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The Effect of Primary Open Angle Glucoma on Progression of Diabetic Retinopathy in Type 2 Diabetic Patients in Alsayem Eye Hospital

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Abstract:

Background: Diabetic retinopathy is a serious complication of diabetes. Five percent of patients of type 2 diabetes (NIDDM) have signs of eye problems when diabetes is diagnosed.Control of blood sugar, blood pressure and cessation of smoking, have an important role in slowing the progression of retinopathy and other eye problems caused by diabetes.

Objectives: To determine whether there is a difference in progression of diabetic retinopathy among patients with and without primary open angle glucoma (POAG).

Design: comparative cross –sectional study.

Participants: 160 patients who were on regular follow up and treatment in both retina and glaucoma clinics in Al-Sayem Eye Hospital were enrolled in the study. Patients were divided into 2 groups, the study group: included 80 patients who were type 2 diabetics with POAG (group A) .The control group were having type 2 diabetes without POAG (group B).The patients were compared for the grade of diabetic retinopathy according to international clinical diabetic retinopathy disease severity scale. For maculopathy patients were also classified according to international clinical diabetic macular edema disease severity scale. Risk factors for both groups were studied as follow: age, duration of DM, control of DM, systemic hypertension and smoking.

Results: In multivariate analyses adjusting for above risk factors and examination for both groups. Diabetic retinopathy was not found in the study group (100%), compared to patients in the control group (patients without POAG) in which no diabetic retinopathy was found in only 8.8%. Mild NPDR was found in 14 patients (43.7%), moderate non prolifrative diabetic retinopathy(NPDR) was observed in 70 patients (32.5%), and severe NPDR in 24 patients (15%). Mild maculopathy was observed in only 4 patients in the study group (5%), all of them were poorly controlled with duration of diabetes of >11 years.In the control group, the majority of patients had no diabetic macular edema(DME) (65%). Mild DME was found in 48 patients (30%). Eight patients only in the control group had moderate DME.

Conclusion: POAG and increased cup disc ratio are associated with a lower risk of DR, particularly vision-threatening retinopathy.

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Key words: Glaucoma ,Diabetic retinopathy , Nerve fiber layer Intraocular pressure.

Introduction and Literature Review:

Diabetes is a condition where the body fails to utilize the ingested glucose properly. This could be due to lack of the hormone insulin or because the insulin that is available is not working effectively.(1)

Diabetes is the fastest growing long term disease that affects millions of people worldwide.In the United States 25.8 million people or 8.3% of the population have diabetes. Of these, 7.0 million have undiagnosed diabetes. In 2010, about 1.9 million new cases of diabetes were diagnosed in population over 20

In Sudan the actual prevalence of diabetes is unknown although one small study showed a prevalence of 3.4%. Diabetes is the commonest cause of hospital admission and morbidity due to a non-communicable disease (7 and 10% respectively). (3) The study revealed that problems of diabetes care in Sudan include the lack of efficient diabetes care centers, lack of specially trained personnel, the high cost of anti-diabetic treatments, poor compliance with therapy or diet, ignorance and wrong beliefs, food and dietary factors and gender- related problems .(3)

The pathogenesis includes:

Diabetic retinopathy is predominantly a microangiopathy in which small blood vessels are particularly vulnerable to damage from hyperglycemia. Hypoglycemic effects on retinal cells are also likely to play a role.(4)

Mechanisms of cellular damage: because of intracellular sorbitol accumulation, oxidative stress due to free radical excess, accumulation of advanced glycation end product and excessive activation of several protein kinase c isoforms. Disruption of ion channel function is an important early feature.(4) Capillaropathy: is characterized by death of pericytes, thickening of capillary basement membrane, loss of vascular smooth muscle cells and proliferation of endothelial cells. Hematological changes such as abnormalities of erythrocyte and leukocyte, increased platelet stickiness and increased plasma viscosity may also contribute. Capillary dysfunction manifests with leak and occlusion. (4) Neovascularization: is caused by capillary non-perfusion which leads to retinal hypoxia and new vessels growth extending pre retinally and intraretinally. This is thought to be caused by an imbalance between the elaboration of angiogenic and anti-angiogenic factors putatively in attempt to re-vascularized hypoxic retina.(4)

In 2002 the American Academy of Ophthalmology(AAO) adopted a new system for grading DR and DME .This system is based on an evidence-based approach, namely the findings of the Early Treatment of Diabetic Retinopathy Study (ETDRS) and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).(5) This new classification is simple to use, easy to remember and based on scientific evidence. There are five stages that are recognized. (6) The first is, no apparent retinopathy, as the name emplies there are no diabetic fundus changes.(6)

The second stage is mild non proliferative retinopathy (MNPDR), this stage is characterized by the presence of few microaneurysms. (6)

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The third stage is moderate NPDR, which is characterized by the presence of microaneurysms, intraretinal hemorrhages or venous beading that do not reach the severity of severe NPDR.(6)

The fourth stage is the key level to identify. Data from the ETDRS has shown that eyes in patients with DM type 2 that reach the grade of severe NPDR have a 50% chance of developing high risk characteristics if laser is not instituted. The diagnosis of severe NPDR is based on the 4:2:1 rule of the ETDRS.(6)

If hemorrhages are present in all 4 quadrants, then by definition severe NPDR is present.(6) If 2 quadrants or more have venous beading (VB), then by definition severe NPDR is present. Or if one or more quadrant has intraretinalmicrovascular abnormalities (IRMA).(6)

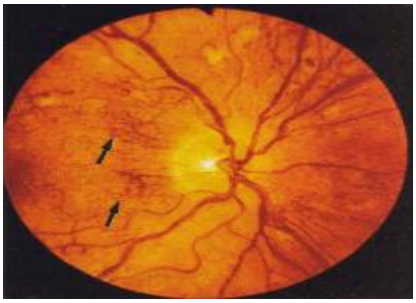
The final stage is "proliferative diabetic retinopathy" (PDR), PDR is characterized by neovascularization of the disc, NV of the retina, NV of the iris, NV of the angle, vitreous hemorrhage or tractional retinal detachment. (6)

With regards to macular edema, it should be noted if macular edema is present or absent. If it is present then it can be further classified as mild, moderate and severe depending on the distance of the exudates and thickening from the center of the fovea (Table 1-2).(6)

Table (1-1): International Clinical Diabetic Retinopathy (DR) Disease Severity Scale

No apparent DR	No abnormalities (R0)
Mild non proliferative DR	Microaneurysms only (R1)
Moderate non proliferative DR	More than "mild" but less than "severe" (R2)
Severe non proliferative DR Any of the following: 20 or more intra retinal hemorrhages in 4 quadrants Definite venous beading in 2 or more quadrants	Prominent IRMA in 1 or more quadrants and no neovascularization (R3)
Proliferative DR	1 or more of the following: Definite neovascularization Pre retinal or vitreous hemorrhage(PDR)

IRMA **Venous beading**



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Intraretinal hemorrhage

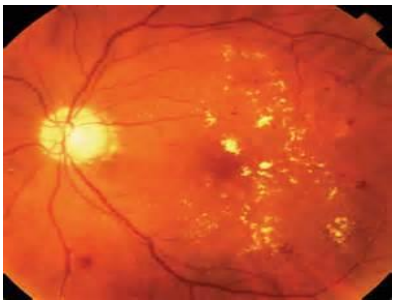
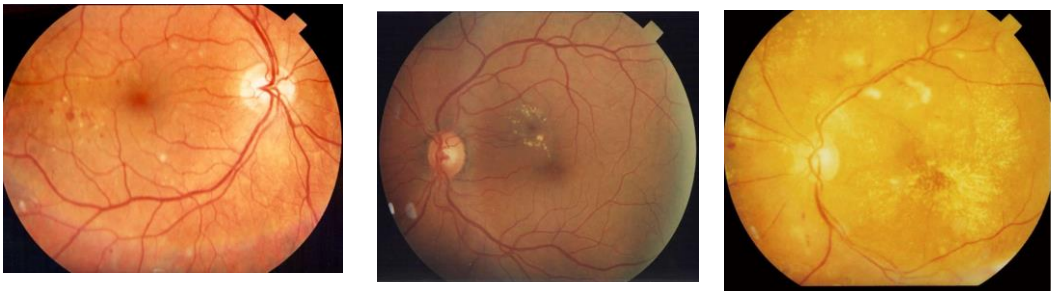


Table (1-2):

International Clinical Diabetic Macular Edema (DME) Disease Severity Scale

DME absent	No retinal thickening or hard exudates present in posterior pole (M0)
DME present	Some retinal thickening or hard exudates present in posterior pole (M1)

Mild DME **Moderate DME** **Severe DME**



The normal retina in dark adaptation uses so much oxygen that it borders on the pathologically anoxic. There is also evidence that, in diabetics, the retina suffers from oxygen lack before the onset of clinical DR. The electroretinogram becomes abnormal years before funduscopic changes can be seen. (7)

Both (photopic) contrast sensitivity and colour vision are impaired even before any microaneurysms are present; and inhaling oxygen from a face mask partially reverses the raised threshold, although the extra oxygen carried to the retina is very small .(7)

Scotopic threshold has been known for half a century to be more seriously affected. Recent investigations suggest that in mild DR, the threshold initially falls normally, but then recovery ceases, as it would if dark adaptation was occurring in the presence of a dim background light.(7)

It is certain that the diabetic retina rather than being hyperoxic, as is commonly supposed, suffers oxygen lack. All recent work on human retinal blood flow shows that at very early stages of diabetic retinopathy, the circulating blood volume decreases slightly. The vasodilatation that occurs slightly later (in the presence of hyperglycaemia) is quite different. (7)

The hypoxia of early diabetic retina is easily explained. The known rheological changes in red blood cells (similar to polycythaesemia vera), the increase in the thickness of

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capillary basal membranes, the alteration in the dissociation curve for glycosylated haemoglobin, and the extra demand for oxygen consequent on higher intracellular glucose levels could all cause functional hypoxia.(7)

How could a decrease in retinal [Po2] cause diabetic retinopathy? This question has recently been answered by studies on the cytokine vascular endothelial growth factor (VEGF). VEGF levels increase in diabetic retina.(7)

A hypothesis which suggests that retinal anoxia is a major underlying cause of DR can be tested. Reduction in retinal metabolism should be associated with a decrease in the development of DR.(7)

This is in fact the case in retinal scars, retinitis pigmentosa, myopia, or advanced glaucoma are all epidemiologically associated with a reduction in DR. Crucially, since rod activity is supposedly responsible for DR, in the absence of rods DR should not occur.(7)

Primary Open Angel Glaucoma:

Glaucoma defined as chronic progressive optic neuropathy caused by a group of ocular conditions which lead to damage of the optic nerve with of visual function. The most common risk factor is a raised intraocular pressure. (7)

The pathogenesis of glaucomatous damage is attributed to a combination of factors affecting axonal health, with each factor being interlinked in it`s effect to all the others .(7)

The two main influences are:

1. Mechanical changes due to raised intraocular pressure(IOP), and

2.Vascular infusion of the optic nerve head.(7)

A raised IOP causes mechanical pressure and inadequate (O_2) on lamina cribrosa altering capillary blood flow and decreasing axoplasmic flow in the initial stages, Later significant displacement and compaction of the laminar plates narrows the openings throw which the axons pass, directly damaging the nerve fibre bundles. (7)A fall in perfusion pressure at the optic disc can also be caused by systamic factors such as hypotension, vasospasm, and acute blood lost.(7)

It is believed that patients with POAG have a susceptibility to damage, in some parts, because of the presence of larger opening in lamina cribrosa that allow for great mechanical displacement of the nerve fibre coming throw.(7)

Finally, dysfunctional axoplasmic transport due to these mechanical or vascular changes causes damage and eventually death of gangelion cells; which triggers apoptosis of adjacent cells.(7)

Correlation between DR and POAG:

Glaucoma and diabetes are associated in more than one way:

Prevalence of primary open angle is higher among diabetics as diabetes is associated with autonomic dysfunction, it can potentially precipitate angle closure too.(9) Diabetes and glaucoma are both age related disease so they can coexist, the optic nerve damage in POAG especially the normal tension glaucoma is vascular in origin, diabetes is a vascular disease too and hence there is a biological possibility of association between the two.(9)

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Many studies have suggested various relationships between IOP and DR, however the exact relationship remains unclear[9]

According to Mooney (1963) raised IOP retards the growth of retinopathy by compressing capillaries and vessels, he did not find diabetic retinopathy in the eyes having glaucoma.[9] Bloods Worth emphasis the degeneration of neurons where by capillaries lose their support and thus period of low IOP could aggravate retinopathy changes. [10] This may also explain in part the variability in the manifestation of the DR resulting from day to day variation in IOP, however it is not definitely known as to how diabetes affect IOP, changes in blood glucose levels may be one of such factors .[10]

Objectives:

A. General objective:

To study the prevalence of DR among type 2 diabetic patients with and without POAG.

B. Specific objectives:

1. To describe the effect of POAG on diabetic retinopathy.
2. To provide baseline data for planning further studies in this topic.

Material and Methods:

2.1: Study Design:

This is a comparative cross –sectional study of 160 patients. All were type 2 diabetics, divided into 2 groups: the study group included patients who were diagnosed as POAG, and the control group which included patients without POAG.

2.2StudyArea:

The study was done in Elsayem Eye Hospital, Wad Madani, Al Gazira state, Sudan, between January 2014 –June 2014.

2.3 Study Population:

All diabetic patients attending Elsayem Eye Hospital were eligible for the study.

2.3.1 Inclusion Criteria:

- Adult patients (40 years or more).
- NIDDM.
- Both genders were selected.
- Eyes of clearer media, mostly affected by POAG in comparison with those affected more by retinopathy.

Exclusion Criteria:

- Pediatric patients.
- IDDM.
- Glaucoma other than POAG.
- Patients with vitreous hemorrhage and PDR.
- Patients with dense cataract obscuring the clarity of fundus view.
- Patients who received laser or had surgical intervention for their DR

2.4 Sample Size:

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160 patients attending both retina and glaucoma clinics in Elsayem Eye Hospital, Wad madani .

2.5 Sampling: All eligible patients who met the inclusion criteria were selected. The diagnosis obtained was evaluated and reviewed by the retina surgeon specialist.

2.5 Procedure 2.5.1 Tools:

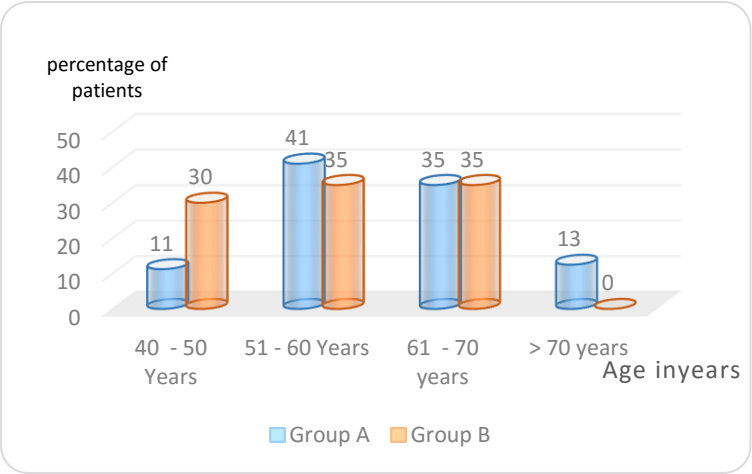
- Snellen chart, retinoscope or auto refractometer.
- Slit lamp biomicroscopic examination with 90 D lens. Applanation tonometry.
- Direct ophthalmoscope.
- Indirect ophthalmoscope.
- Gonioscopic examination (3 mirror contact Goldman lens).

Results:

A total of 160 patients were included in this comparative study. Patients were divided into two groups: the study group (A), which included type 2 diabetic patients with POAG. The control group(B) which included type 2 diabetics without POAG.

Eighty three females (51.8%) and 77 males (48.2%) were studied. Female to male ratio was 1:1.07. The age distribution of patients in both groups of the study ; the majority of the patients were between (51-60 years) making 36%. Retinopathy and progression of diabetic retinopathy was found of statistical significance to the age in control group (P. value 0.020)(figure 3-1).

Duration of diabetes was found to be more between 5-10 years in this sample .The increase in the duration of diabetes was statistically significant to the progression of DR in the study (P.value 0.05) (figure 3-2).



X^2= 15.031 **P. Value =0.020**

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Figure (3-1): Age distribution of patients enrolled in comparative study of diabetic retinopathy in type 2 diabetics with and without POAG in Elsayem Eye Hospital between January- June 2014.

Group A = Type 2 diabetic patients with primary open angle glaucoma (Study Group).

Group B = Type 2 diabetic patients (control Group).

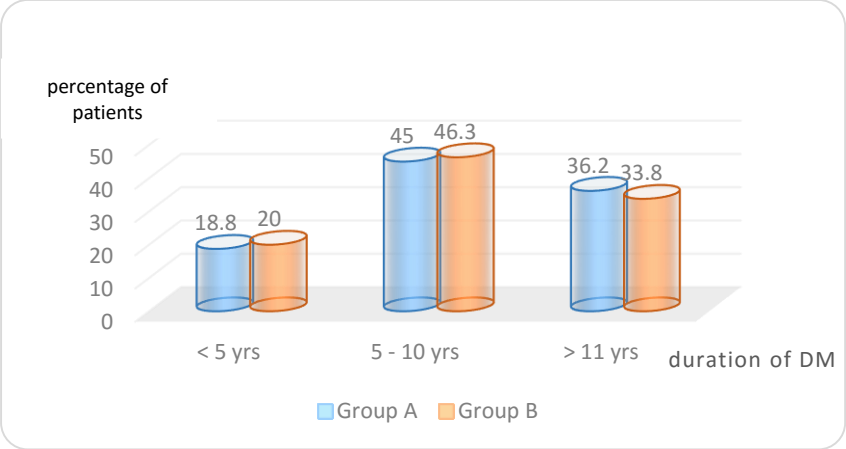

Figure (3-2): Duration of diabetes in patients enrolled in the comparative study of diabetic retinopathy in type 2 diabetes with and without POAG in Elsayem Eye Hospital between January–June 2014.

$X^2 = 12.507$ P. Value: 0 .00

Group A = Type 2 diabetic patients with primary open angle glaucoma (Study Group).

Group B = Type 2 diabetic patients (control Group).

Systemic hypertension was found in 24 patients in the study group (30%) and in 18 patients (22%) of control group. The majority of patients were not smokers in the study. HbA1C and fasting blood sugar were the parameters for the control of diabetes, results were defined as good control or bad control accordingly. Over 50% of patients were poorly controlled .This was significantly related to the presence of diabetic retinopathy (P. value 0.001) (figure 3-3).

Glaucoma group were all well controlled with regular anti glaucoma drugs and intra ocular pressure was normal in majority.

Best corrected vision among patients in study group was normal except for 5 patients (6.2%), where vision was 6/60 and other 6 patients of less than 5/60 (7.5%).

Cup disc ratio ranged from (0.2-0.9), the variety of ratios found in 2 groups. The cup disc ratio was statistically significant to the presence of retinopathy (P. Value= 0.001) and statistically significant to maculopathy (P. Value = 0.007) in the study group.

Diabetic retinopathy was not found in the study group (patients with POAG), compared to patients in the control group where No diabetic retinopathy was found in only 8.8%.

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In the control group (patients without POAG), Mild NPDR was found in 14 patients (43.7%), moderate NPDR was observed in 70 patients (32.5%), and severe NPDR in 24 patients (15%)(figure 3-4).

Mild maculopathy was observed in only 4 patients in the study group (5%), all of them were poorly controlled with duration of diabetes of >11 years.

In the control group (diabetic patients without POAG), the patients who had no DME were 104 (65%). Mild DME was found in 48 patients (30%). Eight patients only in the control group had moderate DME.

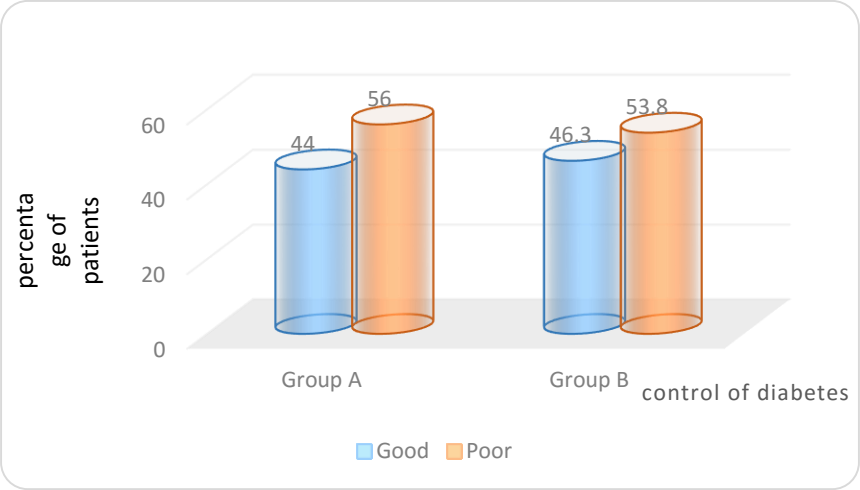

Figure (3-3): Control of diabetes in patients participated in comparative study of DR in type 2 diabetics with and without POAG.
Elsayem Eye Hospital between January- June 2014

X^2=17.57 P. Value = 0.001

Group A = Type 2 diabetic patients with primary open angle glaucoma (Study Group)

Group B = Type 2 diabetic patients (Control Group).

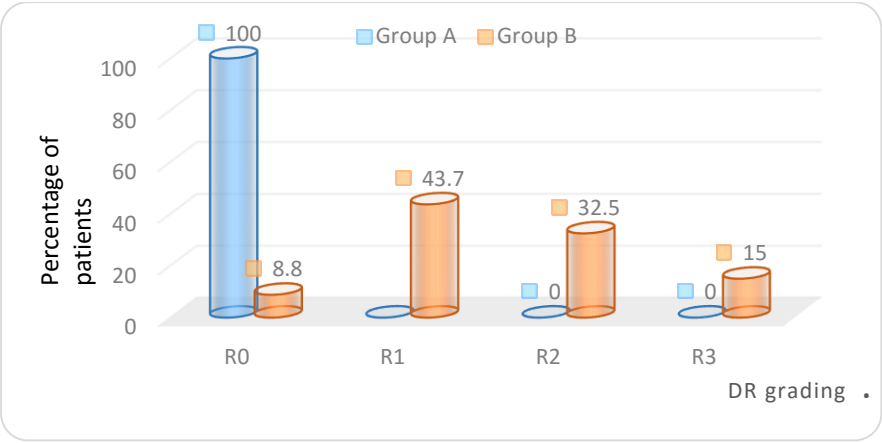

Figure (3-4): Diabetic Retinopathy grading in patients enrolled in the comparative study of DR in type 2 diabetics with and without POAG in Elsayem Eye Hospital between January –June 2014.

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GroupA = Type 2 diabetic patients with primary open angle glaucoma (Study Group).
Group B = Type 2 diabetic patients (Control Group).

Discussion:

Diabetes mellitus is a global problem and DR is a common complication of this systemic disorder. Increasing age, long duration of diabetes, systemic hypertension, poor control and smoking[11] ,were related to development and progression of DR among type 2 diabetics.[12]

The number of females in this study was more than males (51.8%) and (48.2%) respectively. This may be due to high percentage of females worldwide. Though they were less in number, males were found to have a bit high percentage in R1 and R2 forms of DR in the control group only (p.value0.18) (table 4-1). This result was supported by a study done in Pakistan, which concluded that DR was associated with male gender more .[12]

Ages of the patients in this study ranged between (40 - >70) years, majorities were between (51-60 years) making (36%) in the 2 groups of the study. Progression of DR was found of statistical significance to the increase age in control group only (P. value 0.020). This is also supported by the study mentioned above. [12]

In our study the duration of diabetes was significantly related to DR progression. (p.value =0.05).This is consistent with study of Incidence and progression of DR in Japanese adults with type 2 diabetes) which

states that the strength of association between duration of diabetes and incidence of DR increases rapidly during a period of 5-10 years duration of diabetes.[13]

Because most of the patients were not hypertensive nor smokers, in this small sized study sample ,both risk factors were not significantly related to the progression of diabetic retinopathy nor maculopathy. In this study, the good control of diabetes was associated with low risk of progression of DR, this finding is also compatible to the diabetes control and complication trial. [14]

In this study it was found that DR in the study group was (0%), this was associated with significant p. value (0.00) of increased cup: disc ratio.These results are supported by study done by Mooney (1963) who suggested that raised IOP retards the progression of retinopathy by compressing capillary and venules, he did not find DR in eyes having glaucoma. He did not find diabetic retinopathy in the eyes having glaucoma. Jain et al (1967) in their analysis of 100 patients concluded that higher IOP has some influence in delaying or preventing the retinopathy. The finding of lower intraocular pressure (15.98 mm) is in agreement with the findings of Cristiansson (1961), Money (1963), Yenoff (1969), Igersheimer (1944) and Tiwari et al (1984).[8]

The presence of diabetic maculopathy was statistically significant to the severity of diabetes retinopathy in the both groups (P. Value: 0.011). This was also found in another cross sectional study carried out to determine the relationship between the severity of retinopathy and maculopathy in Japanese patients.[16]

In this study, maculopathy was significantly related to the advance age and long standing diabetes (P. Value: 0.039 and 0.018 respectively). Many studies had discussed the same result, and in all, increased cup disc ratio in patients with POAG was

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associated with no DR. These results may be explained by reduced retinal metabolic activity due to decreased viable ganglion cells and due to decreased perfusion pressure due to high IOP. [7, 10,15, 17]

This study has its limitations because of small population sample size and lack the property of prospective study in long duration follow up to bring more data about the issue of this study.

Conclusions:

- There was statistical correlation between POAG and decreased incidence of DR.
- Majority of diabetic patients who were diagnosed as POAG had no diabetic retinopathy.
- There is a correlation between the DR and the increased IOP.
- Increased cup: disc ratio is associated with decrease the progression of DR.
- Males were more prone to severe type of DR.
- POAG is associated with very mild type diabetic maculopathy.

Recommendations:

- To avoid severe reduction of IOP in diabetic patients with POAG which will enhance the activity and progression of DR, especially in those undergoing filtrating surgery with or without antimetabolites.
- Studies should be conducted to adopt therapeutic high IOP in future as preventative measure against DR with caution of optic nerve damage.
- This study could be considered as a base for more studies to come in near future which concern the effect of high IOP on DR progression. More studies should be done to obtain an optimal intraocular pressure which will cure the chronic simple glaucoma as well as guard against development of sight threatening DR.

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