ISSUE 3

Cipla

Glaucoma ESSENTIALS

Impact of diabetes on glaucoma

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Contents

Introduction

Diabetes is one of the leading causes of morbidity and mortality worldwide and a major problem in India. The prevalence of diabetes in 2013 in India is only slightly higher than the world average (9.1% vs. 8.3% worldwide). However, **due to a very large population, India has the world's largest population living with diabetes after China. In 2013, there were 65.1 million people between 20 and 79 years of age with diabetes and this number was predicted to rise to 109 million by 2035. The growing epidemic of type 2 diabetes in India has been highlighted in several studies.**[1]

Although there are several long-term effects of diabetes, some effects can develop after only 6 or 12 months of high levels of glucose in the blood. Diabetes complications can cause major health problems such as blindness, heart disease, stroke and kidney failure.[2] Diabetic retinopathy is the most well-known ocular complication of diabetes and a leading cause of blindness worldwide. However a range of ocular diseases are associated with diabetes, which may result in vision loss. One such disease is glaucoma.[3]

As per a study conducted at AIIMS hospital in India, 29.4% of patients with glaucoma suffered from diabetes. Nearly one third of glaucoma patients suffer from diabetes. The prevalence of diabetes was found to be significantly higher in patients with primary open angle glaucoma in comparison to primary angle closure glaucoma.[4]

The link between diabetes mellitus (DM) and glaucoma has been addressed in many studies, with conflicting results. Many earlier clinic-based studies were limited by small sample sizes, inadequate controls, and lack of proper diagnostic criteria. Even large population-based studies conducted to determine the strength or weakness of an association between these two disorders has shown inconsistent results. Positive correlations were reported in the Beaver Dam, Rotterdam, and Blue Mountain studies, with odds ratios calculated to be 1.68, 3.11, and 2.12, respectively. However, the largest study, the Baltimore Eye Survey, revealed no association after adjusting for age and race (Table- 1).The authors commented that an increased mortality risk associated with diabetes could have led to an underestimation of the frequency of both diabetes and glaucoma, a limitation accompanying the prevalence based approach.[5]

Table 1: Summary of epidemiological trials considering the association between diabetes mellitus and open angle glaucoma.[6]

Author(s)	Location	Study design	Association between diabetes & glaucoma	Odds ratio (95% CL)
Klein et al	Beaver Dam, USA	prevalence	Yes	1.68
Tielsch et al	Baltimore, USA	prevalence	No	1.03
Dielemans et al	Rotterdam, Holland	prevalence	Yes	3.11
Mitchell et al	Blue Mountains, Australia	prevalence	Yes	2.12
Ellis et al	Scotland	incidence	No	1.57
Gordon et al, OHTS	USA	prevalence	No	0.40 (0.18-0.92)
De Voogd et al	Rotterdam, Holland	Incidence	No	0.65
Pasquale et al	USA	incidence	Yes	1.82
Miglior et al	Europe	Prevalence	No	0.89 (0.36-2.17)
Chopra et al,	Los Angeles USA	prevalence	Yes	1.4
Gordon et al, OHTS	USA	Additional data	No	0.70 (0.45-1.10)
CL= confidence limits				

This issue on diabetes and glaucoma aims to put forth documented evidence from recent meta-analysis on association between glaucoma and diabetes. Also it describes the effect of diabetes on glaucoma along with the impact of anti-glaucoma drugs on patients with diabetes.

Recent meta-analysis published in Ophthalmology 2014 & plos one 2014 have shown that individuals with DM have an increased risk of developing primary open angle glaucoma (POAG).

Study 1

Diabetes, Fasting Glucose And The Risk Of Glaucoma[7]

Reference: *Ophthalmology. 2014;-:1e7http://dx.doi.org/10.1016/j.ophtha.2014.07.051*

A systematic review and meta-analysis was conducted to summarize the association between diabetes, diabetes duration, metabolic syndrome and glucose levels with risk of glaucoma and with intraocular pressure (IOP) level in the general population. This meta-analysis was published in ophthalmology 2014.

All studies reporting an association between diabetes, metabolic syndrome, or glucose levels with glaucoma, IOP levels, or ocular hypertension (OHT) in adults 18 years of age or older by searching PubMed and EMBASE database were identified. Relative risks were summarized. Mentioned below is the description of the studies involved in the meta-analysis.

- **47 studies, including 29,81,342 individuals from 16 countries were identified.**
- Sixteen studies were performed in North America, 15 in Asia, 11 in Europe, 2 in Australia, 1 in Africa, 1 in the Middle East, and 1 in the West Indies.
- **Thirty two studies were cross-sectional, 9 were case-control, and 6 were longitudinal.**
- Twenty-nine studies reported on the association between diabetes and glaucoma, 5 on diabetes duration and glaucoma, 2 on hemoglobin A1c and glaucoma, 1 on metabolic syndrome, glucose levels and glaucoma, 11 on diabetes and IOP levels, 6 on glucose and IOP levels, 6 on diabetes and OHT, and 1 on glucose and OHT.

Risk of glaucoma

- **The pooled relative risk (RR) for glaucoma comparing patients with diabetes with those without diabetes was 1.48.**
- The estimates from cross-sectional, case-control, and longitudinal studies were similar (RR, 1.58, 1.44, and 1.37, respectively).
- The results also were similar by country, method for ascertainment of diabetes, criteria for defining glaucoma, and year of publication. However, the pooled RR for studies using exclusively POAG as outcome was 1.23, whereas the RR for studies using open-angle glaucoma or glaucoma as outcome was 1.71.
- **Among 5 studies with dose-response data on the association of diabetes duration with glaucoma, the risk of glaucoma increased by 5% (95% CI, 1%-9%) for each year since diabetes diagnosis.**

Effect on Intraocular pressure (IOP)

- **The pooled average difference in IOP comparing patients with diabetes with those without diabetes was 0.18 mmHg** (95% CI, 0.09-0.27).
- The pooled estimates were not statistically different by study design, country, method for ascertainment of diabetes, method of IOP measurement, and year of publication (<2000, ≥2000).
- **The pooled average increase in IOP associated with an increase in 10 mg/dl in fasting glucose was 0.09 mmHg (95% CI, 0.05-0.12).**

Effect on ocular hypertension

- One case-control study, 4 cross-sectional studies, and 1 longitudinal study reported data on the association between diabetes and OHT.
- **The pooled RR for OHT comparing participants with diabetes with those without diabetes was 1.52.**
- Finally, one study reported data on the association between impaired fasting glucose (defined as ≥100 mg/dl) and OHT (RR,2.12;95% CI, 1.30-3.45).

These finding further support the need for patients with longer duration of diabetes to adhere to optimal glaucoma screening examinations and management.[3]

Limitations

- There was substantial heterogeneity in the methods and quality of the original studies, and the methods used to ascertain exposure and outcomes varied widely across studies, likely contributing to the high degree of heterogeneity in the results.
- There was also heterogeneity in the covariates adjusted for in each study.
- Another concern was the lack of evidence of the effect modification by types of diabetes. The association between diabetes and the glaucomatous process may be different in type 1 diabetes, in which lack of insulin production leads to increased blood glucose, compared with type 2 diabetes, in which insulin resistance is the primary underlying mechanism. However, detailed information on the type of diabetes was not available in the original studies. It was found in this meta-analysis, that patients with diabetes treated with insulin had a higher risk for glaucoma compared with patients with diabetes not treated with insulin, but whether insulin was used in the context of type 1 or type 2 diabetes could not identified. Future studies should characterize the implications of the different types of diabetes on glaucoma risk.

Conclusion

Diabetes, diabetes duration and fasting glucose levels were associated with a significantly increased risk of glaucoma, and diabetes and fasting glucose levels were associated with slightly higher IOP. As a consequence, the importance of glaucoma screening in patients with diabetes, particularly those with long-standing disease should be underlined and could be considered when these patients are receiving diabetic eye screening.

Study 2

Diabetes Mellitus As A Risk Factor For Open-Angle Glaucoma: A Systematic Review And Meta-Analysis[8]

Reference: *PLoS One. 2014 Aug 19;9(8):e102972. doi: 10.1371/journal.pone.0102972. eCollection 2014.*

A systemic review and meta-analysis was performed of case controlled and cohort studies in order to determine the association between diabetes mellitus and primary open angle glaucoma. This meta-analysis was published in Plos one 2014. Mentioned below is the description of the studies involved in the meta-analysis:

- **Thirteen studies, 7-case control studies and 6 cohort studies that presented results on DM and the risk of POAG were included in this meta-analysis.**
- **Characteristics of the various studies included is as follows:-**

Case based	Cohort based
Studies were published between 1987-2009	Studies were published between 2000 and 2011
Three studies originated from the United States, one from Korea, one from the Congo, and two from Europe (France and Denmark).	Three studies originated from the United States, one from the Netherlands, one from the Barbados, and one from the United Kingdom.
In total, 11,472 cases and 75,631 controls were included in this meta-analysis.	A total of 46,360 cases of POAG in a cohort of 3,393,011 individuals were included in this meta-analysis.
Four studies reported a positive association between DM and the incidence of POAG.	Three studies reported a positive association between DM and POAG.
The pooled OR for the seven case-control studies was 1.49 (95% CI, 1.17–1.88)	The pooled RR for the five cohort studies was 1.40 (95% CI, 1.25–1.57)

- **The results from this case-control and cohort studies were quite similar. The findings from this meta-analysis showed that compared with non-diabetic individuals, individuals with DM have an approximately 1.4 fold increased risk of developing glaucoma in cohort studies.**
- **The results from case-controlled studies showed that they have an about 49% increased odds of developing POAG compared with individuals without DM.**

Limitations

- Significant heterogeneity existed in the case-control studies.
- In the cohort studies, the effect size of one study was the IRR
- DM was self-reported in some studies, and this may have introduced a recall bias.
- Publication bias is a major problem in published studies and in meta-analyses of published studies.

Conclusion

In summary, the results of this meta-analysis point to a significant association between DM and the risk of POAG. Further studies are needed to elucidate the exact underlying mechanisms linking DM with POAG.

Impact of Diabetes on Glaucoma

- **Increased IOP in diabetes may be the result of hyperglycemia**, which may induce an osmotic gradient that draws excess aqueous humor into the anterior chamber and to autonomic dysfunction. Hyperglycemia also may increase IOP by interrupting the trabecular meshwork function.[7]
- **Diabetes may increase corneal stiffness and central corneal thickness (CCT)**, which may raise IOP readings artificially. **Singapore Malay Eye Study showed that on average, person with diabetes had central corneal thickness 6.5µm thicker than those without diabetes.** Mean CCT was positively related with increasing levels of serum glucose and $HbA_{1c.}$ **Variations in glucose level upto 3 months probably affect CCT to a greater extent than short term fluctuations of glucose levels.**[7,9]
- **Several mechanisms have been speculated for the same-** Hyperglycemia may cause corneal endothelial dysfunction with resultant stromal hydration and swelling of the cornea. Indeed, abnormalities of corneal endothelial morphology such as polymorphism, polymegatheism, decrease in percentage of hexagonal cells, higher coefficient of variation, and increased CCT have been detected on specular microscopy in persons with diabetes.[9]

However, the association between diabetes and IOP was weak, suggesting that the association between diabetes and glaucoma in part may be independent of raised IOP. This is also supported by the fact that the association between diabetes and glaucoma in the above mentioned meta-analysis was similar in studies that used IOP as criteria for defining glaucoma compared with those that did not use IOP.[7]

Vascular mechanisms have been implicated to explain the increased risk of glaucoma in patients with diabetes regardless of IOP levels.[7]

- Diabetes causes microvascular damage and may affect vascular autoregulation of the retina and optic nerve.
- Vascular damage can reduce blood flow and impair oxygen diffusion. Endothelial cell injury and dysfunction can reduce the autoregulatory capacity to protect against fluctuations of IOP and blood pressure, which could lead to relative hypoxia and to damage of the optic nerve head and of the retinal nerve fiber layer.
- Furthermore, vascular changes in diabetes may increase the susceptibility of the retina to additional stress related to POAG or IOP elevation.

Color Doppler Imaging of ophthalmic artery and central retinal artery in glaucoma patients with and without diabetes mellitus.[10]

A prospective comparative study was conducted on 50 POAG patients, total 100 eyes to assess the ocular blood flow in diabetic and non-diabetic primary open angle glaucoma (POAG) patients. Patients were divided into 2 groups- Group 1 (25 POAG patients without diabetes mellitus) and Group 2 (25 POAG patients with diabetes mellitus).Colour Doppler Imaging (CDI) of ophthalmic artery and central retinal artery were studied and peak systolic velocity (V max), end diastolic velocity (V min) and Resistivity Index (RI) were assessed.

Results

- The mean age of patients in the non-diabetic group was 58 years (50-73) with 15 males & 10 females. In the diabetic group the mean age of the patients was 56 years (52-75) and included 14 males and 11 females.
- The table below represents the various parameters measured by Color Doppler Imaging

	Diabetics	Non-diabetics	
Ophthalmic artery blood flow			**Difference was not statistically significant**
Peak systolic velocity	43.34 cm/sec	46.62 cm/sec	
RI	0.71	0.65	
Retinal artery blood flow velocity			**Difference was statistically significant**
Peak systolic velocity	17.93 cm/sec	29.72 cm/sec	
RI	0.72	0.50	

- **There is a definitive alteration in RI in diabetics with POAG which indicates disturbance in ocular blood flow as a significant cause of the pathology in addition to elevated IOP in patients with POAG and diabetes mellitus.**
- Colour Doppler Imaging has shown significant optic nerve head perfusion abnormality in patients with both POAG and diabetes mellitus.
- This study supports the vascular theory of POAG as well as establishing further the role of diabetes mellitus in predisposing to POAG.

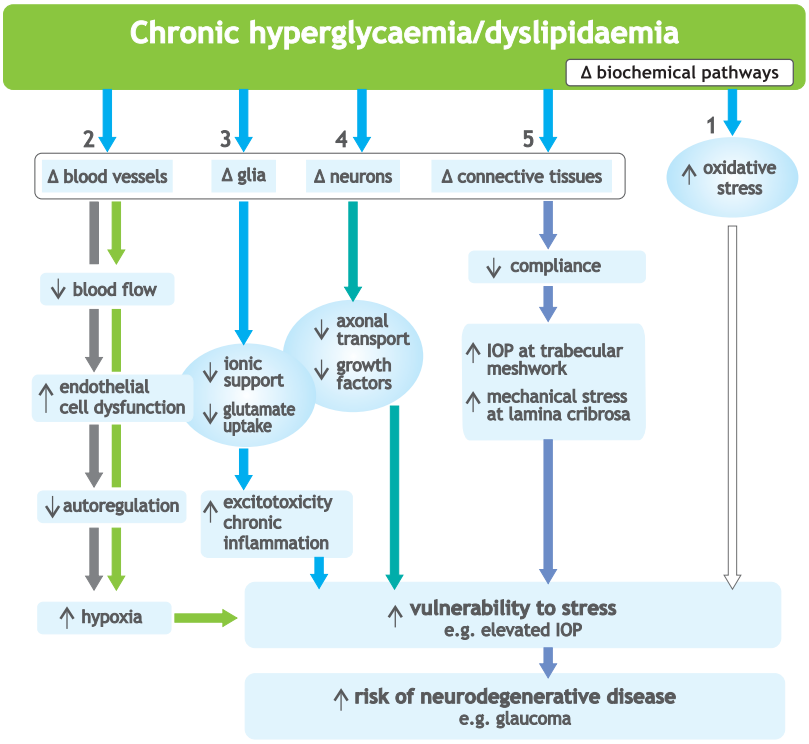
Conclusion

Colour Doppler imaging has shown significant optic nerve head perfusion abnormality in patients with both POAG & diabetes mellitus. This study showed the value of Colour Doppler imaging in the assessment of PAOG in a non-invasive and reproducible way.

Apart from vascular changes, diabetes impairs physiological glial and neuronal function in the retina, which may increase the susceptibility of retinal ganglion cells to glaucomatous damage.

There is a growing body of evidence that the presence of longstanding hyperglycaemia, along with lipid anomalies, may increase the risk of neuronal injury from stress. In particular, the laboratory data provide robust evidence for an association. The various pathways whereby diabetes and glaucoma might converge to produce an increased risk of neurodegeneration are schematised in Figure 1 and can be summarised as follows.[6]

Figure 1: Summary of the possible changes resulting from chronic hyperglycaemia and dyslipidaemia seen in diabetes mellitus. These pathways are not meant to imply causation but rather to illustrate the possible ways in which diabetes might promote neurodegenerative diseases such as glaucoma. Much research is needed to define these links.[6]



- Altered biochemical pathways compromise cells and also increase oxidative stress.
- Vascular changes can reduce blood flow and impair oxygen diffusion. Endothelial cell injury and dysfunction can reduce the capacity for autoregulation to protect against fluctuations in eye and blood pressure. These lead to relative hypoxia.
- Glial cell activation can lead to impaired ionic support and possibly reduced glutamate uptake. This might increase the chance of excitotoxicity. Excessive glial cell activation may also contribute to chronic inflammation.
- Changes to neurons may impair their ability to function, including axonal transport, leaving these neurons, which are already vulnerable, under additional stress.
- Connective tissue remodelling might reduce compliance at the trabecular meshwork and lamina cribrosa, promoting increased IOP and greater optic nerve head mechanical stress, respectively.[6]

Further studies are needed to directly determine mechanisms underlying any potential association between diabetes and glaucoma[6]

Impact of Anti-Glaucoma Drugs In Diabetic Patients[5]

- For the medical management of glaucoma in patients with diabetes, several factors must be considered. Two important physiological processes, in response to hypoglycemia, are glycogenolysis and gluconeogenesis, which are activated in the liver through stimulation of beta 2 receptors.[5]

Anti-glaucoma drugs	Effect in diabetics
Beta blockers	• Can alter and slow the subsequent glucose release, and mask the sympathetic response to hypoglycemia, such as diaphoresis and tachycardia. • Timolol has been reported to alter the hypoglycemic response in diabetic patients,there is no absolute contraindication to the use of topical nonselective beta blockers in diabetic patients. • Beta 1 selective antagonists may be preferable to minimize the effect on blood glucose levels.
Adrenergic agonists	• Can decrease the effect of insulin in diabetics and may stimulate hyperglycemia.
Carbonic anhydrase inhibitors (CAIs)	• Systemic CAI can result in excessive excretion of bicarbonate ion in the kidneys, accompanied by loss of sodium and potassium. The resultant hypokalemia may increase blood sugar in diabetic patients. • These electrolyte imbalances maybe minimized with the use of a topical CAI.
Hyperosmotic agents	• May result in severe dehydration, by virtue of caloric content and osmotic diuresis. Of the various oral osmotic drugs, glycerol is more likely to produce hyperglycemia. • Isosorbide, which is not metabolized, is a more desirable hyperosmotic agent for diabetic patients, but is no longer commercially available.

Effect of Metformin on The Risk of Open Angle Glaucoma[11]

Reference: *JAMA Ophthalmol. 2015; doi:10.1001/jamaophthalmol.2015.1440*

Caloric restriction mimetic drugs have geroprotective effects that delay or reduce risks for a variety of age-associated systemic diseases, suggesting that such drugs might also have the potential to reduce risks of blinding ophthalmologic conditions for which age is a major risk factor. A retrospective cohort study was conducted to determine the association of reduced risk of open angle glaucoma in diabetic patients on the drug metformin.

Data was utilized from a large nationwide health care claims database containing detailed billing records for more than 1,50,000 older individuals with diabetes mellitus, some of whom were being prescribed metformin, to compare the risk of developing open angle glaucoma (OAG) among users vs nonusers of metformin and to determine whether a dose response relationship exists such that those who consume more metformin show a greater OAG risk reduction. This study used 10 years of data from the Clinformatics Data- from January 1, 2001, through December 31, 2010.

Inclusion criteria

- All patients aged 40 years or older enrolled in the plan continuously for more than 2 consecutive years and
- Diagnosed as having diabetes during their first 2 years in the plan
- Patients selected had at least 1 eye examination during this 2-year period to exclude those with preexisting OAG
- At least 1 eye examination after this period to identify incident OAG.

Exclusion criteria

- Patients with incomplete, missing, or duplicate data or discontinuous enrollment

Methods

Patients were followed up from the index date (ie, the date corresponding to their first eye examination on or after the 2-year look-back period) until incident OAG or their last eye examination, whichever came first. Use of metformin and other medications for diabetes came from a review of outpatient medication prescriptions filled.

Cumulative amount of metformin hydrochloride use based on prescriptions filled during a 2-year moving time window was stratified into 4 quartiles: 1 to 315 g (first quartile), 316 to 660 g (second

quartile), 661 to 1110 g (third quartile), and more than 1110 g (fourth quartile). Risk of developing OAG for persons with each of the 4 dosage quartiles against persons with no prescriptions for metformin were compared.

Results

- **Of 1,50,016 individuals with diabetes who met the inclusion criteria, 5893 (3.9%) developed incident OAG.**
- The population included 73,117 men (48.7%), 1,10,884 individuals (82.2%) Of European ancestry, 10,601 individuals (7.9%) of African ancestry, 8,545 individuals (6.3%) of Latino ancestry, and 3,537 individuals (2.6%) of Asian ancestry. **Open-angle glaucoma developed in individuals of African (6.7%) and Latino (4.6%) ancestry at a higher rate than in populations of European (3.6%) and Asian (3.7%) ancestry.**
- For patients who did not develop OAG, the mean (SD) duration from the first eye examination until the last eye examination without incident OAG was 52.8 (20.9) months; for those who developed OAG, the mean (SD) duration from the first eye examination until initial OAG diagnosis was 63.3 (23.4) months.
- **The mean (SD) HbA1c level was 7.2% (1.5%), indicating that, on average, the blood glucose levels were relatively well controlled. Throughout the study period, 60,214 patients (40.1%) filled at least 1 metformin prescription,** 46,505 (31.0%) filled at least 1 sulfonylurea prescription, 35,707 (23.8%) filled at least 1 thiazolidinedione prescription, 3,663 (2.4%) filled at least 1 meglitinide prescription, and 33,948 (22.6%) filled at least 1 insulin prescription. Some patients filled prescriptions for multiple medication classes.
- After adjusting for time-dependent and time-constant covariates, **taking more than 1110 g of metformin hydrochloride cumulatively over 2 years (>75th percentile among users of this medication) was associated with a 25% reduced risk of developing OAG compared with those with no metformin use** (HR = 0.75; 95% CI, 0.59-0.95; P = .02).
- **Those who were prescribed more than 1110 g of metformin hydrochloride had a 22% reduced risk of OAG compared with those who were prescribed 1110 g or less.**
- Using cumulative **metformin dosage during a 2-year window, every 1-g increase in metformin hydrochloride use was associated with a 0.16% reduction in OAG risk** (adjusted HR = 0.99984; 95%CI, 0.99969-0.99999; P = .04), **which predicts that taking a standard dose of 2 g of metformin hydrochloride per day for 2 years would result in a 20.8% reduction in risk of OAG.** A confident effect of other classes of diabetes medications used to control blood glucose levels on the risk of developing OAG could not be identified (P ≥ .10 for all comparisons).
- **The largest risk reduction was seen for persons taking more than 1110 g of metformin hydrochloride cumulatively during a 2-year period in those who had the highest inherent OAG risk and the worst glycemic control.**

Discussion

- This study suggests that metformin is associated with reduced risk of developing OAG in people with diabetes. Every 1 g of metformin hydrochloride conferred a 0.16% reduction in OAG risk (model 3), so that those taking a standard dose (2 g/d, or 1460 g over 2 years) experienced a 20.8% OAG risk reduction.
- In model 2, those taking more than 1110 g over 2 years showed a 22% OAG risk reduction compared with those taking 1110 g or less over 2 years. Similarly, in model 1, those taking the highest quartile dosage (>1110 g over 2 years) experienced a 25% OAG risk reduction compared with nonusers.
- The findings of this study that greater metformin quantity is associated with a greater reduction in OAG risk is consistent with previous findings that metformin has dose-dependent effects on cellular processes in studies of other diseases.
- Metformin may be affecting OAG risk on multiple levels, some involving improved glycemic control and some involving other mechanisms.

Conclusion

Metformin use is associated with reduction in risk of developing OAG, and risk is reduced even when accounting for glycemic control in the form of glycated hemoglobin level. Other diabetes medications did not confer a similar OAG risk reduction. This study suggests that metformin may be affecting OAG risk on multiple levels, some involving improved glycemic control and some involving mechanisms outside glycemic control such as neurogenesis, inflammatory systems, or longevity pathways targeted by caloric restriction mimetic drugs. If confirmed by prospective clinical trials, these findings could lead to novel treatments for this sight-threatening disease.

Take Home Message

- 29.4% of glaucoma patients suffer from diabetes.
- Diabetes was associated with an increased risk of glaucoma (RR is 1.48), OHT, and increased level of IOP.
- Positive associations between diabetes duration and the risk of glaucoma and a weak association between fasting glucose levels and increased IOP levels is reported.
- Longer duration of diabetes was associated with higher risk of glaucoma.
- This finding further supports the need for patients with longer duration of diabetes to adhere to optimal glaucoma screening examinations and management.

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Notes

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PG - Prostaglandin * POAG - Primary open angle glaucoma $ OHT - Ocular hypertension

^ IOP - Intraocular pressure % 3PG - Prostaglandin (Latanoprost 0.005%, Bimatoprost 0.03%, Travoprost 0.004%)

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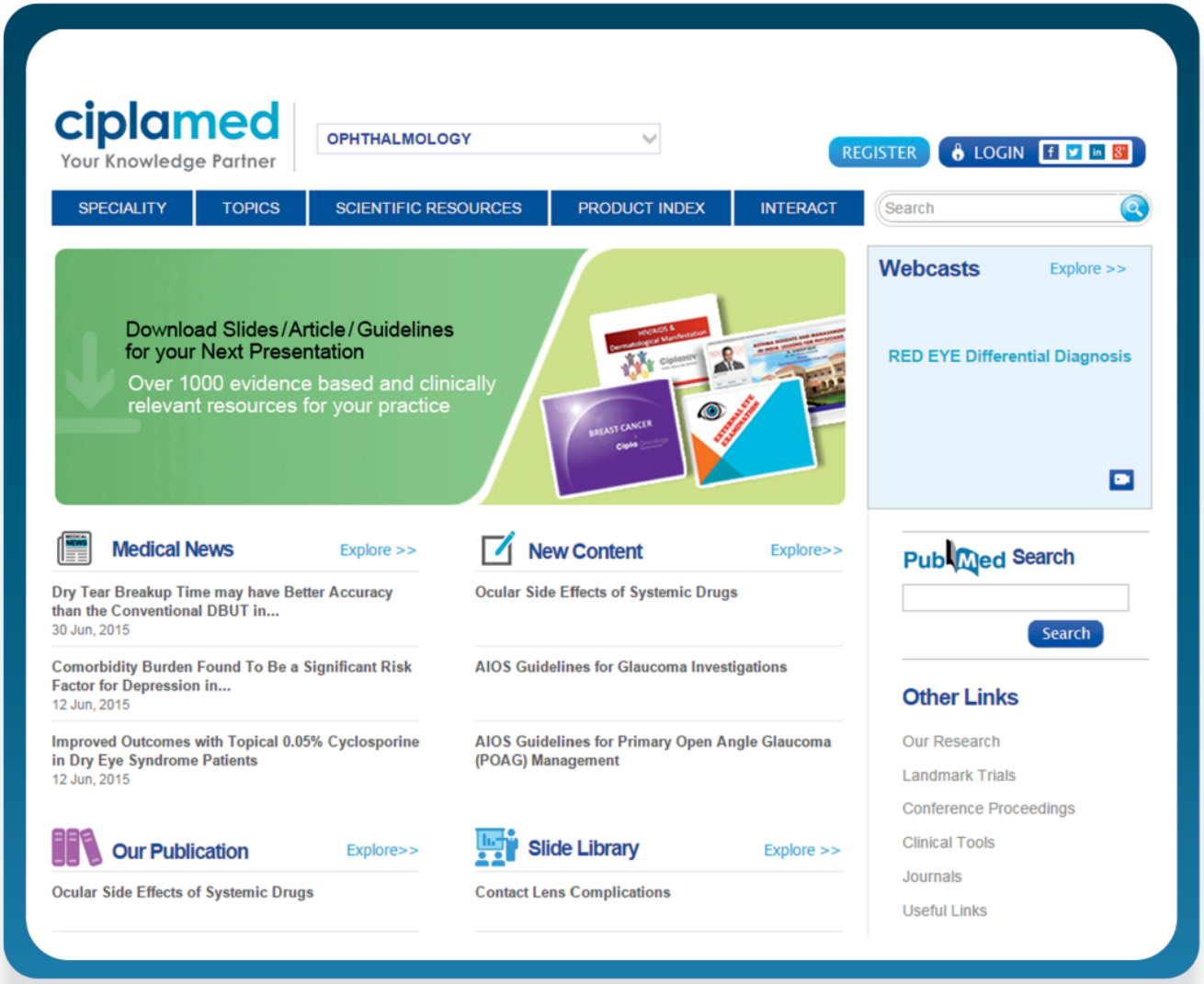

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