

**OCULAR FINDINGS IN PATIENTS
WITH
HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLAEMIA**

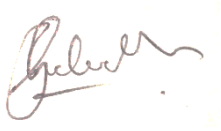
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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Ophthalmology

Johannesburg, 2017

DECLARATION

I, Adisha Goberdhan, declare that this Research Report 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 any other University.

A handwritten signature in brown ink, appearing to read 'Adisha', with a stylized flourish extending to the right.

29th day of June, 2017 in Sandton

DEDICATION

For my Mum, Dad & Nimalin....

Being loved by you

I feel eternally Blessed.

Your sacrifices have allowed me

To be my Best.

Resonating your faith in God

I'm still standing despite Life's beating Rod.

And in this moment of accomplishment I wish to Dwell

But I know I must continue to Study Well.....

ABSTRACT

Homozygous familial hypercholesterolaemia is a fatal disease if untreated and has a high prevalence of premature coronary artery disease. Ocular findings may help with earlier identification and coronary artery disease risk stratification.

Objectives: The primary objective was to determine ocular findings in patients with homozygous familial hypercholesterolaemia. The secondary objective was to correlate ocular findings with clinical and biochemical data.

Design and Method: A cross-sectional study was conducted in 2011. Thirty patients were recruited from the Lipid Clinic at Charlotte Maxeke Johannesburg Academic Hospital.

Results: Xanthelasma palpebrarum, corneal arcus, retinal arteriosclerosis and visual field defects were detected. Xanthelasma palpebrarum and corneal arcus were common in patients with overt coronary artery disease.

Conclusion: In addition to well-known ocular features of hyperlipidaemia, i.e. xanthelasma palpebrarum, corneal arcus and retinal arteriosclerosis, we detected visual field defects. The assessment of xanthelasma palpebrarum and corneal arcus may help to prognosticate coronary artery disease risk.

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NOMENCLATURE

Arteriole to venule ratio: AVR

Charlotte Maxeke Johannesburg Academic Hospital: CMJAH

Coronary artery disease: CAD

Coronary heart disease: CHD

Familial hypercholesterolaemia: FH

High-density lipoprotein cholesterol: HDL-C

Homozygous familial hypercholesterolaemia: HoFH

Interquartile range: IQR

Intraocular pressure: IOP

Low-density lipoprotein cholesterol: LDL-C

Not applicable: N/A

Ocular Coherence Tomography: OCT

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1. CHAPTER 1- INTRODUCTION

1.1 GENERAL INTRODUCTION AND LITERATURE REVIEW

Homozygous familial hypercholesterolaemia (HoFH) is a metabolic disorder with an autosomal co-dominant inheritance pattern.¹ Mutations in genes coding for low-density lipoprotein receptors lead to elevated serum cholesterol levels.¹ Homozygotes are severely affected with low-density lipoprotein cholesterol (LDL-C) levels approximately six times greater than the ideal level for patients at risk for heart disease.²

The estimated prevalence of HoFH in South Africa is 1 in 30 000.³ In comparison, the global prevalence of HoFH is about 1 case per 1 million persons.⁴ The significant prevalence of HoFH in South Africa was a valuable resource to elucidate the ocular findings in these patients.

Elevated LDL-C levels and decreased levels of high-density lipoprotein cholesterol (HDL-C) are known to be risk factors for coronary heart disease (CHD).⁵ According to the Centers for Disease Control and Prevention, ischaemic heart disease was the leading cause of death in the United States of America in 2014.⁶ The early detection and treatment of familial hypercholesterolaemia (FH) can ease the burden of CHD.

The presence of elevated LDL-C levels may be inferred from the observation of lipid deposition in the eye which occurs in conditions such as corneal arcus and xanthelasma palpebrarum. Arteriosclerosis of retinal vessels has been strongly correlated with the severity of atherosclerotic changes within coronary arteries.⁷ Therefore, ophthalmoscopy can be an invaluable, non-invasive, tool for clinicians to gauge systemic atherosclerosis from ocular findings.

Corneal arcus is a common, non-sight-threatening, ocular sign in hypercholesterolaemic patients.⁸ The width and circumference of corneal arcus have been associated with the extent and duration of elevated LDL-C levels.⁹ Corneal arcus has been associated with higher LDL-C levels, lower HDL-C levels and LDL-C: HDL-C ratio > 5.⁸

Corneal arcus has also been proposed as a cardiac risk factor.⁹ Literature examining this association has yielded mixed results. A study showed that corneal arcus was not a predictor of coronary artery disease (CAD) after the adjustment of age and gender.¹⁰ The majority of the patients with corneal arcus were graded as having slight corneal arcus. In patients with severe corneal arcus, such as patients with HoFH, these findings may differ. A correlation, however, between corneal arcus and severe calcific atherosclerosis was demonstrated in a small number of patients with HoFH.¹¹

Another, easily identifiable, ocular manifestation of hyperlipidaemia is xanthelasma palpebrarum which manifests as yellow plaque-like lesions near the inner canthus of the eye.¹² Patients with xanthelasma palpebrarum may have an increased risk for CAD.¹²

Hypercholesterolaemia has been linked to other ocular pathologies such as conjunctival xanthoma¹³, lens opacification¹⁴, retinal vein occlusion¹⁵ and age-related macular degeneration.¹⁶ Most of these diseases have the potential to severely affect vision and increase morbidity. Atherosclerosis-related thrombosis is the most common cause of central retinal artery occlusion.¹⁷ Other findings associated with hypercholesterolaemia are changes in visual field testing¹⁸ and cholesterol emboli seen in retinal vasculature (Hollenhorst plaques)¹⁹.

Visual field abnormalities in the absence of ophthalmological or neurological disease may indicate defective processing capabilities of the cerebral cortex due to hyperlipidaemia.¹⁸ Perimetry values (mean deviation, pattern standard deviation, short-term fluctuation,

corrected pattern standard deviation and foveal threshold) measured in dyslipidaemic patients revealed a worsening of all perimetry variables.¹⁸

1.2 RESEARCH AIM

The aim was to describe pathological ocular findings in patients with HoFH.

1.3 RESEARCH OBJECTIVES

The primary objective was to investigate the spectrum of ocular findings in patients with HoFH. The secondary objective was to determine the association between ocular findings and clinical and biochemical data.

2. CHAPTER 2- METHODS

2.1 STUDY DESIGN

A cross-sectional study was conducted from the 05 April 2011 to the 19 July 2011. A convenience sample of 30 patients, attending the Lipid Clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), was recruited to the study. They were examined after their routine follow up visit to the Lipid Clinic.

2.2 DATA COLLECTION

A research protocol was submitted to and reviewed by the Human Research Ethics Committee (Medical), University of the Witwatersrand. A clearance certificate was issued, Reference M110313 (Appendix A). The study commenced once approval was received. Permission was obtained from the Chief Executive Officer of CMJAH and the Head of the Division of Endocrinology & Metabolism at CMJAH, to review clinical records.

The Lipid Clinic at CMJAH is one of the two main lipid clinics in the country, the other clinic being based at Groote Schuur Hospital. The drainage area of the clinic at CMJAH includes the whole of Gauteng and extends as far afield as Bloemfontein, Richards Bay and Harrismith.

Thirty eligible participants were approached and invited to participate in the study. The sample size was limited by the number of subjects with this condition attending the Lipid Clinic at CMJAH. However, 30 is a large cohort for this rare condition.³ The period of the patients follow up visits determined the duration of the study. Patients and parents of paediatric patients were verbally informed about the study and the clinical examination. They were also provided with information sheets (Appendix B, Appendix C and Appendix D). Informed consent was obtained from patients (Appendix E) or parents/ legal guardians of

paediatric patients (Appendix F). An assent form (Appendix G) was signed by older paediatric participants when appropriate.

Patients were examined at the eye clinic at CMJAH by the primary researcher. Visual field examination, ocular coherence tomography (OCT) images and colour fundus photographs were captured by Mrs Linda Malan. Corneal photographs were taken by the primary researcher. Professor I Mayet, a retinal expert, graded the colour fundus photographs. On the day of examination routine fasting lipid profiles were taken at the Lipid Clinic. Medical, surgical and biochemical data were collated from clinical records.

2.2.1 Inclusion Criteria

Adult and paediatric patients were invited to participate if they had HoFH. This was diagnosed by the following as noted in a review article by Raal and Santos.¹

- a) Genetic testing detecting 2 mutated alleles at the low-density lipoprotein gene locus.
- b) Clinical diagnosis
 - Cutaneous or tendinous xanthomas occurring at a young age (<10 years)
 - Untreated LDL-C >13mmol/L
 - Treated LDL-C $\geq$ 7.76mmol/L
 - A non-HDL-C $\geq$ 8.5mmol/L
- c) Hypercholesterolaemia in both parents or CAD in a first degree relative (male < 55years and female < 60years)

2.2.2 Exclusion Criteria

Exclusion criteria were:

- Diabetes mellitus. This was defined as fasting blood glucose of $\geq$ 7.0 mmol/l²⁰, a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis and a random glucose level $\geq$ 11.1mmol/L²⁰, self-reported diabetes or patients taking glucose lowering medication. Patients with diabetes mellitus were excluded because it has been linked to cataract formation, increased intraocular pressure (IOP) and retinal vein occlusion.

- Hypertension. This was defined as a clinic blood pressure of 140/90 mmHg or higher and subsequent ambulatory blood pressure monitoring daytime average or home blood pressure monitoring average of 135/85 mmHg or higher²¹, self-reported hypertension or patients on therapy for hypertension. Hypertensive patients were excluded from the assessment of retinal arteriosclerosis because hypertension can also cause arteriosclerosis of the retinal arteries and is a risk factor for retinal vein occlusion. Hypertensive retinopathy closely resembles atherosclerotic disease of retinal arteries. Due to the small sample size, the 3 hypertensive patients were included in the evaluation of all other ocular signs but excluded from the retinal examination for arteriosclerosis.
- History of eye trauma, or ocular inflammation because they can lead to cataract formation, increased IOP and visual field defects.
- Corticosteroid usage as it may lead to increased IOP and cataract formation.
- Current smokers and/or excessive alcohol intake i.e. >30g/day. These are also CAD risk factors which may confound the evaluation of hypercholesterolaemia as a CAD risk factor. Smoking is also a risk factor for age-related macular degeneration.
- History of glaucoma, or IOP > 21mmHg, Cup to disc ratio > 0.3. Glaucoma leads to defects in visual field testing.
- Refractive defects > 6 dioptres and neuro-ophthalmological diseases that can affect perimetry results.
- Patients in which the posterior segment was not visible.
- Previous eye surgery. Complications of eye surgery include increased IOP and cataract formation. Topical steroids are also used to treat patients postoperatively which can lead to IOP elevations and cataract formation as mentioned above.

2.2.3 Data Collection

Confidentiality was maintained regarding patients names, hospital numbers and clinical information obtained. Each patient was identified by a study number only. Only the primary researcher had access to the study number-patient identity key. All information was kept confidential. The Lipid Clinic provided the primary researcher with patients' demographic

data, biochemical data, and past medical and surgical history on a Microsoft Excel spread sheet.

The following information was extracted from the clinic record (Appendix H):

- a) Age
- b) Sex
- c) Race
- d) Afrikaner Descent

Due to the founder effect described by Seftal et al, there is a high prevalence of Afrikaner descent among patients with HoFH.³

- e) Overt coronary artery disease:
 - 1. Coronary artery bypass graft
 - 2. Aortic valve replacement
 - 3. Percutaneous transluminal coronary angioplasty
 - 4. Aortic arch procedure
 - 5. Combination of any of the above procedures
 - 6. Myocardial infarction
- f) Other vascular surgery:
 - 1. Abdominal aortic surgery
 - 2. Carotid surgery
 - 3. Other vascular procedures
- g) Cutaneous or tendinous xanthomas in the first decade
- h) Cholesterol-year score

This was calculated using the average yearly LDL-C level and the age of the patient.²²
- i) Total cholesterol, LDL-C and HDL-C levels.

There was provision on the data capture sheet for information regarding angina, heart failure, cerebrovascular accident and transient ischaemic attacks. However, given the small number of patients in these groups we decided to rather focus on overt CAD and other vascular surgery as the clinical characteristics that would be investigated.

The ocular examination was documented on a data capture sheet (Appendix H). It was performed by the primary researcher and took place at the ophthalmology clinic at CMJAH. Mrs Malan performed the 24-2 visual field test using a Humphrey^R 740i Field Analyzer (Carl Zeiss, Oberkochen, Germany). She also captured OCT images with a Stratus OCT machine (Carl Zeiss, Oberkochen, Germany) and colour fundus pictures with a TRC-50DX retinal camera (Topcon, Tokyo, Japan).

Upon arrival visual acuity was tested using a Snellen chart. Thereafter visual fields were tested. Patients were then examined for the presence of xanthelasma palpebrarum, conjunctival xanthomas and corneal arcus using a SL990-Zoom slit lamp (CSO, Firenze, Italy). Corneal photographs of both eyes were taken by the primary examiner using a 3.15 megapixel camera (Blackberry, Ontario, Canada), held approximately 15cm from the corneal surface, to document corneal arcus. IOP was measured using a Goldman applanation tonometer.

Eyedrops containing cyclopentolate and phenylephrine were used for pupillary dilation. One drop was instilled in each eye. An additional drop was given after 10 and 20 minutes until there was adequate pupillary dilation. Slit lamp examination recommenced to assess for cataract formation. Direct ophthalmoscopy of the optic disc, macula and retinal vasculature was performed using a 78 dioptre lens (Ocular Instruments, Washington D.C, United States of America). Thereafter patients proceeded to have an OCT and colour fundus image captured. Retinal photographs were then sent to the retinal expert on a CD disc for grading.

A circular overlay, designed using Microsoft PowerPoint 2010 (Microsoft, United States of America), with a radius larger than the corneoscleral junction was superimposed on corneal photographs (Figure 1). The circle was divided into eight equal sectors. A score of 1 was given for corneal arcus completely or half filling a sector. Each eye was scored from 0 (no arcus) – 8 (complete circumferential arcus). The scores from both eyes were added and

divided by 16, producing a final grade ranging from 0 (no arcus bilaterally)-1 (complete circumferential arcus bilaterally).¹¹ The grading of corneal arcus was performed by the primary researcher.

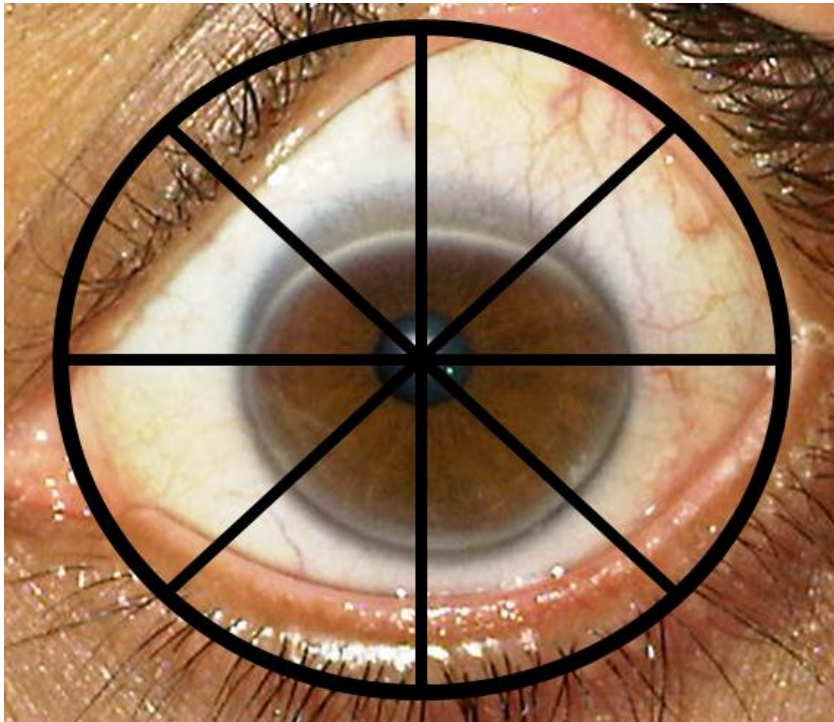


Figure 1: Circular overlay over corneal pictures to grade corneal arcus

Visual field tests were analysed by the primary researcher. Firstly, it was determined whether or not the visual field results were reliable. This assessed if the patient followed instructions on how to perform the test. The blind spot which correlates with the optic disc was tested to determine if the patient maintained fixation. If fixation losses were in excess of 20% the test was deemed to be of poor reliability²³ and not analysed. Secondly, if false positive or false negative scores were >20-30%, the test was noted to be of questionable reliability and not further interpreted.²³ One of the numerical indices on the visual field test is the mean deviation. It is a measure of the global deviation from normal values.²³ Once a test was found to be reliable, the mean deviation was then assessed. A mean deviation <-2db is considered abnormal.²³

Colour fundus photographs were only taken on 2 days over which 25 patients were examined. Unfortunately colour fundus photographs could only be captured in 17 patients as a result of poor patient co-operation (2 paediatric patients and the lengthy examination process) or malfunctioning of the retinal camera. One hypertensive patient was excluded from the retinal arteriosclerosis examination. The other 16 patients were assessed for retinal arteriosclerosis by a retinal expert, Professor I. Mayet. The primary researcher also examined all fundi for retinal arteriosclerosis. This was done as the primary researcher was aware of demographic and clinical data and may have been biased. Additionally, the subtle change in Grade 1 arteriosclerosis is challenging to detect. This is a crucial finding as it determines the presence or absence of disease. This grading was therefore carried out by a retinal expert. The photographs were labelled with a number and the laterality of the eye. He was blind to the patients' demographic and clinical data. The Scheie classification was used to grade retinal arteriosclerosis.

Table 1: Scheie classification²¹

Stage	
0	No abnormality.
1	Widening of arteriole light reflex. Absent or minimal arteriolo venous compression.
2	More noticeable light reflex and crossing changes.
3	Copper wire appearance of arterioles. More arteriolo venous compression.
4	Silver wire appearance of arterioles. Most severe arteriolo venous crossing changes.

2.3 STATISTICAL ANALYSIS

The primary researcher performed the statistical analysis using Microsoft Excel version 14 (Microsoft, United States of America) and Statistica version 12 (Soft Inc., United States of America). Mr Nimalin Moodley and Mr Deepak Soowamber offered assistance with statistical queries. Microsoft Excel was used to compute the descriptive statistics of demographic variables and ocular findings. Continuous variables were described using means and standard deviations for normally distributed data and medians and interquartile ranges (IQR) for non-normally distributed data. Categorical data was described using percentages. When comparing categorical and numerical variables, if normally distributed, a t-test was performed. The Kruskal-Wallis test was used if normality was not met. When comparing categorical variables with categorical variables, the chi squared test was performed. A linear regression analysis was performed to determine the significance between corneal arcus grade and selected clinical characteristics. Those relationships found to be statistically significant were then adjusted for age and gender using a multiple regression analysis. A linear regression analysis was also used to evaluate the relationship between retinal arteriosclerosis grade and selected clinical characteristics. Statistical significance was defined as a p value <0.05.

2.4 STAFF AND ADMINISTRATION

Professor F.J. Raal took the fasting blood samples at the Lipid Clinic on the day of examination. The ocular examination and corneal photographs were done by Dr Adisha Goberdhan (Ophthalmology registrar) at the CMJAH eye clinic. Mrs Linda Malan performed the visual field examinations and captured the OCT images and retinal photographs. Professor I. Mayet graded retinal arteriosclerosis by assessing the colour fundus photographs. The primary researcher interpreted the visual field tests and OCT images.

2.5 ETHICAL CONSIDERATIONS

Approval for the study was obtained from the Human Research Ethics Committee, University of the Witwatersrand (Appendix A). Confidentiality was maintained regarding patients names, hospital numbers and clinical information obtained.

3. CHAPTER 3- RESULTS

3.1 STUDY SAMPLE

A convenience sample of 30 patients was obtained from the Lipid Clinic (Table 2).

Table 2: Demographics and clinical characteristics of the sample population

Demographics	
Age (years)	24 (13- 38)
Sex	
Male	15 (50%)
Female	15 (50%)
Race	
White	24 (80%)
Indian	6 (20%)
Afrikaner Descent	22 (73%)
Clinical characteristics	
Overt CAD	10 (33%)
Other vascular surgery	2 (7%)
Cholesterol-year score (mmol-year/L)	281.16 (161.4- 509.1)
Total Cholesterol (mmol/L)	11.9± 3.6
LDL-C (mmol/L)	10.4 ± 3.5
HDL-C (mmol/L)	1.0 (0.8- 1.2)

3.1.1 Age

The youngest patient was 6 years old and the oldest was 49 years old. Fourteen patients were younger than 18 years of age.

3.2 OCULAR FINDINGS

3.2.1 Xanthelasma palpebrarum

Xanthelasma palpebrarum was found in nine (30%) patients. There were four unilateral and five bilateral cases. In unilateral cases, it predominantly (75%) occurred on the right eyelid.

Table 3: Xanthelasma palpebrarum occurring in the right and left eye in unilateral and bilateral cases

Xanthelasma palpebrarum	Right eye (n=8)	Left eye (n=6)
Unilateral (n=4)	3	1
Bilateral (n=5)	5	5

Table 4: Location of the xanthelasma palpebrarum in each eye

Xanthelasma palpebrarum	Right eye (n=8)	Left eye (n=6)
Upper eyelid only	2 (25%)	1 (17%)
Lower eyelid only	2 (25%)	2 (33%)
Upper and lower eyelid	3 (38%)	3 (50%)
Inner canthus	1 (13%)	0

Xanthelasma palpebrarum was located more commonly on the upper and lower eyelids (Table 4).

Table 5: Demographic and clinical characteristics of patients with and without xanthelasma palpebrarum

	Xanthelasma palpebrarum (n=9)	No Xanthelasma palpebrarum (n=21)	p-value
Age (years)	34 (30- 43)	17 (12- 36)	0.049
Males	7 (78%)	8 (38%)	0.046
Females	2 (22%)	13 (62%)	0.046
Race			
White	7 (78%)	17 (81%)	0.842
Indian	2 (22%)	4 (19%)	0.842
Afrikaner descent	6 (67%)	16 (76%)	0.589
Overt CAD	6 (67%)	4 (19%)	0.011
Other vascular surgery	0 (0%)	2 (10%)	0.338
Cholesterol-year score (mmol-year/L)	448.6 (281.5- 538.5)	234.8 (131.0- 450.7)	0.067
Total cholesterol (mmol/L)	11.7± 4.0	12.0± 3.6	0.807
LDL-C (mmol/L)	10.1± 3.9	10.5± 3.5	0.763
HDL-C (mmol/L)	1.0 (0.7- 1.2)	1.0 (0.9 - 1.1)	0.584

Xanthelasma palpebrarum was more common in older patients, men and those with overt CAD (Table 3).

Table 6: Age of patients with xanthelasma palpebrarum vs age of male patients with xanthelasma palpebrarum

Age of patients with xanthelasma palpebrarum	Age of male patients with xanthelasma palpebrarum	p- value
34 (30- 43)	32 (23- 46)	0.916

Table 7: Age of patients with xanthelasma palpebrarum vs age of xanthelasma palpebrarum patients with Overt CAD

Age of patients with xanthelasma palpebrarum	Age of xanthelasma palpebrarum patients with Overt CAD	p- value
34 (30- 43)	40 (35- 47)	0.289

Table 8: Demographic and clinical characteristics of patients with unilateral and bilateral xanthelasma palpebrarum

	Unilateral Xanthelasma palpebrarum (n= 4)	Bilateral Xanthelasma palpebrarum (n= 5)	p-value
Age (years)	23 (14- 31)	43 (36- 48)	0.014
Males	4 (100%)	3 (60%)	0.151
Females	0 (0%)	2 (40%)	0.151
Race			
White	2 (50%)	5 (100%)	0.073
Indian	2 (50%)	0	0.073
Afrikaner descent	1 (25%)	5 (100%)	0.018
Overt CAD	1 (25%)	5 (100%)	0.018
Other vascular surgery	0	0	N/A
Cholesterol-year score (mmol- year/L)	244.1 (204.9- 293.6)	538.5 (532.8- 538.8)	0.014
Total cholesterol (mmol/L)	9.4± 3.1	13.5± 3.8	0.126
LDL-C (mmol/L)	8.0± 3.2	11.8.4± 3.8	0.160
HDL-C (mmol/L)	0.9 (0.7- 1.2)	1.0 (0.9- 1.2)	0.712

3.2.2 Conjunctival Xanthomata

Conjunctival xanthomata were not detected in any patient.

3.2.3 Corneal Arcus

Of the 30 patients, 29 were assessed for corneal arcus. Two patients were excluded from the assessment of corneal arcus due to poor quality images.

Table 9: Demographic and clinical characteristics of patients with and without corneal arcus

	Corneal arcus (n= 22)	No corneal arcus (n= 6)	p-value
Age (years)	33 (15- 41)	13 (12- 16)	0.016
Males	12 (55%)	1	0.099
Females	10 (45%)	5	0.099
Race			
White	18 (82%)	5 (83%)	0.932
Indian	4 (18%)	1 (17%)	0.932
Afrikaner descent	16 (73%)	5 (83%)	0.595
Overt CAD	10 (45%)	0	0.039
Other vascular surgery	2 (9%)	0	0.443
Cholesterol-year score (mmol-year/L)	402.5 (218.3- 532.8)	155.2 (121.8- 250.9)	0.016
Total cholesterol (mmol/L)	11.6± 3.7	11.9± 3.2	0.855
LDL-C (mmol/L)	10.0± 3.7	10.4± 2.9	0.828
HDL-C (mmol/L)	1.0 (0.8- 1.2)	1.1 (0.9-1.1)	0.538

Patients with corneal arcus were significantly older and had higher cholesterol-year scores compared with those without corneal arcus. Importantly, overt CAD was more common in those with corneal arcus (Table 7).

A 15 year old female, non-Afrikaner, Caucasian patient had unilateral corneal arcus. She did not have any history of overt CAD or other vascular surgery. Her cholesterol-year score was 234.8mmol-year/L, total cholesterol was 4.8mmol/L, LDL-C was 3.3mmol/L and HDL-C was 1.2mmol/L. The corneal photograph was of a poor quality to accurately grade the degree of corneal arcus. Twenty one patients had bilateral corneal arcus. The median age was 34 with an IQR of 17-42. Twelve patients (57%) were male. The majority were White (81%) and of Afrikaner descent (76%). Ten patients (48%) had overt CAD and 2 (10%) had other vascular surgery. The median cholesterol-year score was 448.6mmol-year/L with an IQR of 218.3mmol-year/L - 532.8mmol-year/L. The mean total cholesterol was 11.9mmol/L and the mean LDL-C was 11mmol/L. The median HDL-C was 1.0mmol/L with an IQR of 0.8mmol/L- 1.2mmol/L.

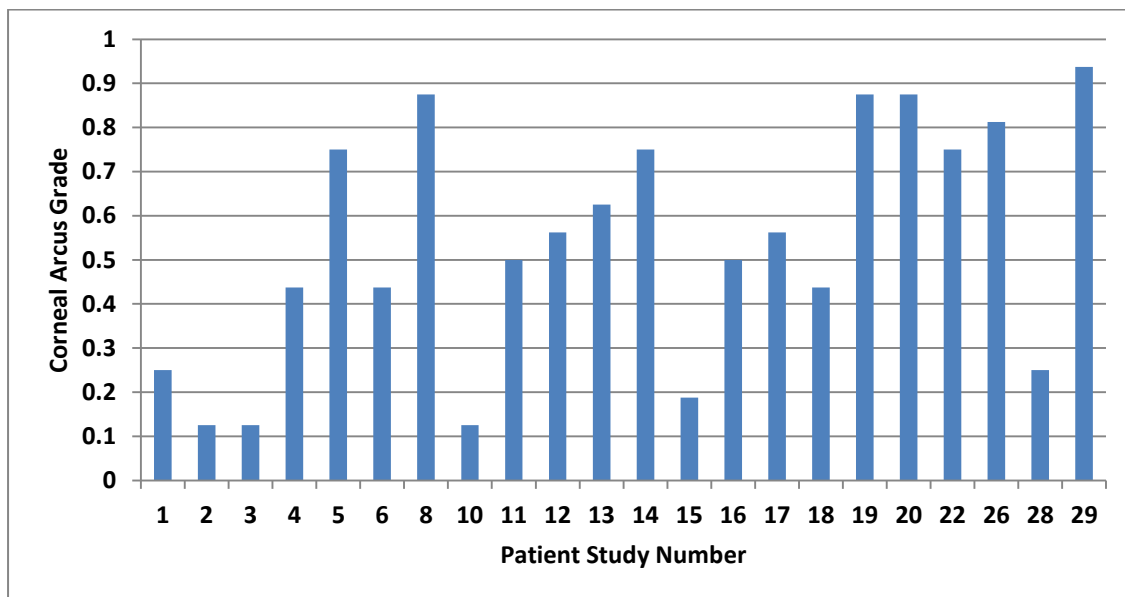


Figure 2: Corneal arcus grade in patients with corneal arcus

Table 10: Unadjusted relationship between corneal arcus grade and selected clinical characteristics

	Regression coefficient	p-value
Age	0.445	0.018
Overt CAD	0.389	0.041
Other vascular surgery	0.042	0.830
Cholesterol-year score	0.493	0.008
Total cholesterol	0.192	0.327
LDL-C	0.174	0.378
HDL-C	0.167	0.410

In unadjusted analyses, there was a significant relationship between corneal arcus grade and age, overt CAD and cholesterol-year score. All of these relationships were attenuated by adjustment for age and gender.

3.2.4 Cataracts

Cataract formation was not detected in 29 patients. Assessment of cataract formation was incomplete in one patient who declined dilation.

3.2.5 Intraocular pressure

IOP was measured in 22 patients. Of the eight patients without documented IOPs, six were paediatric patients in whom IOP examination was deferred and two patients IOPs were not documented possibly due to patient discomfort. All pressures taken were within normal range. The median pressure in the right and left eye was 11.5mmHg and 11.0mmHg respectively.

3.2.6 Retinal Arteriosclerosis

Seventeen patients had fundus photography, but 16 were assessed as one was excluded due to hypertension.

Table 11: Demographic and clinical characteristics of patients with and without retinal arteriosclerosis

	Retinal arteriosclerosis (n= 9)	No Retinal arteriosclerosis (n= 7)	p-value
Age (years)	31 (22- 36)	13 (6- 17)	0.013
Males	4 (44%)	3 (43%)	0.949
Females	5 (56%)	4 (57%)	0.949
Race			
White	7 (78%)	4 (57%)	0.377
Indian	2 (22%)	3 (43%)	0.377
Afrikaner descent	7 (78%)	4 (57%)	0.377
Overt CAD	4 (44%)	1 (14%)	0.197
Other vascular surgery	0	0	N/A
Cholesterol-year score (mmol-year/L)	356.5 (218.3- 475.4)	149.0 (104.0- 280.8)	0.010
Total cholesterol (mmol/L)	12.1± 3.4	12.0± 2.8	0.946
LDL-C (mmol/L)	10.6± 3.3	10.5± 2.6	0.972
HDL-C (mmol/L)	0.9 (0.8- 1.4)	1.0 (0.9 - 1.1)	0.831

Patients with retinal arteriosclerosis were significantly older and had higher cholesterol-year scores than those without retinal arteriosclerosis. (Table 10)



Figure 3: Colour fundus picture of the right eye in a patient with grade two retinal arteriosclerosis

All patients with retinal arteriosclerosis had bilateral disease. Of the 9 patients with retinal arteriosclerosis, 4 (44%) had overt CAD. The maximum grade of retinal arteriosclerosis in patients with overt CAD was 2 compared to patients without overt CAD who had a maximum grade of 3.

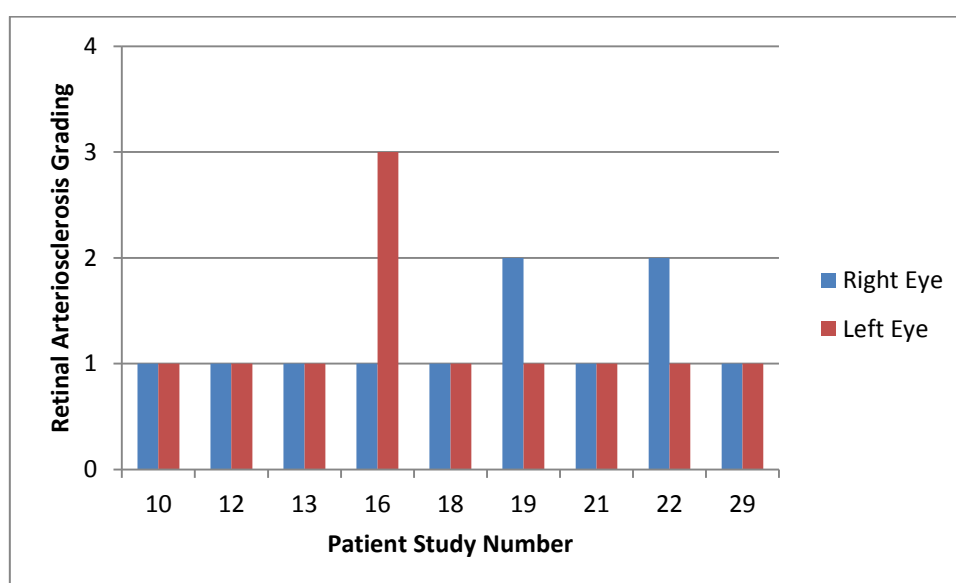


Figure 4: The retinal arteriosclerosis grade of patients with retinal arteriosclerosis

Table 12: Relationship between the maximum retinal arteriosclerosis grade and selected clinical characteristics

	Regression coefficient	p-value
Age	-0.388	0.302
Overt CAD	-0.254	0.51
Cholesterol-year score	-0.371	0.33
Total cholesterol	0.057	0.89
LDL-C	0.091	0.82
HDL-C	-0.447	0.23

The lack of colour fundus photographs in patients with other vascular surgery prevented the assessment of retinal arteriosclerosis. No significant relationships were found between the retinal arteriosclerosis grade and the above selected clinical characteristics.

3.2.7 Ocular Coherence Tomography

OCT images were captured on 22 patients. Eight of these patients were <18 years of age. The youngest patient was 6 years old and the oldest was 49 years old. Of the 8 patients in whom OCT images were not obtained, 4 patients were <18 years old.

3.2.8 Retinal Vein Occlusion

There was no evidence on clinical examination and OCT of present or previous episodes of retinal vein occlusion.

3.2.9 Retinal Artery Occlusion

There was no evidence of present or previous episodes of retinal artery occlusion in either eye in any patient.

3.2.10 Age-Related Macular Degeneration

Neither dry nor wet ARMD was detected in any eye on clinical examination and OCT (Figure 5).

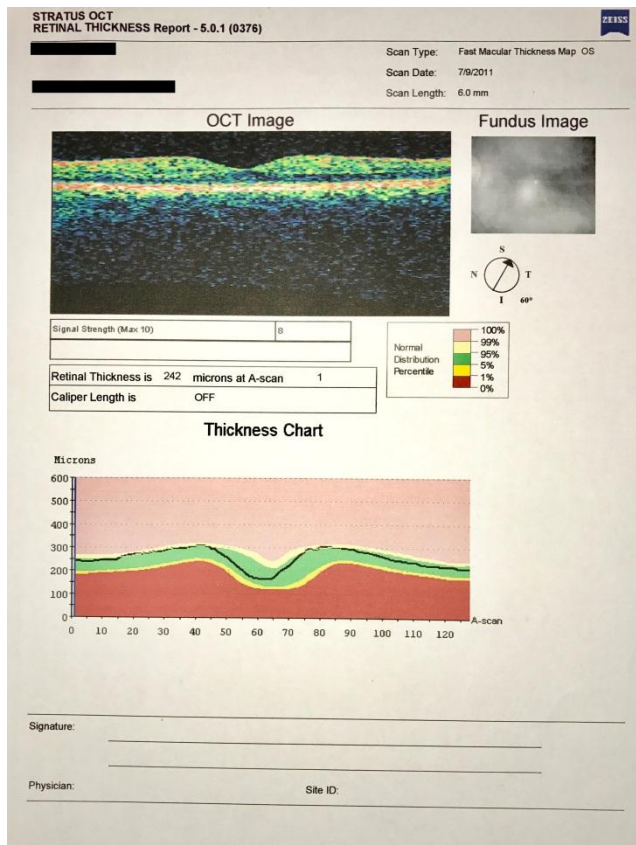


Figure 5: Normal OCT image

3.2.11 Hollenhorst Plaques

Hollenhorst plaques were not found in any patient.

3.2.12 Visual fields

Visual field testing was performed bilaterally in 23 patients. Nineteen patients had reliable visual fields either unilaterally or bilaterally. Five paediatric patients were not offered this test because of the level of understanding and concentration required to perform it reliably. Two adult patients refused testing.

Table 13: Demographic and clinical characteristics of patients with and without abnormal mean deviations on reliable visual field tests

	Unilateral/ bilateral reliable visual field/fields with abnormal mean deviation (n= 7)	Unilateral/ bilateral reliable visual field/ fields without abnormal mean deviation (n= 12)	p-value
Age (years)	13 (8- 42)	31 (19- 39)	0.237
Males	3 (43%)	7 (58%)	0.515
Females	4 (57%)	5 (42%)	0.515
Race			
White	5 (71%)	9 (75%)	0.865
Indian	2 (29%)	3 (25%)	0.865
Afrikaner descent	5 (71%)	9 (75%)	0.865
Overt CAD	1 (14%)	5 (42%)	0.216
Other vascular surgery	1 (14%)	5 (42%)	0.433
Cholesterol-year score (mmol-year/L)	206.7 (131.0- 450.7)	331.2 (262.0- 535.8)	0.052
Total cholesterol (mmol/L)	10.9± 3.7	12.4± 3.3	0.266
LDL-C (mmol/L)	9.5± 3.7	10.9± 3.2	0.301
HDL-C (mmol/L)	1.1 (0.8 - 1.1)	1.0 (0.8 - 1.3)	0.931

Of the 23 patients tested, 5 (22%) had a reliable right eye visual field test with an abnormal mean deviation and 5 (22%) had a reliable left eye visual field test with an abnormal mean deviation.

Table 14: Median and IQR of unilateral and bilateral abnormal mean deviations in each eye

	Median (IQR)
Right eye Abnormal Mean Deviation (n= 5)	-2.3 (-6.2- -2.2)
Left eye Abnormal Mean Deviation MD (n= 5)	-5.4 (-5.7- -4.4)

4. CHAPTER 4- DISCUSSION AND CONCLUSION

This study primarily sought to determine the ocular features in patients with homozygous familial hypercholesterolaemia attending the Lipid Clinic at CMJAH. Xanthelasma palpebrarum, corneal arcus, retinal arteriosclerosis and visual field defects were detected. Conjunctival xanthomata, cataracts, retinal vein occlusions, retinal artery occlusions, age-related macular degeneration and Hollenhorst plaques were absent. The majority of patients were Caucasian and of Afrikaner descent. This is in keeping with the founder effect elucidated by Seftal et al.³

Xanthelasma palpebrarum is commonly found on the upper lid.²⁴ However, in our study, it was found to occur more commonly on the upper and lower eyelids simultaneously. A male predominance was also noted. This differs from the lack of sex predilection noted in the literature.²⁵ The majority of unilateral cases were found to be right sided. Unilateral carotid plaques were found to be twice as common on the left rather than on the right ($p < 0.001$) in a large population based cohort, The Rotterdam Study.²⁶ The characteristics of carotid atherosclerotic plaque deposition was analysed using MRI imaging.²⁶ It would be of diagnostic value in our patients to determine whether laterality of xanthelasma palpebrarum correlates with carotid atherosclerotic deposition.

Xanthelasma palpebrarum was more common in older patients, men and those with overt CAD. Subanalyses examining the distribution of age in patients with xanthelasma palpebrarum and the distribution of age of the male xanthelasma palpebrarum patients as well as those with overt CAD showed that there was no significant difference between these groups. Therefore, even though xanthelasma palpebrarum was more prevalent in males and those with overt CAD, age could be a confounding factor.

The pathogenesis of xanthelasma palpebrarum seems to resemble the formation of atherosclerotic plaques.²⁴ This has stimulated research to determine whether xanthelasma can serve as a predictor of cardiovascular disease.^{25,27} A large Danish prospective study by Christoffersen et al showed that xanthelasma palpebrarum was able to determine the risk of ischaemic heart disease, severe atherosclerosis, myocardial infarction and death in the general population.²⁵ It was carried out from 1976/1978 up until May 2009. Being part of the Copenhagen City Heart Study, 12745 people were included in the study and 563 participants had xanthelasma palpebrarum at the initial examination. There was a 100% follow up. The diagnosis of myocardial infarction and ischaemic heart disease were determined and confirmed by analysing the national Danish Patient Registry for all hospital admissions, the national Danish Causes of Death Registry and evaluating hospital and general practitioner records.²⁵

Ozdol et al performed a case-control study between January 2002 and October 2004.²⁷ One hundred patients with xanthelasma palpebrarum were compared with 100 age and sex matched patients. The cardiovascular risk factors were comparable between the groups except that the patients with xanthelasma palpebrarum had a higher prevalence of hyperlipidaemia. Clinically overt cardiovascular disease was similar between the groups. History and a resting ECG were used to determine the presence of cardiovascular disease. This could have lead to underdiagnosis in asymptomatic patients with cardiovascular disease who did not perform strenuous daily activities or those with silent ischaemia. The use of a resting ECG for diagnosis may have missed patients with significant CAD or angina.²⁷

We found that overt CAD was more common in those with xanthelasma palpebrarum ($p= 0.011$). Xanthelasma palpebrarum is a grossly detectable sign that can be easily detected by a clinician and does not necessarily require an ophthalmologist to assist with diagnosis. Therefore its ability to identify patients at risk for CAD can help to reduce the cardiovascular morbidity and mortality associated with HoFH. We also found that all patients with bilateral xanthelasma palpebrarum had overt CAD ($p= 0.018$). This can be an additional factor for determining patients at risk for CAD.

Corneal arcus is a known peripheral corneal opacity associated with hypercholesterolaemia. A review article by Fernández et al credits Virchow as the first person to suggest that corneal arcus was a cardiac risk factor.⁹ However, this relationship has remained controversial.^{9,10} A large prospective study used the Framingham Heart Study Original Cohort and Offspring database.¹⁰ Of the 23376 people examined, 3890 had corneal arcus. Corneal arcus was found to be a predictor for cardiovascular and CHD. But this relationship was not sustained after an adjustment for age and gender. Corneal arcus was only diagnosed and graded on visual inspection without the use of a slit lamp. This may have contributed to under-diagnosis.¹⁰

A study of 17 homozygous familial hypercholesterolaemic patients by Zech and Hoeg found that the presence of corneal arcus correlated with the existence of calcific atherosclerosis.¹¹ The number of patients with corneal arcus (n=9) was small. We used their grading system to quantify the extent of corneal arcus in our study. They noted that patients with more extensive corneal arcus had more severe atherosclerosis.¹¹ We found that overt CAD was more common in those with corneal arcus. Therefore the presence of corneal arcus may be a marker for CAD. The statistically significant relationship between the grade of corneal arcus and overt CAD was not maintained after adjustment for age and gender.

The prevalence of corneal arcus in dyslipidaemic patients has been shown to strongly correlate with risk factors implicated in the development of various circulatory diseases.⁸ A study by Meyer et al, of 115 dyslipidaemic patients, revealed significantly higher levels of LDL-C, higher LDL-C: HDL-C ratios and lower levels of HDL-C in the subgroup of patients with corneal arcus.⁸ In comparison to our study there were a larger number of patients with corneal arcus (n=43) and all patients were treatment naïve.⁸ Our study revealed a slightly lower mean LDL-C level (p= 0.828) and total cholesterol level (p= 0.856) in those with corneal arcus. The median HDL-C levels (p= 0.535) were the same in patients with and without corneal arcus. We additionally used the cholesterol-year score as a clinical variable which was more than two times greater in patients with corneal arcus (p=0.016). The cholesterol-year score may have proved to be a more valuable predictor because it

correlates with the patients' lifetime exposure to elevated cholesterol levels whereas other lipid parameters are merely a reflection of the patients' cholesterol at a single point in time. The relationship between the corneal arcus grade and the cholesterol-year score was not statistically significant after adjustment for age and gender.

The gold standard for diagnosing CAD is coronary angiography. This intensive procedure is not indicated for patients considered at early risk for CAD.²⁸ Retinal microvasculature can be viewed much more easily. This has fueled research into finding correlations between retinal vessel abnormalities and CHD in the hope of easily identifying and stratifying patients with CHD.^{28, 29} Our colour fundus photographs were graded by a retinal specialist. We found no significant relationship between the presence or grade of retinal arteriosclerosis and CAD. However, the grading of retinal vasculature in an Australian population based study, The Blue Mountains Eye Study, revealed that a reduced arteriolar calibre and reduced arteriole to venule ratio (AVR) was associated with a greater risk of CHD related death in women only.³⁰ A larger venule calibre was associated with a greater risk of CHD related death in both sexes.³⁰ Their study was strengthened by the use of a computer based program to determine the calibre of vessels and the AVR.³⁰ This objective measure of the retinal vasculature and the examination of additional parameters such as venule calibre and AVR can be used in future studies to help elucidate this relationship in our study sample. A larger population based study in the United States of America, The Atherosclerosis Risk in Communities Study, found that retinal arteriolar and venular calibres correlated with CHD in women.³¹ The postulation that microvascular disease is more severe in women thus garners momentum.³⁰ Of note, the additional use of retinal vessel calibre to determine the atherosclerotic cardiovascular disease event risk changed 21% of women from a low risk category to an intermediate risk category.³¹ This has substantial clinical implications and thus provides impetus to delve further into this relationship.

We noted abnormalities in mean deviation on visual field testing in some patients. There were no associated abnormal IOPs or glaucomatous changes of the optic nerve head. Therefore, these changes may be suggestive of abnormalities in the cortical processing of

visual stimuli in hypercholesterolaemic patients.¹⁸ A wide range of statistically significant visual field abnormalities (mean deviation, pattern standard deviation, short-term fluctuation, corrected pattern standard deviation and foveal threshold) were detected in a case control study, on treatment naïve patients, conducted by Alcalá et al.¹⁸ Our patients were not treatment naïve and statin usage has proved beneficial in improving visual field defects due to hypercholesterolemia.³² The study by Alcalá et al consisted of a larger study population and patients performed visual field tests twice to improve the reliability of the test.¹⁸ Based on our study, further research is required to assess other perimetry values. The reproducibility and progression of found defects also needs to be evaluated on repeated visual field testing.

The major confounder in our study was that all patients were on statin therapy. Statins have been noted to increase the velocity and flow in retinal arteries and veins³³, significantly decrease IOP³³, decrease the risk of cataract formation³⁴ and have protective effects in age-related macular degeneration³⁵. The major limitation of the study was the small sample size. This was accounted for by the rarity of the disease³. Pooling data from the other Lipid Clinic based at Groote Schuur Hospital may improve the statistical power of future studies. A weakness of the study was that there was no masking in the grading of corneal arcus photographs, interpretation of visual fields and interpretation of OCT images as it was done by the primary investigator. However, retinal arteriosclerosis was graded by a retinal expert who was unaware of the patient's medical history and clinical examination.

In conclusion, ischaemic heart disease is a leading cause of death⁶ and thus remains a focus for ongoing research. The prevalence of HoFH in South Africa afforded us the unique opportunity of studying the ocular features in this rare subset of patients. Our patients, all of which were <50 years of age, displayed well-known ocular features of hyperlipidaemia such as xanthelasma palpebrarum, corneal arcus and retinal arteriosclerosis. In addition, we detected visual field defects. Xanthelasma palpebrarum, particularly when bilateral, and corneal arcus were common in patients prevalent with overt CAD. These non-invasive clinical signs may prove to be an invaluable tool in reducing the burden of CAD.

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6. APPENDIX A: ETHICS CLEARANCE CERTIFICATE

M110313

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Adisha Goberdhan

CLEARANCE CERTIFICATE

M110313

PROJECT

Ocular Findings in Patients with Homozygous
Familial Hypercholesterolaemia

INVESTIGATORS

Dr Adisha Goberdhan.

DEPARTMENT

Division of Ophthalmology

DATE CONSIDERED

25/03/2011

DECISION OF THE COMMITTEE*

Approved unconditionally

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

DATE 13/05/2011

CHAIRPERSON
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Professor Trevor Carmichael

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...

7. APPENDIX B: INFORMATION SHEET FOR PATIENTS ATTENDING THE LIPID

CLINIC AT CMJAH

Dear Patient

My name is Dr Adisha. I am currently training to be an eye specialist. I am doing a study to find out what eye changes are associated with high cholesterol levels. High cholesterol levels can cause changes to the eye. This study will help doctors know which changes to look for in patients with high cholesterol levels. It will also allow health workers to identify signs that may be associated with increased cholesterol levels so that the disease can be picked up earlier and treatment can be started.

The study will be performed at the Johannesburg Hospital. The examination will be as follows:

- You will read letters off a chart that is placed at a distance. This allows us to assess how well you can see.
- I will perform a routine eye examination looking at the different parts of the eye.
- The pressure within the eye will be measured. This will not be painful.
- Your pupil (central black part of the eye) will be enlarged with the use of eye drops so that the back of the eye can be adequately seen. We recommend that you should not drive or engage in hazardous activities when your pupil is dilated. Transport will be arranged for your convenience.
- Colour pictures and photographs of the eye will be taken.
- A test will be done to assess your field of vision.

Taking part in the study is voluntary (your choice). Your management will not be affected if you choose not to be part of the study. If your decision to participate changes, you are free to leave the study at any time. The results of this study are intended to be presented at a

conference and to be published. Your identity, examination findings and blood results will remain confidential.

If you have any questions or concerns, please contact me, Dr Adisha Goberdhan, on 0787573050.

8. APPENDIX C: INFORMATION SHEET FOR PARENTS/ LEGAL GUARDIANS OF CHILDREN ATTENDING THE LIPID CLINIC AT CMJAH

Dear Parent/ Legal Guardian

My name is Dr Adisha. I am currently training to be an eye specialist. I am doing a study to find out what eye changes are associated with high cholesterol levels. I would like to invite your child to be part of this study.

High cholesterol levels can cause changes to parts of the eye. This study will help doctors know which changes to look for in patients with high cholesterol levels. It will also allow health workers to identify signs that may be associated with increased cholesterol levels so that the disease can be picked up earlier and treatment can be started.

The study will be performed at the Johannesburg Hospital. The following examination will be performed:

- Your child will read letters off a chart that is placed at a distance. This allows us to assess how well he/she can see.
- I will perform a routine eye examination looking at the different parts of the eye.
- The pressure within the eye will be measured. This will not be painful.
- Your child's pupil (central black part of the eye) will be enlarged with the use of eye drops so that the back of the eye can be adequately seen. We recommend that your child should not be involved in dangerous activities when their pupil is dilated.
- Colour pictures and photographs of the eye will be taken.
- A test will be done to assess their field of vision.

You are free to choose whether or not you would like your child to participate in this study. The management of your child will not be affected if you decide that he/she should not be

part of this study. You are free to remove your child from the study at any time. The examinations required to carry out this study are once off and a follow up visit is not necessary. However, your child will be followed up at the eye clinic if any abnormality that is found requires monitoring and/or investigation. The results of this study are intended to be presented at a conference and to be published. Your child's identity, examination findings and blood results will remain confidential.

If you have any questions or concerns, please contact me, Dr Adisha Goberdhan, on 0787573050.

9. APPENDIX D: INFORMATION SHEET FOR CHILDREN ATTENDING THE LIPID CLINIC

Hello, my name is Dr Adisha. I am training to become an eye specialist. I am studying patients who have high cholesterol levels to learn more about how cholesterol affects the eye. I would like you to be part of my study.

The study will be performed at the Johannesburg Hospital. The following examination will be performed:

- You will read letters off a chart. This tells us how well you can see.
- I will look at the different parts of your eyes in detail. During this examination you will be seated. I will need you to sit still and look straight ahead.
- The pressure within your eye will be measured. This will not be painful.
- Eye drops will be used to make your pupil (round, black part in the centre of the eye) bigger so that the eye can be properly examined. Your eye sight will be blurry when your pupil is enlarged.
- Colour pictures and photographs of your eye will be taken.
- A test may be done to assess how well you can see lights coming from the side while looking ahead.

The study has been discussed with your parent/ legal guardian. They have decided to allow you to participate in this study. However, you can still choose whether or not you would like to be part of the study. Your treatment will not be affected if you choose not to be part of the study. All information will be kept confidential.

If you have any questions or concerns, please feel free to contact me on 0787573050.

10. APPENDIX E: CONSENT FORM FOR PATIENTS

I, _____

hereby agree to be a part of this study. I have read and understood the information sheet provided to me. I am aware that participation in this study is voluntary and that I can leave this study at any time.

_____	_____	_____
Name	Signature	Date

_____	_____	_____
Doctors Name	Signature	Date

_____	_____	_____
Witness	Signature	Date

11. APPENDIX F: CONSENT FOR PARENTS/ LEGAL GUARDIANS

I, _____

hereby agree that my child,

can be a part of this study. I have read and understood the information sheet provided. I understand that participation in this study is voluntary and that my child can leave this study at any time.

Name of parent/ legal guardian

Signature

Date

Name of study doctor

Signature

Date

Witness

Signature

Date

12. APPENDIX G: ASSENT FORM FOR CHILD PARTICIPANT

I, _____

agree to be part of this study. The study has been explained to me and I understand the tests that will be performed on me. I have read or have had explained to myself, the information contained in the information sheet.

_____	_____	_____
Name	Signature/Thumbprint	Date

_____	_____	_____
Doctors Name	Signature	Date

_____	_____	_____
Witness	Signature/Thumbprint	Date

13. APPENDIX H: DATA CAPTURE SHEET

Participant number:

Date (dd/mm/yyyy): **Time:** **Date of birth (dd/mm/yyyy):**

Race: White ☐ (Afrikaner Descent Y/N) Indian ☐ Black ☐ Coloured ☐

Gender: Female ☐ Male ☐

Past medical history: Myocardial infarction ☐ Angina ☐ Heart failure ☐ CVA ☐ TIA ☐

Coronary artery bypass grafting ☐ Coronary stent/ angioplasty ☐ Carotid surgery ☐

Other vascular procedure/surgery: Y/N

If yes, list the procedure: _____

Treatment:

Type of Medication	Patients Treatment			Dose of Medication	Duration of Treatment (months)
1. Statins	1	2	9		
2. Fibrates	1	2	9		
3. Bile acid sequestrant	1	2	9		
4. Ezetimibe	1	2	9		
5. Niacin	1	2	9		
6. Other	1	2	9		

1= Yes 2= No 9= Information is missing

Examination findings:

Right eye		Left eye
	Visual acuity Pinhole visual acuity	
Xanthelasma Y/N	Eyelids	Xanthelasma Y/N
Xanthomata Y/N	Conjunctiva	Xanthomata Y/N
Corneal arcus Y/N If Yes Grade:	Cornea	Corneal Arcus Y/N If Yes Grade:
	Anterior chamber	
	Iris	
	Pupil	
Lens opacity Y/N If yes 1/2/3/4 1= Cortical cataract 2= Nuclear cataract 3= Subcapsular cataract 4= Other	Lens	Lens opacity Y/N If yes 1/2/3/4 1= Cortical cataract 2= Nuclear cataract 3= Subcapsular cataract 4= Other
	Goldman applanation tonometry	
	Vitreous	
RVO Y/N If yes 1= Branch retinal vein occlusion 2= Central retinal vein occlusion RAO Y/N If yes 1= Branch retinal artery occlusion 2= Central retinal artery occlusion AMD Y/N If yes 1= Dry AMD 2= Wet AMD Retinal arteriosclerosis Y/N If yes:	Fundoscopy	RVO Y/N If yes 1=Branch retinal vein occlusion 2= Central retinal vein occlusion RAO Y/N If yes 1= Branch retinal artery occlusion 2= Central retinal artery occlusion AMD Y/N If yes 1= Dry AMD 2= Wet AMD Retinal arteriosclerosis Y/N If yes

1= Grade 1 2= Grade 2 3= Grade 3 4= Grade 4 Hollenhorst plaque Y/N *Other findings:		1= Grade 1 2= Grade 2 3= Grade 3 4= Grade 4 Hollenhorst plaque Y/N *Other findings:
Reliable Y/N MD: PSD: CPSD:	Visual field findings	Reliable Y/N MD: PSD: CPSD:
	OCT findings	

MD= Mean deviation

PSD= Pattern standard deviation

CPSD= Corrected pattern standard deviation

Blood results:

Total Cholesterol	
LDL	
HDL	
Triglycerides	

*Description of the disc and macula were documented under other findings.

14. APPENDIX I: PLAGIARISM FORM



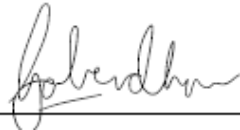
PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Adisha Goberdhan (Student number: 376017) am a student registered for the degree of MMed in Ophthalmology in the academic year 2016.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: 

Date: 12 December 2016

15. APPENDIX J: TURNITIN ORIGINALITY REPORT

Turnitin3.docx			
ORIGINALITY REPORT			
% 10	% 5	% 8	% 1
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS
PRIMARY SOURCES			
1	Andersen, R. Brot, C. Mejbørn, H. Molgaa. "Vitamin D supplementation does not affect serum lipids and lipoproteins in Pakistani immigrants.(SHO", European Journal of Clinical Nutrition, Sept 2009 Issue Publication	% 1	
2	Raal, Frederick J., and Raul D. Santos. "Homozygous familial hypercholesterolemia: Current perspectives on diagnosis and treatment", Atherosclerosis, 2012. Publication	% 1	
3	Submitted to Queen Mary and Westfield College Student Paper	% 1	
4	S. Vurgese. "Corneal Arcus and Its Associations with Ocular and General Parameters: The Central India Eye and Medical Study", Investigative Ophthalmology & Visual Science, 12/20/2011 Publication	% 1	
5	Vitreous, 2014. Publication	<% 1	