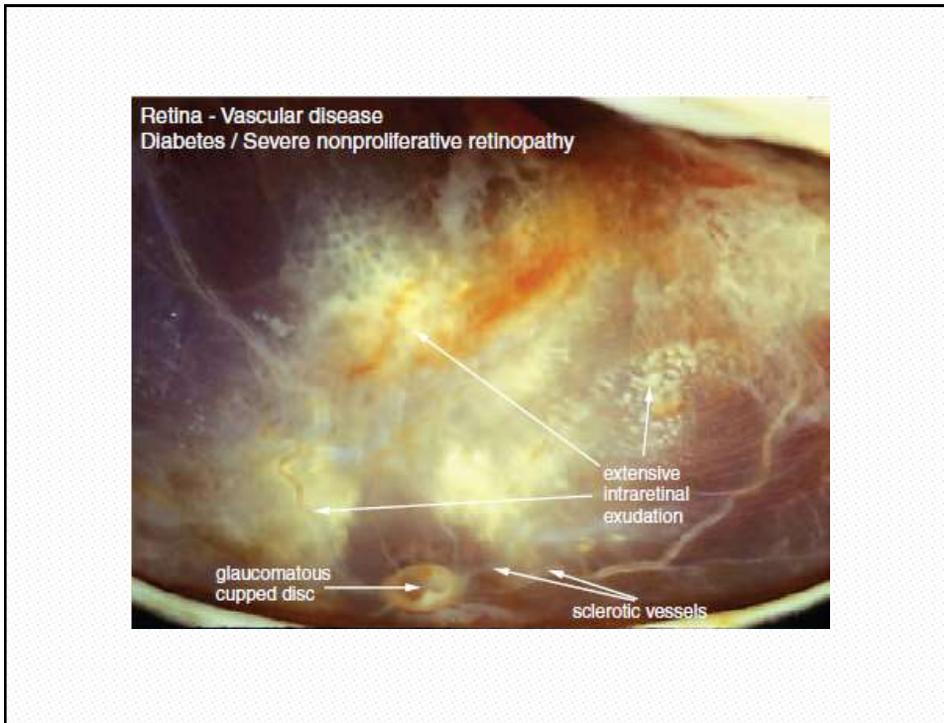
- Decreased tissue oxygenation
- Vascular leakiness
- Increased blood viscosity
- Capillary shunting
- Capillary non perfusion.



## Ocular effects include:

- Changes in aqueous humor dynamics
- Increase or decrease in IOP
- Presence of aqueous flare
- Increased permeability of the blood-ocular barriers
- Abnormalities in the retinal vasculature.





- ▶ Studies by Hayreh have shown a close association between glaucomatous optic neuropathy and systemic vascular disorders such as diabetes.
- ▶ While Flammer and Orgul believed there was currently very little evidence linking glaucomatous optic neuropathy to arteriosclerosis or its risk factors (gender, obesity, hypercholesterolemia, smoking and diabetes).
- ▶ They attributed increased local resistance to blood flow to a functional rather than a structural change, namely to abnormal or defective autoregulation of blood flow.

## Reduced IOP in diabetics



- ▶ Aqueous humor dynamics have been studied in patients with diabetes and reduced IOP.
- ▶ The cause of the lower IOP is a reduction in the rate of aqueous flow.

- ▶ IOP and aqueous flow were correlated with severity of diabetic retinopathy, age of onset, duration of diabetes, and age of the patient.
- ▶ There was a significant negative correlation between the degree of retinopathy and aqueous flow rate, i.e. as the severity of retinopathy increased, aqueous flow decreased.

- ▶ Patients with type 1 diabetes are prescribed insulin to control circulating glucose levels.
- ▶ Insulin is a hormone with vasoactive properties that could directly affect the production rate of aqueous humor.
- ▶ It has been proposed that the insulin treatment and not the disease might account for the reduction in aqueous flow in diabetes.

- ▶ A study designed to control for the insulin treatment during the time of aqueous flow assessment maintained insulin at one of two fixed levels by a hyperinsulin-emic-euglycemic glucose clamp.
- ▶ During each clamp, aqueous flow was measured in 11 patients with type 1 diabetes and 17 age-matched healthy control subjects.
- ▶ At the higher insulin level, aqueous flow was slightly greater than at the lower insulin level but this did not reach statistical significance ( $p=0.09$ ).

- ▶ A more important finding was that despite the normal IOPs and the absence of microvascular complications (retinopathy and microalbuminuria), a significant reduction in aqueous flow was found.
- ▶ For IOP to be normal in the presence of reduced aqueous flow, other parameters of aqueous humor dynamics must change.
- ▶ When measured by tonography, patients with type 1 (insulin dependent) diabetes had normal outflow facilities
- ▶ Uveoscleral outflow and episcleral venous pressure have yet to be investigated in diabetes.

## Studies looking at the association between POAG and Diabetes



- ▶ Several studies investigated the possible relationship between POAG and diabetes.
- ▶ In the **Beaver Dam Eye Study**, prevalence of POAG was higher in diabetic individuals compared to non-diabetics (4.2% vs 2.0%;  $p = 0.004$ )\*
- ▶ In the **Blue Mountains Eye Study**, glaucoma prevalence and ocular hypertension (OHT) were also more common in people with diabetes .\*\*

\* BE Klein, R Klein, SC Jensen: Open-angle glaucoma and older-onset diabetes. The Beaver Dam Eye Study. *Ophthalmology*.101:1173-1177 1994

\*\* P Mitchell, W Smith, T Chey, et al.: Open-angle glaucoma and diabetes: the Blue Mountains Eye Study, Australia. *Ophthalmology*.104:712-718 1997

- ▶ Other prospective studies of glaucoma management reported a greater likelihood of progression in patients with diabetes.

MC Leske, A Heijl, M Hussein, et al.: Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. *Arch Ophthalmol.* 121:48–56 2003  
The Advanced Glaucoma Intervention Study (AGIS): 12: Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. *Am J Ophthalmol.* 134:499–512 2002

- ▶ Conversely, the **Baltimore Eye Survey** showed that the association between glaucoma and diabetes was *weak* (odds ratio:1.03)
- ▶ However, patients whose POAG had been diagnosed before they enrolled in the study showed a positive association with diabetes , indicating that selection bias into the healthcare system may have influenced the positive results of associations between diabetes and POAG.

- ▶ The **Ocular Hypertension Treatment Study** suggested that diabetes actually protected against progression to POAG

- ▶ **MO Gordon, JA Beiser, JD Brandt, et al.**: The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 120:714-720 2002
- ▶ **MA Kass, DK Heuer, EJ Higginbotham, et al.**: The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 120:701-713 2002

- ▶ The effect of diabetes on the development of POAG remains controversial.

## Conclusion

- ▶ Diabetes has been listed as a risk factor for glaucoma, but in some studies IOP in diabetes mellitus has been reported to be below normal with reduced risk of glaucoma.
- ▶ Consensus among studies is lacking.

