FACTORS ASSOCIATED WITH LATE PRESENTATION OF GLAUCOMA: A STUDY IN A BLACK SOUTH AFRICAN POPULATION.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Ophthalmology.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Kraukamp

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080815**
PROJECT	Factors Associated with Late Presentation of Glaucoma: A Study in a Black South African Population
INVESTIGATORS	Dr P Kraukamp
DEPARTMENT	Division of Opthalmology
DATE CONSIDERED	08.08.29
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.10.09 **CHAIRPERSON** .....
pp (Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr GD McLaren

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

DECLARATION

I, Philip Kraukamp, hereby declare that this research is my own unaided work. It is being submitted for the degree of Master of Medicine in the branch of Ophthalmology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

…….

…….Day of ……2013

DEDICATION

To my wife, Angela, for her love and support throughout my career.

To my mom and dad, Marietjie and Johan, for supporting me throughout my life.

To my son Xavier, and daughter Liana, for being the light in their parents' lives.

PRESENTATIONS

The Ophthalmological Society of South Africa congress

Port Elizabeth

South Africa 2011

Presenter: Philip Kraukamp

The South African Glaucoma Society congress

Stellenbosch

South Africa 2011

Presenter: Philip Kraukamp

ABSTRACT

OBJECTIVES: To determine the association between various ocular and non-ocular factors and late presentation of glaucoma.

DESIGN & METHOD: This study represents a comparative study between patients who at their first clinic presentation were assessed as having advanced chronic glaucoma and glaucoma patients who presented early in the course of their disease. The study adhered to the tenets of the declaration of Helsinki. 133 Glaucoma patients who attended the St John Eye Hospital in Soweto from December 2008 to October 2009 consented to participate in the study. They completed a questionnaire, underwent a complete ophthalmological examination and their hospital records were reviewed. 68 of the patients were assessed to be 'late presenters' with typical glaucomatous field loss and a mean deviation (MD) of greater than -14 dB in the better seeing eye, as well as typical glaucomatous cupping of 0.8 or more. 65 of the patients were assessed to be 'early presenters' with typical glaucomatous field loss and a MD between 0 dB and -11 dB in the worse eye as well as a cup to disc ratio of 0.5 or more or an interocular difference of 0.2 or greater between the discs.

RESULTS: Presenting IOP in 'late presenters' (OD 33.56mmHg +/- 9.61: OS 33.46mmHg +/- 10.37) was significantly higher (P<0001) than those of 'early presenters' (OD 18.37mmHg +/- 5.95 : OS 19.24mmHg +/- 7.21). Other factors associated with late presentation include poor English language ability (52.9% vs. 16.9%)(P<0001), previous/current rural inhabitants (44.1% vs. 27.7%)(P=0.048), informal housing (17.6% vs. 6.1%)(P=0.041), smoking (16.1% vs. 4.6%)(P=0.029) and smaller optic discs [(OD 1.98mm+/-0.27 : OS 1.97mm+/-0.27) vs.(OD 2.11mm+/-0.35 : OS 2.10mm+/-0.37)](P<0.05). A history of previous eye trauma was more common in 'early presenters' (18.4% vs 5.8%)(P=0.025) as was a medical history of diabetes mellitus (33.8% vs 16.1%)(P=0.018). The following factors were found to be statistically

insignificant: age, sex, hypertension, primary vascular dysregulation, patient education, a positive family history of glaucoma and the presence of pseudocapsular exfoliation.

CONCLUSION: In this patient cohort we found that the IOP at presentation was significantly higher in patients presenting with advanced glaucoma than in those presenting earlier in the disease process. Our data has also identified other factors which may be associated with late presentation.

ACKNOWLEGDEMENTS

1. To my supervisor, Professor Grant McLaren, for his encouragement and continuous support.
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3. All the staff at St John Eye Hospital for their neverending help and support.

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1.1 GLAUCOMA – THE THIEF OF SIGHT

Glaucoma refers to a group of diseases that have in common a characteristic optic neuropathy with associated visual field loss for which elevated intraocular pressure is one of the primary risk factors.

The diagnosis of glaucoma is often delayed due to the lack of early symptoms. It is often irreversible, slowly progressive, remains asymptomatic until late and thus represents a significant public health problem.

There will be 60.5 million people with Open angle glaucoma (OAG) and angle closure glaucoma (ACG) in 2010, increasing to 79.6 million by 2020, and of these, 74% will have OAG. Bilateral blindness will be present in 4.5 million people with OAG and 3.9 million people with ACG in 2010, rising to 5.9 and 5.3 million people in 2020, respectively.[1] There is still no definition of blindness which is universally accepted. The 1965 International Classification of Diseases of the World Health Organization (WHO) includes blindness believed to be congenital, but excludes impaired vision due to refractive error. Specifically defined, it refers to a central visual acuity of 3/60 or worse with the best correcting lens, or a field defect in which the field has contracted to such an extent that the widest diameter of visual fields subtends an angular distance no greater than 10 degrees around fixation or 20 degrees in diameter.[2]

1.2 GLAUCOMA IN AFRICA

Research has shown that most African people living with glaucoma are not aware of it and at least half of eyes are already blind at the time of presentation to an ophthalmologist.[3,4,5]A study conducted by Salmon et al[6] in the mid 1990's reported that open angle glaucoma had a prevalence of 1,5% in the western Cape. However, the population in this study included a distinctive ethnic mix of mainly South East Asian ancestry mixed with east African and European.

Rotchford and Johnson[7] studied the prevalence of glaucoma in an indigenous population in rural Zululand. They found that 4,5% of subjects studied had glaucoma. It was also found that 41% of people with POAG were blind, compared to 75% of those with secondary open angle glaucoma. Overall, glaucoma ranked as the second most common cause of blindness, the most common being age-related cataract. With considerable emphasis now being placed on the provision of cataract surgery among the indigenous people of South Africa, and with the population ageing at a rapid rate, the prevalence and proportion of blindness due to glaucoma are likely to increase even further.[7]

1.3 GLAUCOMA AND LATE PRESENTATION

Earlier studies have shown late presentation to be the major cause of blindness in 29% to 41% of patients registered as blind from glaucoma.[8,9,10]

Oliver et al found that patients at greatest risk of blindness had visual field loss at the time of diagnosis of glaucoma[9]. Kwon et al[10] concurred. They stated that eyes which start out with more glaucomatous damage will become blind more quickly.

Relatively few studies have looked at the factors associated with late presentation of glaucoma. However, studies have looked at the risk factors for glaucoma progression, which include structural, vascular and genetic factors.[11] In their pilot study, conducted in England, Fraser et al identified some basic characteristics of people who present with late glaucoma. These included being female, age over 40 and intraocular pressures of greater than 31 mmHg.[12] Socioeconomic status was also shown to be strongly associated with the risk of late attendance, with those of highest socioeconomic status at lowest risk.[13] Those with lower socioeconomic status and lower education levels were more likely to present with more advanced field loss.[14]

Those with a family history of glaucoma were found to be about one third as likely to present with advanced field loss as those with no family history. People referred from any source other than an optometrist with the correct diagnosis (of glaucoma) were four and a half times more likely to be late attenders.

People of African-Caribbean origin were found to be four and a half times more likely to present with late glaucoma compared to Caucasians.[12,13,14] To date, only one study has looked at the risks of late presentation in an African population. Ntim-Amponsah et al[15] conducted their research in Ghana where referrals to hospital eye services are usually from mass screening exercises by ophthalmic nurses and a few practicing optometrists. While the study from England[13] showed an average age difference of approximately 9 years between early and late presenters, the Ghanaian study pointed out that their average age difference between cases and controls

was only 3 years. This difference in average age at presentation for the early stage versus the late stage of glaucoma, may provide an estimate of the average rate of progression of field loss before diagnosis and treatment.[15,16] This viewpoint supports the general conception that primary open angle glaucoma in people of African origin runs a more aggressive course than in Caucasians[15]. In addition an intraocular pressure of greater than 31mmHg was another important factor for glaucomatous optic neuropathy in the Ghanaian African.

Since impaired optic nerve perfusion may be responsible for glaucomatous optic nerve damage, it would be important to know the role of systemic vasculopathies (including diabetes mellitus and blood pressure) as risk factors in advanced glaucomatous damage.[15] In a recent report of the "Blue Mountains Eye study", systemic hypertension was found to be modestly, but significantly, associated with an increased risk of POAG.[17] However, in the Barbados Eye Studies it was found that higher blood pressure parameters were consistently related to lower risk of developing POAG. Leske et al reported a low systolic blood pressure to be a risk factor for progression of glaucoma amongst patients with a lower baseline IOP (< 21 mmHG).[18]

It seems logical that factors associated with glaucoma progression might also predispose patients to present late. Various factors have been mentioned as risk factors for glaucoma progression. Exfoliation has been shown to be a major factor predicting glaucoma progression. The presence of it more than doubles the risk of progression. Vascular factors may be the possible mechanisms contributing to this increased progression, given the reports of altered haemodynamics in patients with exfoliative glaucoma.[19] A study by Rotchford et al confirmed the high prevalence of exfoliation across several different Bantu tribal groups in South Africa. The rates of 16,1% and 12,5% for those older than 60 in Hlabisa and Temba, respectively, are not far below the highest published figures from Scandinavia, where the syndrome was first reported.[20] Interestingly, in their study population, nearly one fourth of cases with open angle glaucoma were associated with exfoliation.

In an investigation of progression factors, which was restricted to patients in the untreated arm of the Collaborative Normal Tension Glaucoma Study (CNTGS), progression was related to female gender, migraine and Raynauds disease. However, none of those factors were significant in the Early Manifest Glaucoma Trial, a divergence that could be due to the difference in study populations.[19] The presence of disc haemorrhages during follow up has also been confirmed as conferring a worse prognosis for the patient.[19]

IOP fluctuation, blood pressure dips, and disturbed ocular blood flow (OBF) autoregulation have all clearly been linked to progression of glaucomatous damage. The main cause for the disturbed autoregulation of OBF is the primary vascular dysregulation syndrome.[21]Vascular dysregulation is known to contribute to cellular oxidative stress at the mitochondrial level and it may increase susceptibility to intraocular pressure in patients with glaucoma.[22] Vascular dysregulation can be primary or secondary. Secondary vascular dysregulation (SVD) is caused by a number of conditions including autoimmune and infectious diseases. Patients with primary vascular dysregulation (PVD) have an inborn tendency to respond differently with their vascular system to various stimuli. Among the most prominent pathological reactions are the vasoconstrictions, leading to the previously used term vasospastic syndrome.[22] SVD reduces baseline OBF without having a major impact on autoregulation. In contrast, PVD, although only mildly influencing baseline OBF, has a major impact on autoregulation. Therefore fluctuating perfusion pressure leads to a fluctuation of OBF in patients with PVD but less so in patients with SVD. This explains why PVD is a major risk factor for glaucomatous optic neuropathy whereas SVD remains a minor risk factor.[21] There is no gold standard for the diagnosis of PVD although cold provocation in nailfold capillaromicroscopy is the most often used diagnostic test. There are, however, many clinical signs that points towards PVD: these subjects often have cold extremities, like cold hands or feet, they tend to have normal or low body mass index, the feeling of thirst is often reduced (they drink because they know they have to drink and not so much because they are thirsty), they tend to have low blood pressure especially when they are young, and they suffer more often from migraines than non-PVD subjects.[21] They also, on average have a longer sleep-onset time and

their sleep is more often interrupted. The sleep-onset time depends on the body temperature; warm feet are a prerequisite for falling asleep. Patients with PVD, on average, have colder feet and therefore need longer to warm them up, explaining the prolonged sleep-onset time.

As mentioned, increased IOP is one of the main risk factors for glaucomatous optic neuropathy. Flammer and Mozaffarieh states that all factors known to be risk factors for atherosclerosis are also risk factors for an increase in IOP. These include age, smoking, dislipidaemia, diabetes mellitus, systemic hypertension, male sex and obesity. Why does this happen? On one hand ischaemia (from atherosclerosis) can damage the outflow system, in particular the trabecular meshwork, and thereby increase IOP. On the other hand, changes brought about at the molecular level in the trabecular meshwork of glaucoma patients have similarities to changes in the vessel walls of atherosclerotic patients.[21]

The influences of healthy lifestyle choices on glaucoma risk or progression are also important. Aerobic exercise may lead to decreases in IOP. It has also been found that oxidative stress at the mitochondrial level (thought to be important in the pathogenesis of glaucoma) can be reduced by an intake of the polyphenolic flavenoids found in certain food and drinks, eg. resveratrol which is found in red wine and grapes.[23]

Large optic disc size in combination with the reportedly higher glaucoma susceptibility in Afro-American population compared to whites has led to the hypothesis that eyes with large optic discs may be more prone to glaucomatous damage. However, others have found that optic disc size is not associated with the progression of glaucomatous visual field defects.[24]

It is well known that African derived populations have thinner central corneal thicknesses compared to other populations.[25] Although thinner central corneal thickness (CCT) is an important independent risk factor for the development of primary open angle glaucoma, its role in disease progression is less well understood.[11] Leske et al reported that thinner CTT was independently

related to POAG progression. This was only seen in patients with higher baseline intraocular pressures (>25mmHg).[18] It goes without saying that these patients would have a high risk of presenting late.

CHAPTER 2 – AIM & OBJECTIVES

2.1 AIM

To determine the factors associated with late presentation of glaucoma in black patients at St. John Eye Hospital, Soweto.

2.2 OBJECTIVES

Primary Objective: To determine if a higher intraocular pressure at presentation is associated with more advanced glaucoma (late presentation).

Secondary Objectives: To examine the association between late presentation and the following factors:

- Age
- Gender
- English language ability
- Level of education
- Knowledge about glaucoma as a sight threatening disease
- Family history of glaucoma
- Annual income
- Formal/Informal housing
- Previous ocular trauma
- Systemic vasculopathies (including diabetes and hypertension)
- Possible presence of Primary vascular dysregulation
- Smoking
- Alcohol consumption

- Corneal thickness
- Optic disc size (vertical disc height)
- Presence of pseudocapsular exfoliation

CHAPTER 3 – METHOD

3.1 STUDY DESIGN

Case control study with some cross sectional data collection.

3.2 STUDY PROCEDURE

Consecutive patients presenting to the St. John Eye hospital who qualified for inclusion were approached. All initial hospital files were studied by Dr. Philip Kraukamp to confirm that standard examination protocols were adhered to.

During their initial visit, all participants had visual acuity, blood pressure and random blood glucose tests done by nursing staff in the department. This was followed by a general ophthalmic examination by registrars and/or medical officers in the hospital's outpatient department. A Perkins applanation tonometer was used for all initial intraocular pressure measurements and ophthalmoscopy was performed using a handheld direct ophthalmoscope. Gonioscopy was performed at a slitlamp biomicroscope. Following the examination, a visual field test was done on all patients using an Oculus centerfield 30-2 test. The visual fields were obtained by an ocular technician working in the department. Scanning laser polarimetry was also performed by the technician using a GDx VCC Scanning laser polarimeter. Due to technical difficulties and financial constraints this machine was not readily available for use.

132 patients were recruited. A sample size of 66 cases and 66 controls was calculated to provide the power of 80% to detect a significant difference ($\alpha = 0.05$) in the proportions of patients who presented with an intraocular pressure higher than 25 mmHg.

Cases were defined as typical glaucomatous field loss with a mean deviation (MD) of greater than -14 dB in the better seeing eye. Optic discs had to show typical glaucomatous cupping of more than 0,8. Fields were excluded when visual loss was so advanced that field testing was not possible. They were also excluded if more than 20% fixation losses or more than 33% false positive errors existed. If GDX was available, it had to confirm nerve fiber layer thinning.
Controls were defined as having typical glaucomatous field loss and a MD between 0 dB and -11dB in the worst eye. Fields were excluded if there were greater than 20% fixation losses or false positive errors were more than 33%.A cup to disc ratio of more than 0,5 , or a difference of more than 0,2 had to be noted. Where possible, damage was confirmed by looking at the Gdx.

Dr. Philip Kraukamp extracted the necessary relevant data from the patients initial hospital file. A data capturing sheet was completed by Dr. Kraukamp and a questionnaire filled out by the patient with the aid of Dr. Kraukamp and if necessary a qualified nurse (for translation purposes only). Dr. Kraukamp performed indirect ophthalmoscopy on all patients using a 60 diopter Volk lens to measure vertical disk height. This was followed by central corneal thickness measurements using a Heidelberg engineering IOP_{ac} pachymeter.

Due to the extreme workloads and regular understaffing, the visual acuity measurements done by nursing staff were often found to be irregular and unreliable. It was thus not included in the study parameters.

3.3 STUDY CRITERIA

Patients were included if they had been diagnosed with any chronic open angle glaucoma, were of African descent and 20 years of age or older.

Patients were excluded from the study if the initial hospital file was not available or if they were unable to comply with BOTH visual field testing and scanning laser polarimetry.

3.4 DATA COLLECTION AND STATISTICAL ANALYSIS

Patients' hospital files were used to obtain the necessary information as noted on the initial presentation. A data capturing sheet was completed by Dr. Philip Kraukamp and a questionnaire filled out by the patient with the aid of Dr. Kraukamp and if necessary a qualified nurse (for translation purposes). All patients were examined by Dr. Kraukamp to obtain central corneal thickness and optic disc size.

Data was transcribed from the data collection sheets into an Excel spreadsheet and then imported into the Stata 9 statistical program for analysis.

Descriptive statistics were used to compare the cases and controls and univariate analysis were performed using t tests (continuous data), chi square (categorical data) or non-parametric tests as indicated, to assess significant differences between the two groups.

3.5 ETHICAL CONSIDERATIONS

The study was passed unconditionally by the Ethics Committee of the University of the Witwatersrand on the 29th of August 2008. Ethics no: 080815.

CHAPTER 4 – RESULTS

Data analysis of 66 cases and 66 controls revealed the following:

4.1 PRESENTING INTRAOCULAR PRESSURE

Late presenters had average intraocular pressures of 33.56 mmHG (SD 9.62) and 33.46 mmHG (SD 10.37) of the right and left eyes respectively. Early presenters had pressure of 18.37 mmHG (SD 5.95) and 19.24 mmHG (SD 7.21).

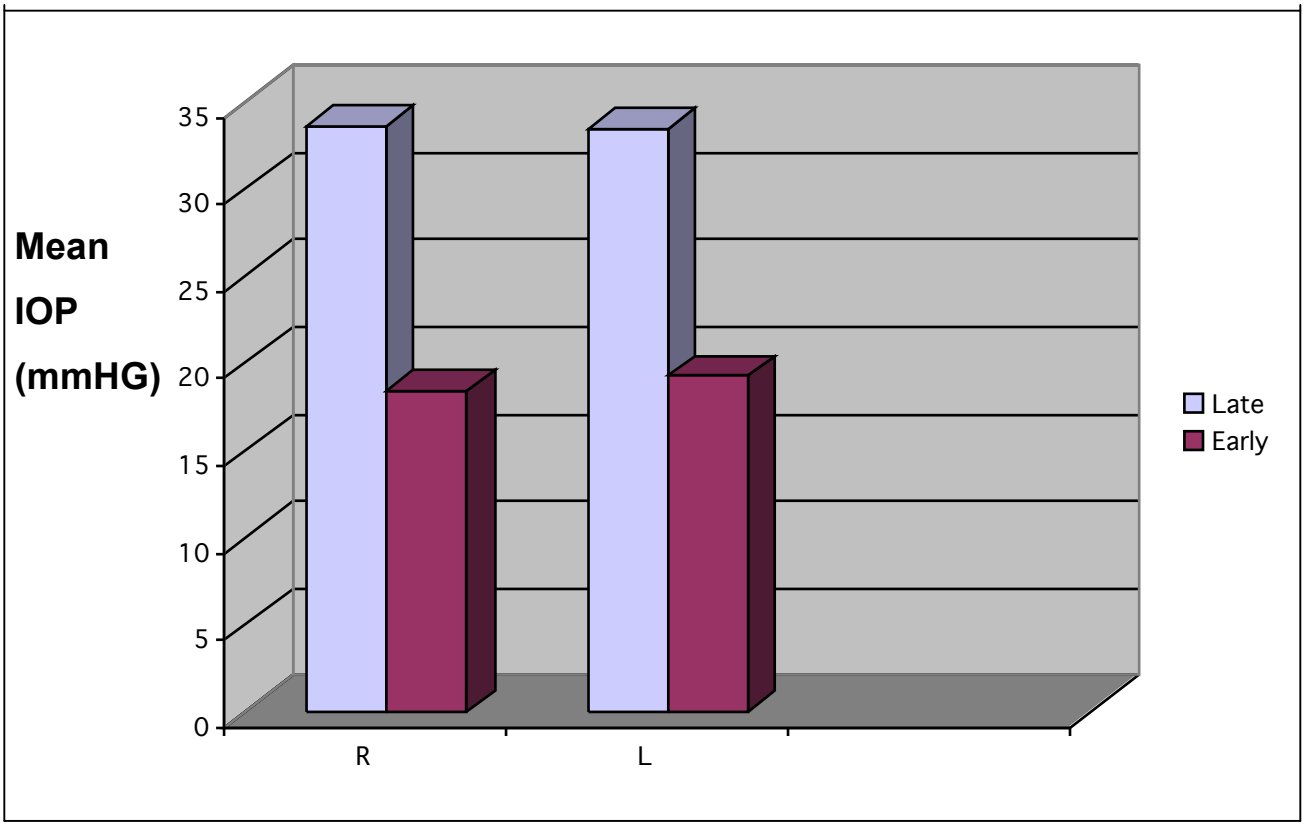


Figure 4.1 Presenting intraocular pressures

There was a very statistically significant difference in pressures between the two study groups. (t-Test p-value < 0.001)

4.2 AGE

Mean age of late presenters was 57.87 (SD 13.50) and early presenters 60.44 (SD 10.44).

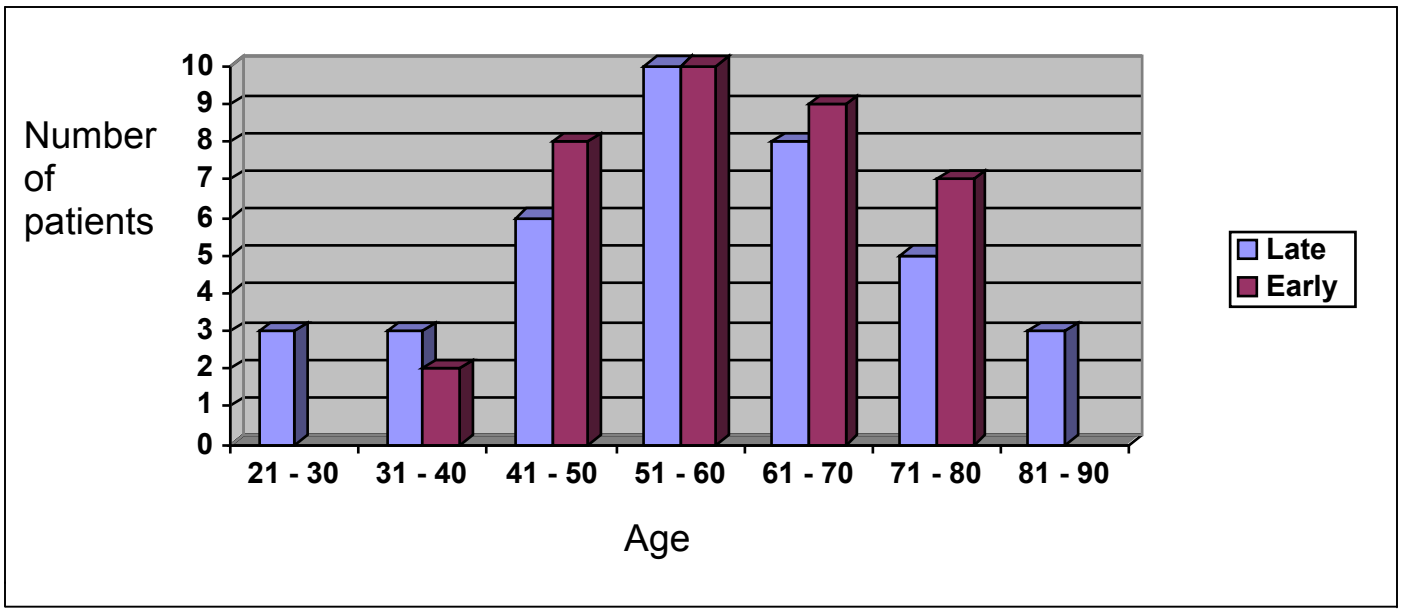


Figure 4.2 Age distribution amongst early and late presenters

This was not statistically significant. (t-Test p-value 0.23)

4.3 GENDER

Overall there were 68 females and 65 males (n=133). 33 females and 35 males presented late. Of the early presenters 35 were female compared to 30 males.

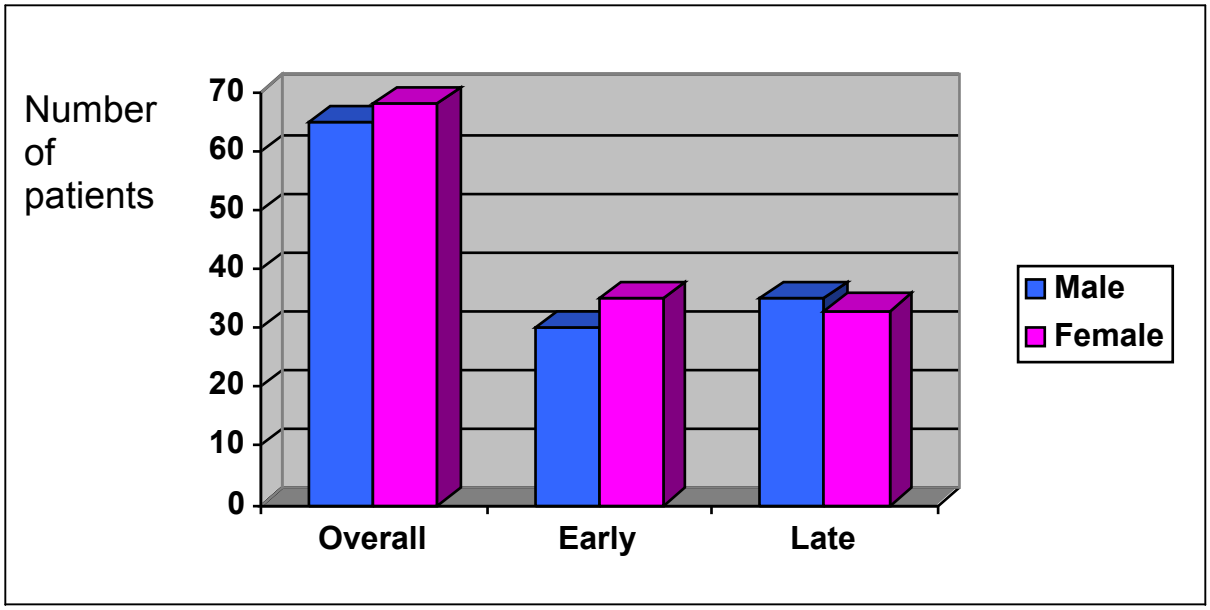


Figure 4.3 Gender distribution

Gender was not statistically significant. (p-value 0.54)

4.4 ENGLISH LANGUAGE ABILITY

When analyzing English language skills I used a modified form of the international English language testing system (IELTS) criteria. Patients were classified into five different groups.

5. Good (Has operational command of the language. May have occasional inaccuracies, inappropriacies and misunderstandings in some situations. Generally handles complex language well.)
4. Modest (Partial command of the language. Can cope with overall meaning in most situations. Likely to make many mistakes.)
3. Poor (Conveys and understands only general meaning in very familiar situations. Frequent breakdowns in communication occurs.)
2. Very poor (No real communication is possible. Has great difficulty understanding spoken and written English)
1. No English language ability

53% (n = 36) of late presenters and 17% (n = 11) of early presenters had poor, very poor or no English language ability. This was statistically significant ($p < 0.001$)

4.5 LEVEL OF EDUCATION

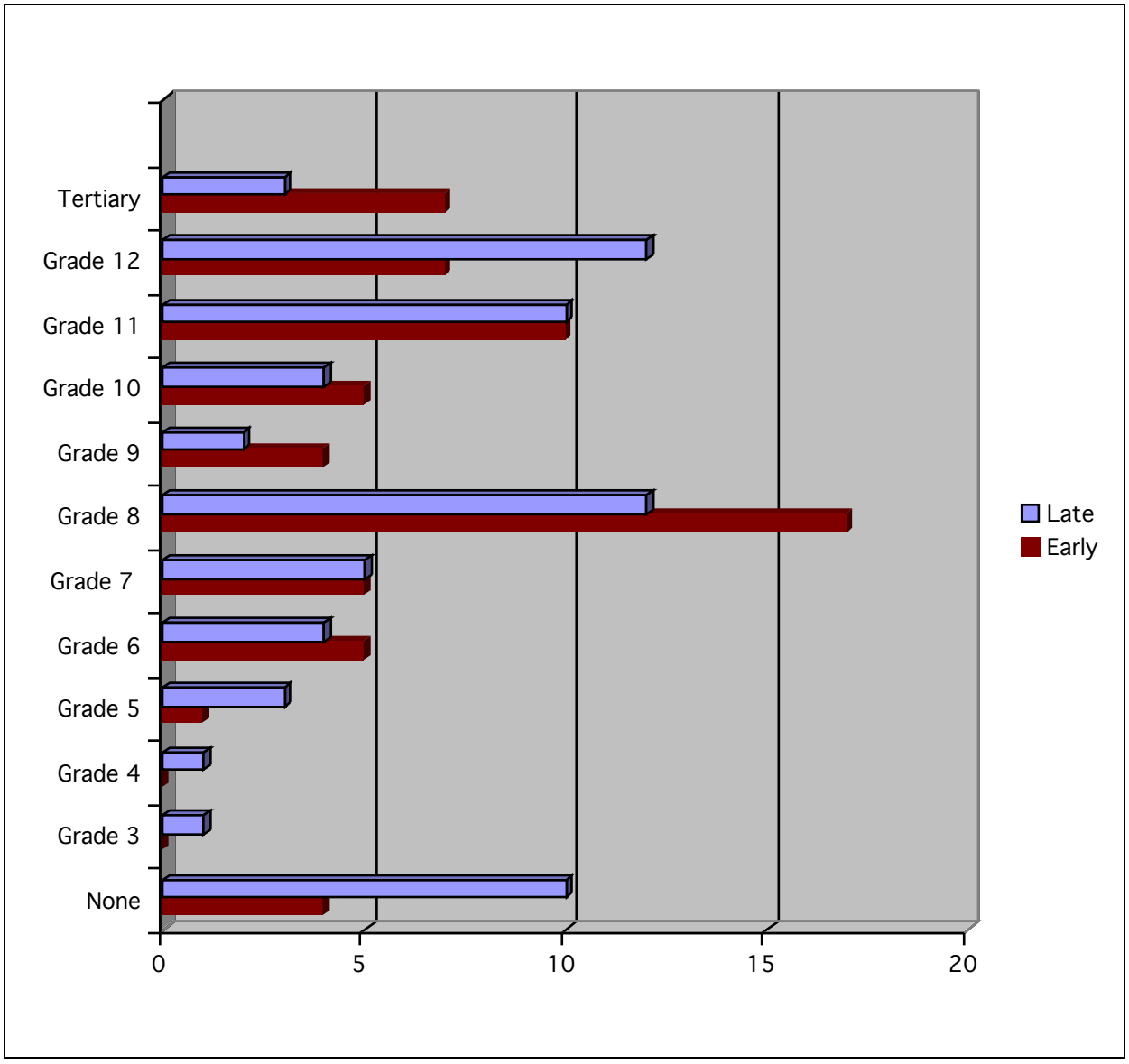


Figure 4.4 Highest level of education reached by participants

There was no statistical significant difference between the groups (p=0.82) with late presenters having 57% (n = 39) and early presenters 55% (n = 36) of participants not completing grade 9.

4.6 KNOWLEDGE OF GLAUCOMA AS A SIGHT THREATENING DISEASE

Table 4.1 Glaucoma knowledge

	YES	**NO**
Early Presenters	15% (n = 10)	85% (n = 55)
Late Presenters	19% (n = 13)	81% (n = 55)

There was no statistical significant difference between the groups. (p=0.41)

4.7 FAMILY HISTORY OF GLAUCOMA

There was no statistical significant difference between the groups. (p=0.33) 86% (n = 58) of late presenters and 91% (n = 59) of early presenters had no relatives that suffered from glaucoma

4.8 ANNUAL INCOME

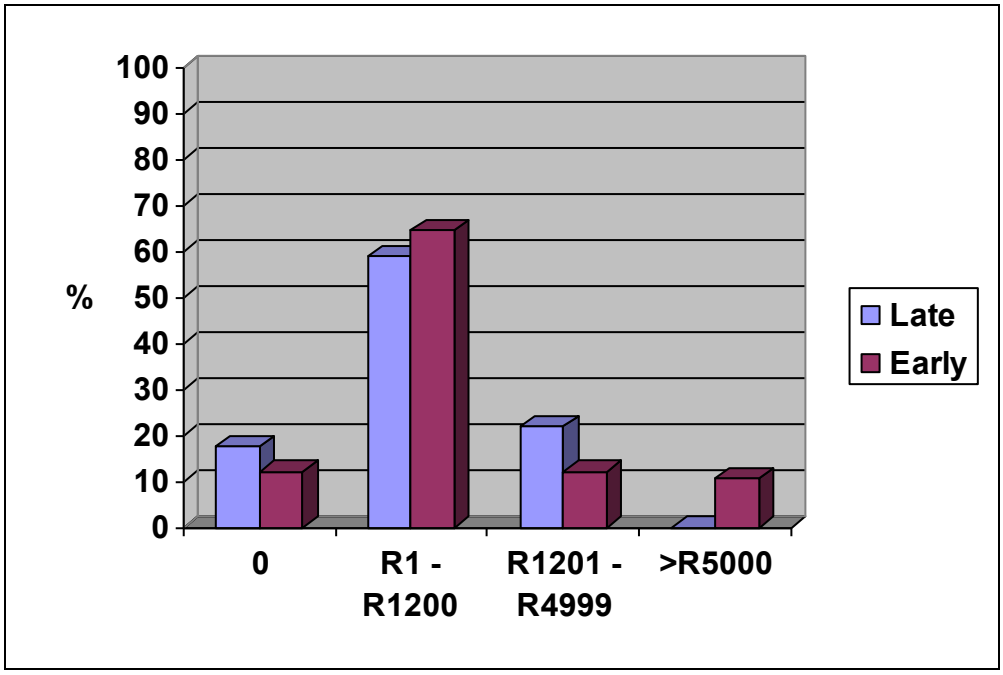


Figure 4.5 Average monthly income per patient

Table 4.2 Income comparison

	Late Presenters	Early Presenters	p-value
R0	18% (n = 12)	12% (n = 8)	0.39
R1 – R1200	59% (n = 40)	65% (n = 42)	0.49
R1201 – R4999	22% (n = 15)	12 % (n = 8)	0.14
> R5000	1% (n = 1)	11% (n = 7)	**0.02**

There was a statistically significant difference between groups when looking at people earning more than R5000 per month. (p = 0.02) The overwhelming majority of people were earning less than R1200 per month and a two-sample test of proportions showed no statistical significant difference. (see Table 4.2)

4.9 HOUSING

Table 4.3 Formal vs. Informal housing

	Late Presenters	Early Presenters	p-value
Formal Housing	82% (n = 56)	94% (n = 61)	
Informal housing	18% (n = 12)	6% (n = 4)	**0.04**

More late presenters (18%) lived in informal settlements compared to early presenters (6%).

This was a statistically significant difference. (p = 0.04)

4.10 PREVIOUS OCULAR TRAUMA

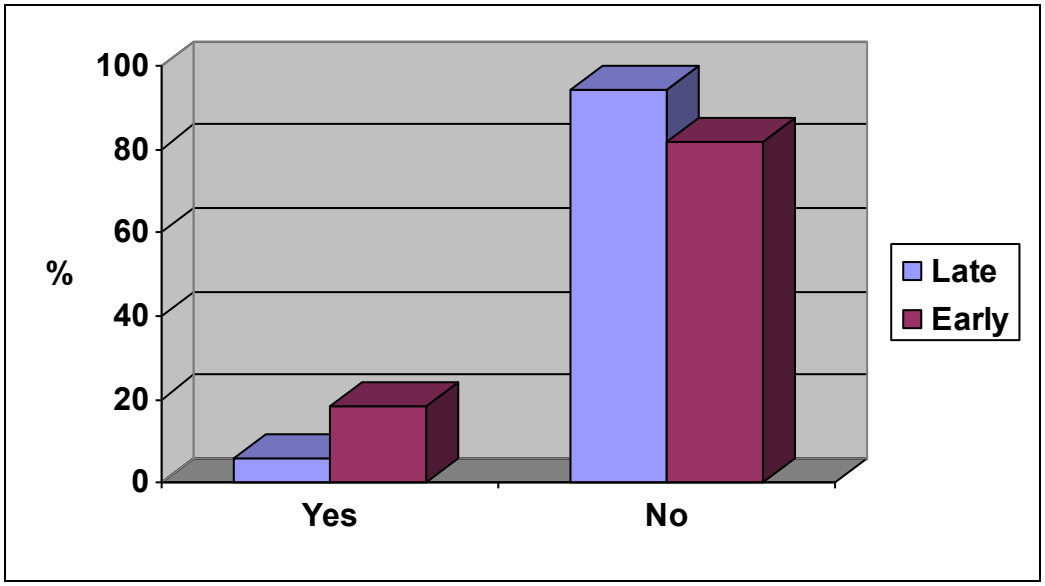


Figure 4.6 Incidence of previous ocular trauma

More early presenters - 18% (n = 12) had previous ocular trauma compared to that of late presenters – 6% (n = 4). This was statistically significant. (p = 0.03)

4.11 DIABETES MELLITUS

16% (n = 11) of late presenters and 34% (n = 22) of early presenters had diabetes mellitus.

This was statistically significant (p = 0.02)

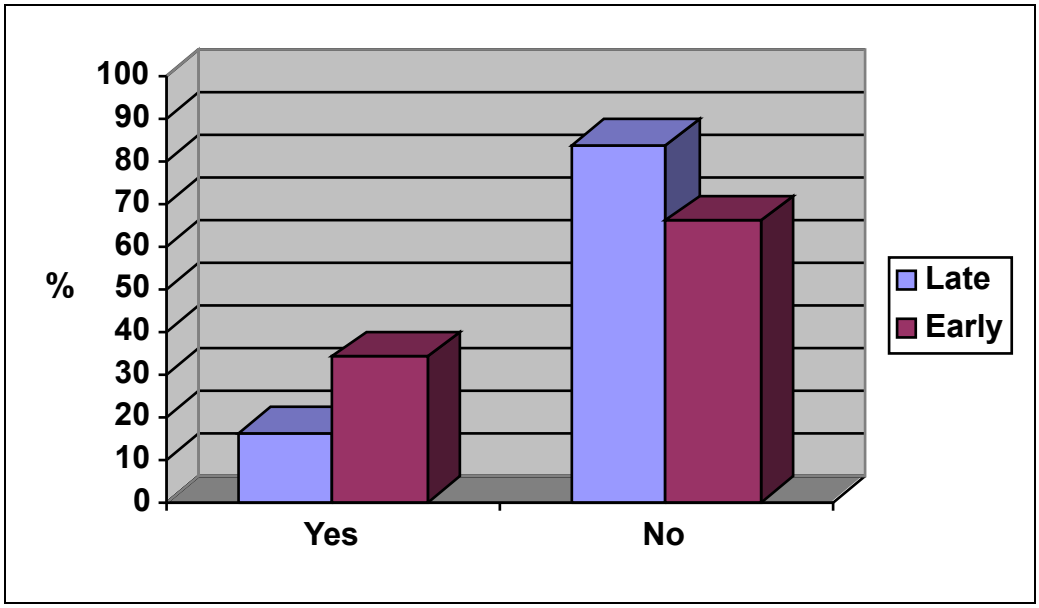


Figure 4.7 Percentage of patients with diabetes mellitus

4.12 HYPERTENSION

62% (n = 42) of late presenters and 63% (n = 41) of early presenters had hypertension.

This was not a statistically significant difference. (p = 0.88)

4.13 PRIMARY VASCULAR DYSREGULATION

Since we were unable to do nailfold capillaromicroscopy, it was felt that patients had to have at least 4 out of 5 typical symptoms of vascular dysregulation including:

- Cold extremities
- Reduced feeling of thirst
- Migraines
- Difficulty in falling asleep (longer sleep onset time)
- History of low blood pressure

in order to qualify as a possible vascular dysregulation suspect.

There was no statistical significant difference ($p = 0.29$) between late (1% n = 1) and early presenters (5% n = 3) when looking at patients with 4 or more symptoms of primary vascular dysregulation.

4.14 SMOKING

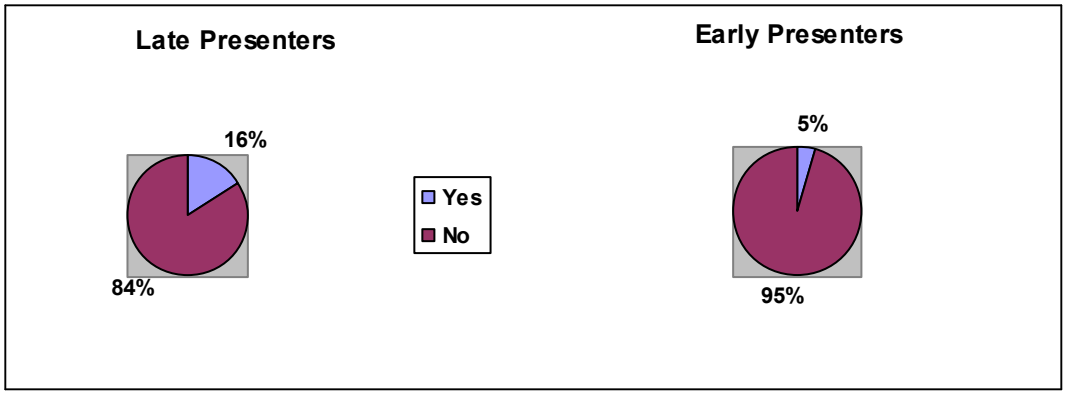


Figure 4.8 Pie charts showing the proportion of patients that smoke

Cigarette smoking was more common in late presenters. 16% (n = 11) of late presenters and 5% (n = 3) of early presenters were smokers.

This was a statistically significant difference. (p = 0.03)

4.15 ALCOHOL USE

69% (n = 47) of late presenters denied using any alcohol. This was echoed in the early presenters with 74% (n = 48) claiming they don't use alcohol.

This was not a statistical significant difference. (p = 0.55)

4.16 CORNEAL THICKNESS

The average corneal thickness was thin in both groups.

Table 4.4 Average corneal thickness

	Right Eye	**Left Eye**
Early Presenters	506µm (SD 45µm)	507µm (SD 37µm)
Late Presenters	508µm (SD 39µm)	507µm (SD 40µm)

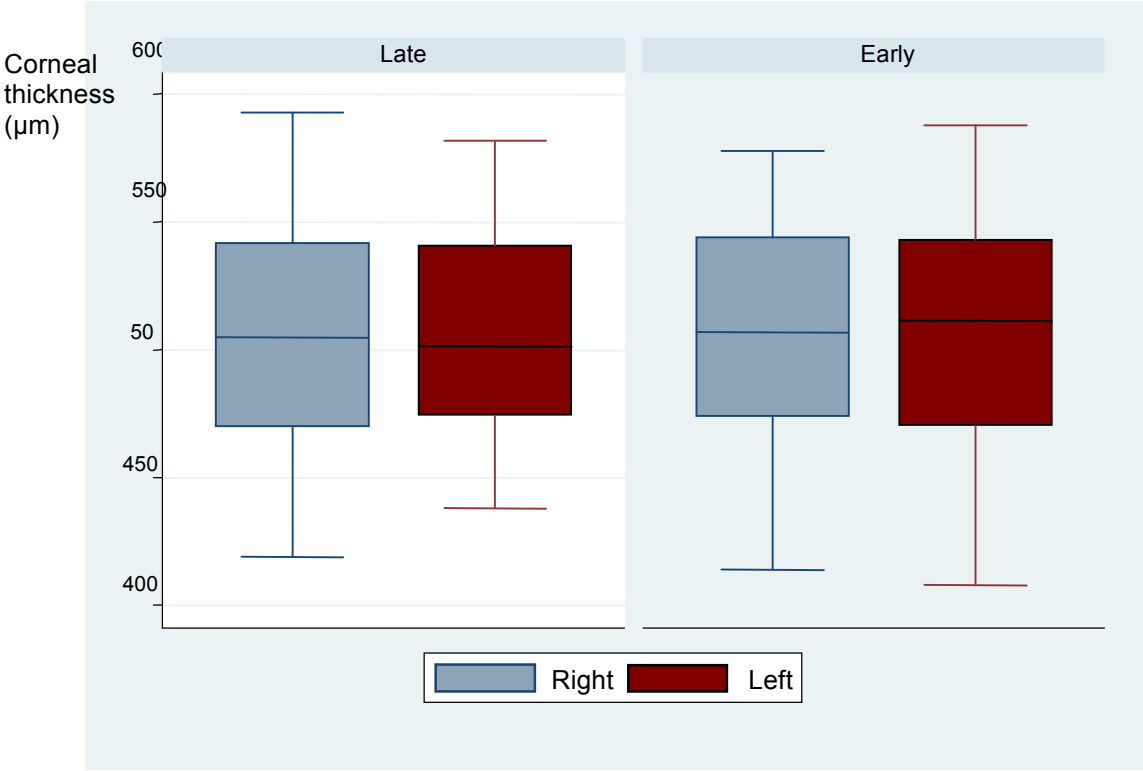


Figure 4.9 Median box plot of central corneal thickness

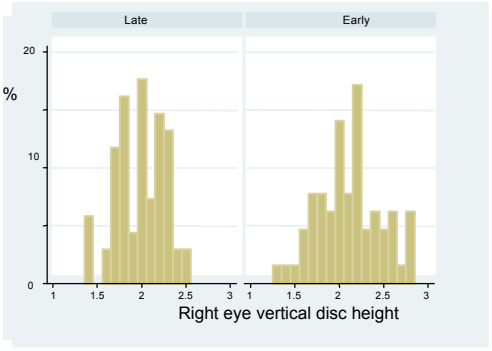
There was no statistical significant difference between the groups when looking at right eyes (p-value 0.74) or left eyes (p-value 0.99).

4.17 VERTICAL OPTIC DISC HEIGHT

Average optic disc size is shown below.

Table 4.5 Average vertical disc height

	Right Eye	**Left Eye**
Late Presenters	1.98mm (SD 0.27mm)	1.98mm (SD 0.27mm)
Early Presenters	2.11mm (SD 0.36mm)	2.10mm (SD 0.37mm)



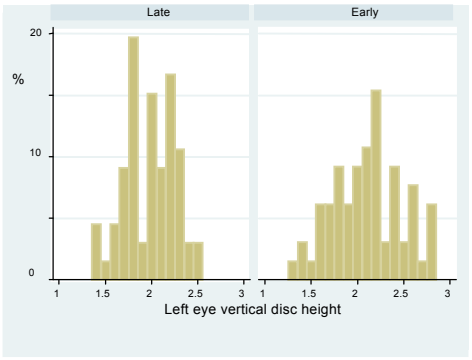


Figure 4.10 Histogram of vertical disc height

A statistical significant difference between the two groups were observed with late presenters having smaller optic nerves. (p-value 0.03)

4.18 PSEUDOCAPSULAR EXFOLIATION

The majority of patients had no pseudocapsular exfoliation, accounting for 84% (n=57) of late presenters and 89% (n=58) of early presenters.

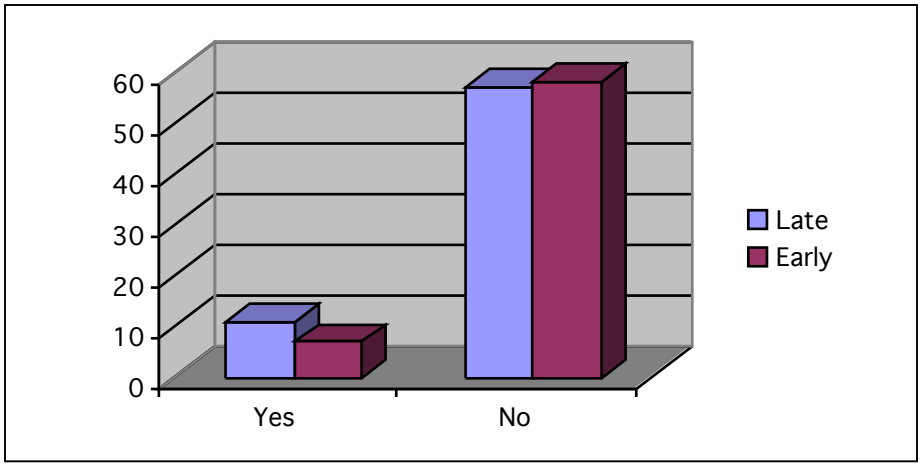


Figure 4.11 Presence of pseudocapsular exfoliation

There was no statistical significant difference between the groups. (p=0.36)

CHAPTER 5 – DISCUSSION

Our results indicate that a high intraocular pressure at initial presentation is strongly associated with advanced glaucomatous optic neuropathy. The findings were consistent with studies done in England [12] and Ghana[15] and we agree that higher intraocular pressures would likely lead to more rapid visual field loss and hence an increased likelihood of delayed attendance. The relationship between IOP and visual field loss have been evaluated in many clinical trials in recent years. Results from the Early Manifest Glaucoma Trial showed that each 1-mmHg higher mean IOP during follow-up was associated with a 12% increase in the chance of developing progressive visual field loss over time.[18] Researchers in the Advanced Glaucoma Intervention Study found that patients with advanced glaucoma who were kept under control with mean IOP levels of 12.3 mmHg had a mean change in visual field scores close to zero.[26] Higher levels of IOP during follow-up were also significantly related to higher rates of progressive retinal nerve fiber layer loss, as seen on the GDx scanning laser polarimeter.[27]

Results from Ghana showed that age greater than 60 years was associated with advanced glaucoma at presentation.[15] This seems plausible since both the prevalence and incidence of glaucoma rise with age.[12] Our results showed no statistical significant difference when looking at patient age. It is possible that older patients in our society might be hindered from attending our hospital due to social isolation or reduced mobility. Hence a relatively smaller number of older patients will attend for vision testing.

Our results showed that gender was not associated with late presentation, while other studies suggest that males are more likely to have advanced glaucomatous change at initial presentation.[12,15] Fraser et al postulated that these results were due to higher rates of sight testing in woman leading to earlier glaucoma detection. I believe that these differences do not occur in our society. Hence our findings reflect my assumption that men and women in our society have similar opportunities and rates of vision testing and thus an equal chance of being detected at an earlier stage.

Our data indicates that overall level of education was very poor. Once again there was no statistical significant difference between groups with more than 50% of cases and controls not completing grade 9.

When studying the English language ability of patients it was noted that early presenters were able to understand and communicate much better than late presenters. This statistically significant finding emphasizes the notion that language plays a major role in preventing glaucoma blindness. When looking at this result one might assume that early presenters should also have a better knowledge of glaucoma – hence their early clinic attendance. Sadly, the majority of our patients lacked glaucoma knowledge. Our results show that more than 80% of both cases and controls had no knowledge of glaucoma as a sight threatening disease. Due to the poor level of education, it is possible that general information regarding glaucoma and other sight threatening diseases might be too complicated for these patients to understand

Of particular interest is the fact that most of these patients had been seen by ophthalmologists in our clinic prior to the study – an indication that our attempts to educate our patients might not be sufficient. As English is the chosen language of most doctors at the time of this study, one has to consider that a language barrier between doctor-patient might foil our attempts at educating non-English speaking patients. In addition, ever increasing patient loads and work stress could hamper our ability to explain patient pathology in an easy, patient friendly manner. Attempts should be directed at improving our communication with patients – preferably in a language of their choice.

It has been shown that a family history contributes to the risk of developing glaucoma.[25] Having a close relative with glaucoma cuts down the risk of late presentation by half in a Ghanaian study.[15] Similar results were found in England.[12] The fact that our results show no association between a positive family history and the degree of glaucomatous damage on presentation might be related to the poor level of education that we encountered. Another possibility is that the majority of patients had no knowledge of glaucoma, which would almost certainly lead to some form of recall bias.

Several reports have noted that glaucoma patients from lower socioeconomic groups have more severe visual field loss at the time of diagnosis, which might increase the risk of becoming blind.[14,15,28,29] Our results support these findings with a statistically significant difference between early and late presenters, especially when looking at people earning more than R5000 per month. ($p = 0.02$). Early presenters earned more than their late presenter counterparts. In addition, it came as no surprise when our data showed that late presenters were more likely to live in poor, informal settlements.

Hoevenaar et al.[28] found that patients from low socioeconomic groups less often knew that the likelihood of getting glaucoma is higher if intraocular pressure is increased, that it is possible to have glaucoma without knowing it and that early detection and treatment will slow down the course of glaucoma. Because they are also less aware of the fact that a family predisposition is a risk factor for glaucoma, they do not encourage their family members to check for glaucoma, leading to more avoidable visual impairment in lower socioeconomic groups.

We found a significant association between previous ocular trauma and early presentation. Trauma would increase the number of eye examinations a patient will have in his/her lifetime and hence increase the likelihood of detecting glaucoma at an early stage.

While some researchers have found that cigarette smoking could be an important risk factor in the occurrence of Glaucoma and Ocular hypertension[30], others dispute this association.[31] Our results indicate that late presenters are more likely to smoke cigarettes. In our view, this once again is an indication of the socioeconomic factors mentioned above, as smoking has been found to be more prevalent in lower income groups.[32]

There is little evidence of an association between alcohol consumption and glaucoma.[33] As for socioeconomic status and alcohol use, epidemiological evidence indicates a positive relationship between income and the prevalence of alcohol abuse in the general population, but an inverse relationship between income and alcohol dependence.[34] We found no association between alcohol use and late presentation glaucoma. It is possible that our data was influenced by a general unwillingness of participants to declare alcohol usage as there is a social stigma attached to it – i.e. response bias.

What about systemic vasculopathies? Diabetes mellitus is known to cause microvascular damage and may affect vascular autoregulation of the retina and optic nerve. Diabetes has been found to be associated with elevated intraocular pressure (IOP)[35] and has therefore been suggested as a possible risk factor for glaucoma, particularly primary open-angle glaucoma (POAG). However, the current evidence to support this relationship remains conflicting.[36] Our results indicate that patients with diabetes is more likely to present to an ophthalmologist with early glaucomatous changes. It is our feeling that these patients are more likely to have regular medical examinations which provide an opportunity for physicians to examine the patients' eyes for diabetic retinopathy, and hence the opportunity to detect glaucoma at an early stage. When looking at hypertension, results from the Blue Mountains Eye study showed a modest, but significant, association with an increased risk of POAG.[17] However, in the Barbados Eye Studies it was found that higher blood pressure parameters were consistently related to lower risk of developing POAG.[25] Whatever the association, it would seem logical that regular attendance for hypertension treatment would also provide an opportunity for early glaucoma detection. Our results showed no statistical significant

difference between early and late presenters. This was a surprising result and one could argue that these patients are less likely to have their eyes examined compared to those patients with diabetes mellitus. It is possible that diabetic patients are more likely to complain of ocular disturbances compared to patients with hypertension.

Another factor associated with glaucoma progression is disturbed ocular blood flow (OBF). We were interested to see if there could be any association with this factor and late presentation. As mentioned before the main cause for the disturbed autoregulation of OBF is the primary vascular dysregulation syndrome.[21] We found no significant difference between the two groups in our study.

Central corneal thickness and its association with glaucomatous damage has been the subject of numerous written reports. A study by Herndon et al.[37] looked at central corneal thickness and its relationship to the level of glaucoma severity at the initial ophthalmic examination. They found that lower central corneal thickness measurements correlated significantly and inversely with the stage of glaucomatous optic neuropathy. Numerous studies have supported these findings.[38,39] While our findings are in keeping with reports that African derived populations have thinner central corneal thicknesses compared to other populations[25], we found no statistical difference between cases and controls. It is well known that high intraocular pressures might give rise to endothelial decompensation and hence interfere with the accuracy of corneal thickness measurements. However, no patients in our study had corneal oedema at the time of examination.

A larger optic disc size in combination with the reportedly higher glaucoma susceptibility in the African derived populations compared to whites has led to the hypothesis that eyes with large optic discs may be more prone to glaucomatous optic nerve fiber loss than eyes with small optic discs.[40,41] Our findings are not consistent with this notion as late presenters had a statistically significantly smaller vertical disc height compared to early presenters. One possible explanation

for this is that patients with larger optic discs (and hence larger physiological cup to disc ratios) are referred to specialists at an earlier stage than those who have physiologically small optic discs.

The Early manifest glaucoma trials have shown that pseudoexfoliation more than doubles the risk of glaucoma progression.[19] When one considers the more severe clinical course of pseudoexfoliative glaucoma, one might assume that these patients have a higher risk of presenting with advanced field loss. It is also reasonable to hypothesize that a higher incidence of associated eye pathology [42](eg. cataracts) might lead to these patients been seen earlier compared to primary open angle glaucoma. However, our results showed neither. No statistical significant difference was found between the incidence of pseudoexfoliation in cases and controls.

This study has several weaknesses. Being a single centre trial it lacks the benefits that a multicenter trial provides. It included a fairly small number of patients, all from the same geographic location. This obviously decreases the generalizability of the study. Because information was taken from initial hospital files, we rely on the accuracy of different examiners. Some of this data might have been inaccurately recorded and might thus be a potential source of bias. In addition, because patients had to answer questionnaires, it introduces the possibility of recall bias. Another weakness is the fact that we only performed univariate data analysis. A multivariate data analysis is needed in order to control for confounding.

CHAPTER 6 – CONCLUSION AND RECOMMENDATIONS

Our findings confirm that raised intraocular pressure is a major factor in patients presenting with advanced glaucomatous optic neuropathy. Being our only modifiable risk factor in the pathogenesis of glaucoma, efforts should be directed at early detection. However, there are several factors that make this a near impossible task. Poverty seems to be a major factor responsible for our failure to detect glaucoma patients at an earlier stage. Unfortunately this is a significant problem in most developing countries and South Africa is no different. As opthalmologists, the scope of this problem is out of our hands. However, efforts could be focused at improving our glaucoma education and screening programs in the community. Our results also suggest that even at tertiary care level we are failing to educate our patients properly. Considering the fact that most of our patients have a very poor level of education, we should direct our attention at simplifying our communication with these patients in a language of their choice. Our results further indicate that there are several factors which might contribute to earlier or more regular medical examinations and hence earlier glaucoma detection. This highlights the fact that although it will be difficult, it may be possible to reduce the number of people with glaucoma related blindness in South Africa.

CHAPTER 7 – APPENDIX

In the following chapter there are examples of the documents that were used in the completion of the study.

7.1 PATIENT QUESTIONNAIRE

- *Participant number*:……..

- *Who told (referred) you to come see us at our hospital*? ……
  ……..
  Did they diagnose you with glaucoma? Y / N

- *Have you ever had your eyes examined by an optometrist or a doctor?*
  Y / N
  If Yes: How many times?.....
  By whom?…….....
  When?.....

- *Have you seen a doctor before?* Y / N

  If yes: When was the last time?.....
  How often do you see the doctor?.....

- *Has anyone in your family got glaucoma*? Y / N

  If Yes: Who?.....

  Has anyone ever advised you to have your eyes checked for glaucoma? Y / N
  Who?.....

- *Did you go to school*? Y / N

  If Yes: What is the highest grade you completed? ……

- *Did you go to university*? Y / N

  If yes: What did you study? …….
  Did you complete your studies? Y / N

- *Do you know what glaucoma is?* Y / N
  If yes: Explain what you know about it……
  ……

  How did you learn about glaucoma?.....
  ……

- *How much money do you earn / receive per month*? ……

  How do you obtain this money? (eg what job? Grant?)……....
  ……...

- *Where do you live*? ……..
- *How long have you lived there?*.....
- *In what structure do you live*?(*eg house, shack, caravan, apartment etc*)……
  ……...
- *Have you ever lived in a rural area?*.....
  When? (eg. 1970 – 1993) ……..
- *Who do you stay with*? …….
- *What language do you speak at home?*……
- *Have you ever been diagnosed with Diabetes (high blood sugar?)* Y / N

  If Yes: How long have you had it? ……..
- *Have you ever been diagnosed with high blood pressure?* Y / N

  If Yes: How long have you had it? ……..
- *Do you smoke?* Y / N
  If Yes: How many cigarettes per day? …….
  For how long? ……..

  If No: Have you ever smoked? …….
  For how long? (eg 1980 – 1992) ……
- *Do you drink alcohol?* Y / N
  If Yes: How often, how much? ……..
- *Do you suffer from any of the following?*

  Cold hands and feet? Y / N
  Migraines? Y / N
  Difficulty in falling asleep at night? Y / N
  Low blood pressure? Y / N

  Would you consider yourself to have a reduced feeling of thirst? I.e. do you seldom get thirsty? Y / N
- *Have you ever had any accident / injury to you eyes?* Y / N

  If yes: Explain……
  ……...

Thank you for taking the time to complete this questionnaire.

7.2 DATA CAPTURING SHEET

1. Patients Participant Number:…….

2. EARLY: Typical glaucomatous field loss and a **MD between 0 dB and -11 dB** in the **worst** eye. A **cup to disc ratio of more than 0,5** must be present or a **difference of more than 0,2** must have been noted.

or

LATE: Typical glaucomatous field loss with a mean deviation **(MD) of greater than -14 dB** in the **better** seeing eye. Optic discs must show typical glaucomatous **cupping of more than 0,8.** Fields will be excluded if visual loss is so advanced that field testing is not possible.

3. Visual Acuity OD…… OS……

4. Presenting intraocular pressure ……..

5. Central corneal thickness ……..

6. Optic disk size (vertical disk height)…….

7. Pseudocapsular exfoliation Y / N

8. Age at first presentation: …….

9. Sex: M / F

10. English language ability: Can patient communicate in English Y / N

If Y: **Good** (Has operational command of the language. May have occasional inaccuracies, inappropriaceis and misunderstandings in some situations. Generally handles complex language well.)

Modest (Partial command of the language. Can cope with overall meaning in most situations. Likely to make many mistakes.)

Poor (Conveys and understands only general meaning in very familiar situations. Frequent breakdowns in communication occurs.)

Very poor: (No real communication is possible. Has great difficulty understanding spoken and written English)

11. Method of referral:

a) None

b) Optometrist Glaucoma suspect / diagnosis? Y / N

c) Medical Practitioner Glaucoma suspect / diagnosis? Y / N

d) Local Clinic Glaucoma suspect / diagnosis? Y / N

12. Previous eye examinations Y / N
How many? …….
When? ……

13. Previous medical examinations Y / N
Frequency ……..
Last visit to doctor …….

14. Family history of glaucoma Y / N Relation to patient ……..

15. Level of education a) No formal education
b) Primary school
-grade ……
c) Secondary school
- grade ……
d) Tertiary institution
- degree/diploma ……..

16. Knowledge about glaucoma: as an eye disease? Y / N
as a cause of blindness? Y / N

17. Average annual income ……

Source of income ……

18. Formal / Informal housing?

19. Ever lived in rural area? Y / N
When? (eg 1970 – 1989)……

20. Home language ……..

21. Diabetes Mellitus Y / N HGT …….

22. Hypertension Y / N BP ……/…….

23. Smoker Y / N

If Y: Pack year history …….

If N: Previous Smoker? Y / N

24. Alcohol consumption Y / N

If Y: Average daily consumption ……

25. Symptoms of Primary Vascular Disease

Cold extremities? Y / N
Reduced feeling of thirst Y / N
Migraines Y / N
Low Blood pressure Y / N
Difficulty in falling asleep Y / N / 5

26. Previous ocular trauma Y / N

CHAPTER 8 – REFERENCES

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