The Prevalence and Severity of Retinopathy in Patients with Coronary Artery Disease at a Tertiary Hospital in Durban, South Africa.

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As the candidate's supervisor, I have approved this thesis for submission

Signed: D P Naidoo 2nd Sept 2021

I, Dr Johannes Frederik de Jager, declare as follows:

1. That the work described in this dissertation has not been submitted to UKZN or any other institution for the purposes of an academic qualification, whether by myself or any other party.

2. That my contribution to the project is as follows:

    a. To coordinate this multidisciplinary project and undertake the ophthalmological procedures in this research,
    b. Taking informed consent, explaining to patients the findings of their eye exam and where appropriate providing referral letters for further follow up or urgent treatment.
    c. Taking of intraocular pressure measurements.
    d. Assisting with visual acuity measurements and pupillary dilation,
    e. Taking of photos with the Zeiss fundus camera, OCT measurements with the Cirrus OCT machine, interpretation and classification of retinopathy findings as per fundus photos and OCT measurements.
    f. Interaction with the statistician, discussing analysis and results.
    g. Research into the relevant topic and writing up of the literature review and manuscript for publication purposes.

3. That the contributions of others to the project are as follows:

    a. Dr Ponnusamy, Clinical Head of the Department of Cardiology at IALCH: for contributing in finding the appropriate patient sample for the study purposes and ensuring the safety of post coronary angiography patients while undergoing ophthalmological assessment.
    b. Dr Linda Visser, Head of Department of Ophthalmology at IALCH: for simplifying retinopathy sub-classification, adding the OCT

measurements and intraocular pressure readings to the study, and for continuous research insight, support and motivation throughout the registrar program.

c. Prof DP Naidoo, Head of Department of Cardiology at IALCH: many thanks go to my supervisor for his continuous support, encouragement, vital input and contribution in making this project a success.

Signed Date: 2nd Sept 2021

Dedication

To my wife Gabi for her continuous support and patience and my children, Kay, Jan-Louis and Mia.

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List of Abbreviations and Acronyms

ACCESS - Acute Coronary Events - a multinational Survey of current management Strategies

ACCF - American College of Cardiology Foundation

AHA - American Heart Association

ACS - Acute coronary syndrome

ASRD - age-standardized related death

ARIC - Atherosclerosis risk in community

BRVO – branch retinal vein occlusion

CABG - Coronary artery bypass graft

CAD - Coronary artery disease

CKD – Chronic kidney disease

CMT – Central macular thickness

CRIC - chronic renal insufficiency cohort

CSA – Chronic stable angina

CSMO – Clinically significant macular oedema

CVD - Cardiovascular disease

DR – Diabetic retinopathy

DVD – Double vessel disease

ETDRS - Early treatment in diabetic retinopathy study

ETODH - Evaluation of target organ damage in hypertension

FAZ – Foveal avascular zone

GCL – Ganglion cell layer

Hb – Haemoglobin

HDL – High density lipoprotein

HR – Hypertensive retinopathy

IALCH – Inkosi Albert Luthuli Central Hospital

ICU – Intensive care unit

IRMA – Intra-retinal microvascular abnormalities

LDL – Low density lipoprotein

MA – Microalbuminuria

Mets – Metabolic syndrome

MVD – Multivessel disease

NCDs - Non-communicable diseases

NCEP-ATP - National Cholesterol Education Program Adult Treatment Panel

NPDR – Non-proliferative diabetic retinopathy

NSTEMI – Non-ST segment elevation myocardial infarction

OCT – Optical coherence tomography

PDR – Proliferative diabetic retinopathy

RNFL – Retinal nerve fibre layer

RVO – Retinal vein occlusion

SD – Standard deviation

STEMI – ST segment elevation myocardial infarction

SVD – Single vessel disease

TVD – Triple vessel disease

UA – Unstable angina

YLL - Years of life lost

Table of contents

Index of tables

Index of figures

Overview of the thesis

Background

Studies have described the prognostic value of retinopathy in coronary artery disease (CAD) but few have examined the relationship between retinopathy and the CAD severity.

Aim

The study investigated the prevalence of retinopathy in CAD patients [acute coronary syndrome (ACS) and chronic stable CAD] and determined the association of retinopathy and other clinical factors with the extent of coronary artery disease as assessed by the number of epicardial vessels involved.

Methods

A cross sectional prospective study of 121 in-patients was undertaken over a ten-month period at Inkosi Albert Luthuli Central Hospital. One hundred and nine patients (12 stable CAD, 97 acute coronary syndrome) had angiographically confirmed CAD and the remaining 12 patients with normal angiograms served as controls. All participants had a comprehensive systemic evaluation and fasting biochemistry. Retinopathy was assessed using five to seven wide field fundus photographs. Macular thickness, vessel density and macular perfusion were assessed with optical coherence tomography (OCT) and OCT angiography.

Results

Compared to subjects with normal angiograms (controls), those with CAD had more frequent diabetes (67.9% vs 16.7%, $p<0.001$). Triple vessel disease (TVD) was present in 43.4% of diabetic patients compared to 35.6% of non-diabetics ($p=0.004$). Multivessel involvement was more frequent in diabetics (79%) compared to non-diabetics (58%), ($p=0.002$).

The prevalence of any form of retinopathy was 66% in the CAD group and 33% in the control group (p=0.026). Subjects with double vessel disease (DVD) were more likely to have any form of retinopathy (77.8%) compared to those with single vessel disease (65.2%) and triple vessel disease (59.2%) (p=0.027).

Diabetic retinopathy (DR) was present in 34 subjects (31.2%) in the CAD group and one subject (8.3%) in the control group (p=0.097). The majority of CAD patients with DR had non-proliferative diabetic retinopathy (NPDR) (n=29, 85.3%) and five (14.7%) had proliferative diabetic retinopathy (PDR). Patients with CAD and DR were more likely to have microalbuminuria compared to those without CAD and DR (p=0.014). An irregular foveal avascular zone (FAZ) was more frequent in the subgroup of CAD with diabetes (n=15) compared to the CAD without diabetes (n=1) group (21.3% vs 2.9%, p=0.013). In bivariate analysis, diabetes was strongly associated with having CAD and any form of retinopathy (OR = 0.238, CI = 0.109-0.517, p<0.001).

Hypertensive retinopathy was present in 43 (40.2%) subjects in the CAD group and three (25%) in the control group (p=0.306). More than 60% of the CAD patients with HR had grade 2 retinopathy; only one CAD subject had grade 3 HR. Subjects with CAD and hypertensive retinopathy were more likely to be between the ages of 55-64 years (41.9%, p=0.016), to be smokers (p=0.034) and have the metabolic syndrome (p=0.004).

Conclusion

Retinopathy was a frequent finding in this sample group of predominantly ACS subjects and was associated with clustering of the major risk factors. The presence of DR, microalbuminuria and foveal abnormalities in diabetic subjects with CAD suggest underlying coronary microvascular disease. This study calls for surveillance of subjects with retinopathy to detect the presence of CAD.

Keywords: Retinopathy; diabetic retinopathy; hypertensive retinopathy; coronary artery disease.

CHAPTER 1

REVIEW OF THE LITERATURE

Introduction

Many patients seen at McCord Provincial Eye Hospital present with diabetes and hypertension and related ophthalmological complications. Many resources, effort and time are spent on these diseases. Due to this burden of disease at our facility other co-morbid non-communicable diseases (NCDs) can go unnoticed. These conditions for example include ischemic heart disease, dyslipidemia and obesity. Patients with diabetes and hypertension related eye problems often present at a late stage when visual rehabilitation is not always possible, and our efforts are focused on preventing further visual regression. Often these patients report a recent missed follow up visit due to ill-health/admission which is frequently related to uncontrolled hypertension and diabetes or cardiovascular problems such as a heart attack or stroke. When these patients present late with microvascular related complications to our department, we ask ourselves: do they also present with established micro- or macrovascular pathology to other specialist disciplines? What is the relationship between these inter-disciplinary micro- and macrovascular complications?

A more important question is how can we as specialist physicians better contribute in more effective ways to prevent these morbid complications of common NCDs, whether from an ophthalmologist or non-ophthalmologist point of view? As specialists we need to shift our attention more towards prevention rather than just the crisis at hand. This also highlights the need for multidisciplinary patient management in an already overburdened health care system across most health facilities. Are there established interdisciplinary referral trends amongst specialists in our country or is it the primary care physicians' responsibility to refer only when a symptom might indicate a soon-to-

be morbidity or even worse mortality? Is there a link between these micro- and macrovascular manifestations of common diseases that can bridge the gap between different disciplines and help to prevent morbidity and mortality in a high-risk community?

These are some of the issues that led to the formulation of this study.

Literature review

1. Non-communicable diseases

The global burden of non-communicable diseases (NCDs) is well described. In 2016 NCDs accounted for 71% of deaths worldwide. Eighty percent of these were due to cancer, cardiovascular disease (CVD), chronic respiratory disease and diabetes. Cardiovascular disease alone accounts for 44% and diabetes for 4% of NCD related deaths (1). The highest risk of dying from an NCD was observed in low- income and middle-income countries, especially in sub-Saharan Africa. It is projected that the number of deaths from NCDs will overtake infectious disease deaths in sub-Saharan Africa by 2035 (2). In South Africa NCDs are estimated to account for 39% to 51% of all deaths. Nineteen percent of these deaths are due to CVD and seven percent due to diabetes. Globally diabetes accounts for almost ten percent of all-cause mortality. The highest proportion of all deaths attributable to diabetes occurring before the age of 60 is in Africa.

2. Diabetes and Hypertension

The global prevalence of diabetes between the ages of 20 to 79 years is 8.8%. Globally, nearly two thirds of diabetics live in urban environments and 79% live in low- and middle-income countries (3). A systematic analysis in 2018 revealed that the prevalence of diabetes has almost doubled from five and a halve percent in 2000 to nine percent in 2009 in South Africa. Demographically the age-standardised prevalence of diabetes is ten percent higher in non-white population groups and almost twice as high as the

average in the Indian/Asian South African population (4, 5). As a consequence, this high prevalence will be accompanied by an increase in diabetes related micro- and macrovascular complications including retinopathy, renal failure and heart disease.

Hypertension is a major NCD that frequently accompanies and complicates diabetes. Despite worldwide population control strategies, the prevalence of hypertension is increasing. It is estimated that more than 30% of the adults worldwide have hypertension. With recent new definitions of hypertension it is expected that the prevalence of hypertension in American adults will increase by 13.5% to 45.6% (6).

According to a systematic analysis of 90 countries there is a disparity in the prevalence of hypertension between low-, middle- and high-income countries. The percentage is slightly lower, 28.5%, in high-income countries and slightly higher, 31.5%, in low- and middle-income countries (7). This is even more prominent in Africa where the prevalence ranges from 54% to 60.5% (8, 9). Amongst low- and middle-income countries South Africa has the highest prevalence in the age group above 50 years with 79% diagnosed with hypertension (10). Local studies in KwaZulu-Natal have found the prevalence of hypertension to be 33.9% and 47.5% in peri-urban rural and Indian communities respectively (11, 12).

The increase in NCDs is a major concern globally and more so in sub-Saharan African countries like South Africa. Hypertension and diabetes are major risk factors for CVD, accounting for higher rates of these NCDs in patients with CAD. In a large meta-analysis of 122000 patients Mahtta et al found the prevalence of hypertension amongst CAD patients ranging from 30% to 70% across 14 international countries (13). Similarly, the prevalence of diabetes amongst out-patient CAD individuals ranges from 17% (East Europe) to 60% (Middle-East) (14). Another systematic review found the prevalence of diabetes amongst patients with occlusive and non-occlusive CAD to be 22% to 15% respectively (15). There is sparse data on these conditions amongst CAD subjects in South Africa. The ACCESS registry surveyed data across several cardiology practices in South Africa. It found that 55.6% of South Africans with CAD had hypertension and 23.9% had diabetes (16). One can conclude that both hypertension and

diabetes frequently coexist in subjects with CAD, either contributing and/or co-existing as causative factors to the macrovascular manifestations of CAD.

3. Coronary artery disease

a. Prevalence

Globally, more than eight million people have CAD (17). In the United States the overall prevalence of CAD was seven percent and this correlates with the five- and ten-year incidence of CAD in European countries of 4.7% and seven percent respectively (18-20). Although CAD is generally considered as an insignificant cause of morbidity and mortality in sub-Saharan Africa (21) the prevalence of CAD is on the rise owing to trends in urbanisation, changes in lifestyle and advances in healthcare technology. In South Africa early surveys have found the prevalence rate of CAD has risen from a low of 0.01% in the 1950s at Baragwanath hospital to 0.6% and 1.4% in other studies in 1970 in Johannesburg and Cape Town respectively. The prevalence of CAD in patients admitted to King Dinizulu hospital in Durban was found to be 2.4% in 1986 (22-25). More recent studies looking at the South African black population found that the prevalence of CAD in those with newly diagnosed CVD was six percent and in those presenting to a hospital with heart disease was ten percent (26, 27). A epidemiological study of CAD in sub-Saharan Africa concluded that the exact prevalence of CAD remains unknown but that the mortality rates of CAD are on the rise (28).

b. Morbidity and mortality

Globally, cardiovascular disease is one of the five leading causes of years of life lost (YLL). CAD was found to be the leading cause of total YLL in 113 countries for men and 90 countries for women between 1990 and 2010 (29). CAD is the leading cause of cardiovascular mortality worldwide, with more than four and a half million deaths occurring in the developing world. The mortality associated with CAD as a cause of death varies across regions. The age-standardised death rate for CAD has declined in Western countries and high-income countries but has increased in Eastern Europe, South Asia, Central Asia and East Asia (30). It is estimated that both CAD mortality and the prevalence of CAD risk factors will continue to rise in developing countries. In 2004 Okrainec projected that CAD mortality rates would double from 1990 to 2020,

with approximately 82% of the increase attributable to the developing world (30) and this has largely been proven to be due to lifestyle changes (31).

Of concern is that the mortality is high among certain ethnic groups. The South African Asian population had distinctively high age-standardised related deaths (ASRDs) for CAD and renal disease in 2010. The ASRD for CAD were almost twice as high as in other population groups in SA and this has been attributed to the high prevalence of the major cardiovascular risk factors in this group (1,32).

c. Diabetes and coronary artery disease comorbidity

People with diabetes are two to three times more likely to have CVD than those without (33). Every year 14 to 47 per 1000 people with diabetes between the ages 50 to 69 living in high to low-income countries have a CVD event. Of these 2 to 26 per 1000 are CAD events. Among people aged between 51 to 69 years with type 1 and type 2 diabetes, the prevalence of CAD ranges from 12% to 31.7% respectively (34). Patients with diabetes are known to have premature CAD, greater severity and extent of the disease, and higher associated morbidity and mortality. Diabetic subjects with retinopathy are also at higher risk for CAD (35, 36).

4. Retinopathy

a. Definition of retinopathy

Retinopathy includes any disease of the retina. Most commonly retinopathy is related to an underlying systemic vascular disease such as hypertension and diabetes manifesting as a microvascular complication (37). Retinopathy classification systems have been well described. Two classification systems describe hypertensive retinopathy (HR). These are the Keith-Barker-Wagener (KBW) and the more recent Mitchell-Wong classification systems (38).

According to KBW, HR is classified into grade 1 to 4. Grade 1 includes mild arterial narrowing, arterial tortuosity and arterial sclerosis. Grade 2 describes definite arterial narrowing, arterial sclerosis, arterial focal narrowing and arterio-venous nipping/nicking. Grade 3 involves copper/silver wiring, cotton wool spots and/or retinal

haemorrhages together with signs of grade 2 and grade 4 describes grade 3 plus papilloedema and retinal edema. The Mitchell-Wong classification has added a cardiovascular risk correlation to the grade of retinopathy but both classifications have been found to be reliable and effective (39).

Table 1 : The Keith-Barker-Wagener hypertensive retinopathy classification (This classification is based on the level of severity (Grade 1 to 4) of the retinal findings)

Grade	Classification	Symptoms
Grade 1 (mild hypertension retinopathy)	Mild generalised retinal arteriolar narrowing or sclerosis	No symptoms
Grade 2 (more marked hypertension retinopathy)	Definite focal narrowing and arteriovenous nipping. Exaggerated arterial light reflex	Asymptomatic
Grade 3	Retinal haemorrhages, exudates and cotton wool spots.	Symptomatic
Grade 4	Severe grade 3 and papilloedema	Reduced survival

Table 2. Classification of hypertensive retinopathy by Wong and Mitchell
(This classification indicates the risk of a systemic event associated with each grade.)

Grade	Description	Systemic associations
No retinopathy	No detectable retinal signs	None
Mild retinopathy (retinal arterial signs only)	One or more of the following arteriolar signs: • Generalised arterial narrowing • Arteriovenous nipping • Focal arteriolar narrowing • Arteriolar wall opacity	Modest association with risk of clinical stroke, coronary heart disease, and mortality
Moderate retinopathy	One or more of the following • Haemorrhage • Microaneurysms • Cotton wool spots • Hard exudates	Strong association with risk of clinical stroke, subclinical stroke, cognitive decline, and cardiovascular mortality
Malignant retinopathy	Moderate retinopathy plus optic disc swelling	Strong association with mortality

The classification of diabetic retinopathy (DR) dates back to 1968 and the same system has been used since. Although slightly modified the early treatment of diabetic retinopathy study has been effective and reliable for the last 50 years (40). Diabetic retinopathy is divided firstly into non-proliferative DR (NPDR), proliferative DR (PDR) and advanced DR. NPDR is further subclassified into very mild, mild, moderate, severe and very severe NPDR. The signs range from micro-aneurysms, splinter (retinal nerve fibre layer) hemorrhages, exudates, intra- and subretinal hemorrhages to intra-retinal microvascular abnormalities (IRMA) and venous changes (beading, segmenting and sausaging) and also depends on the extent of quadrants of retina effected. Proliferative diabetic retinopathy shows any sign of neovascularization. This is further classified into mild to moderate versus high-risk PDR.

b. Diabetic retinopathy and hypertensive retinopathy screening

According to the Standards of Diabetes Care 2019 type 1 diabetics need to be screened for retinopathy within 5 years of diagnosis. Type 2 diabetics should be screened within 1 year of diagnosis. Thereafter every patient should be screened annually or according to the retinopathy found (41). The Gold standard for screening still remains 7-field fundus photography (42). Many countries are adopting a systematic approach where more intensive mass screening tries to ensure the whole diabetic population is screened. This is in contrast to the historical opportunistic approach where patients are screened as they present to health facilities. Despite these established protocols studies show that less than 50% of patients meet these screening guidelines (43-44). A systematic review revealed that socioeconomic deprivation was a major risk factor for non-attendance and linked to sight threatening DR (45).

There are no HR screening guidelines in practice internationally. Grade 1 and 2 HR has a high prevalence. Although hypertension can be a causative factor for retinal vein occlusions the current trend is to treat these ophthalmic complications as they present. The treatment for HR still remains treating the underlying systemic problem as compared to DR treatment which includes laser photocoagulation or intravitreal anti-

vascular endothelial growth factor and/or intravitreal corticosteroid treatment with the purpose to improve, stabilize and minimize further vision loss.

c. Prevalence of retinopathy

According to a systematic review in 2012 the overall global prevalence of any DR is 34.6% excluding countries from the Middle East, Africa, or South America (46). In another study the prevalence ranges between 10-50% depending on method used, age, population (hospital vs population based) and duration of diabetes (47). A recent review estimated that the number of people with DR and vision threatening DR will rise to 191 million and 56.3 million respectively by 2030 (48). Diabetic retinopathy prevalence in developing countries was found to be over 35% (49).

A South African multiethnic photography-based study has shown higher prevalence across ethnic groups (Black African 37%, Europeans 41%, and Indians 37%); with severe retinopathy more frequently seen in African and Indian groups (50). The prevalence depended on the region and the population sampled. In a hospital-based South African population study, Motala et al. (51) found a much higher prevalence of 56% for any DR and 17% for proliferative DR. Black patients showed a DR prevalence of 55.6% and Indian patients 45.5% in those with type 1 diabetes of longer than 10 years' duration. A randomised trial at primary care level in the Tshwane district documented a prevalence of 29% for any DR and 26% for diabetic maculopathy amongst referred diabetics. This study however found that the screening for diabetes related complications was suboptimal with only 8.2% of diabetics referred (52). A similar cross sectional study in the Western Cape found a slightly higher prevalence of 32% with 8.9% having sight-threatening DR (53). At tertiary care level the prevalence of any DR in South Africa was found to be 39% (54).

Hypertensive retinopathy (HR) prevalence rates also vary according to the population sampled. Recent studies looking at the prevalence describe high risk older population groups and its association with other comorbidities. In the Wisconsin 'hypertensive retinopathy and risk of stroke study' Ong et al found the prevalence to be 51% in 2907 hypertensive cohort patients from the Atherosclerosis Risk in Community (ARIC) study (55). In Korea the prevalence was found to be 61.3% in a cardiology patient group (56).

Erden et al found that 66.3% of outpatients in an internal medicine department in Istanbul, had HR (57). The Evaluation of Target Organ Damage in Hypertension (ETODH) study found the prevalence as high as 78% in European patients (58).

The presence of risk factor clustering appears to have an influence on the prevalence of DR. The prevalence of DR is found to be higher in patients with metabolic syndrome (Mets) than those without (59, 60). There is also a strong link between microalbuminuria (MA) in type 2 diabetes and metabolic syndrome and CVD related morbidity and mortality (61-63). Kim et al reported that the prevalence of DR and CAD was higher in type 2 diabetes with MA than those without (61). These authors found that the progression rate to overt proteinuria was higher in the MA with retinopathy group than the MA without retinopathy group. In patients with chronic kidney disease (CKD), a subgroup of the chronic renal insufficiency cohort study (CRIC), retinopathy was associated with increased risk of developing CVD (64). Similarly, Ricardo et al found that retinopathy in CKD was a strong predictor of all cause- and CVD-mortality (65). Since the Mets is associated with CAD one would expect a high prevalence of DR in subjects with CAD. There are few studies that have examined this association.

d. The maculopathy of diabetes and hypertension

Hypertension and diabetes manifests microvascular complications such as retinopathy which can also affect the macula. The macula forms part of the more posterior part of the retina. It constitutes the central retina where a larger concentration of photoreceptors is found. The macula is important for sharp central vision. Central vision can be affected by systemic vascular associated macular conditions like macular oedema, poor macular vascular perfusion and macular atrophy.

Macular oedema is defined as retinal thickening in the macular area, and clinically significant macular oedema (CSMO) is defined according to the Early Treatment Diabetic Retinopathy Study classification protocol (40) as the presence of retinal thickening at or within 500 microns of the centre of the macula or hard exudates at or within 500 microns of the centre of the macula if associated with thickening of the adjacent retina or zones of retinal thickening, one disc area in size, at least part of which is within one disc diameter of the centre.

According to the Wisconsin epidemiological study the incidence of macular oedema and CSMO over 25 years in type 1 diabetes is 29% and 17% respectively. Macular oedema is associated with higher baseline glycosylated haemoglobin, higher systolic blood pressure and proteinuria (66). Measuring macular oedema, the thickness of the central macula (CMT) and deeper retinal layers of the macula is made possible by optical coherence tomography (OCT) (67).

A study conducted looking at these changes found that CMT in diabetics without DR is 195.6 microns and 220.1 microns in those with pre-proliferative DR as compared to 210.7 microns in normal healthy individuals. Conversely the retinal nerve fibre layer (RNFL) thickness was found to be thinner in pre-proliferative DR compared to no DR and healthy individuals (68). Another study confirming the RNFL thinning in type 1 diabetics compared to normal controls also found the ganglion cell layer (GCL) to be 5.1 microns thinner in type 1 diabetics with no or minimal DR (69). A study in China found that in hypertensive patients between the ages of 60 to 70 years the inner RNFL thickness was significantly thinner and the superficial plexus vessel density was significantly lower compared to healthy individuals. It also found that the foveal avascular zone (FAZ) was larger in those with longstanding hypertension compared to healthy individuals (70).

Another feature of OCT is the ability to look at macular microvascular perfusion by OCT angiography (71). Optical coherence tomography angiography is a rapid and non-invasive diagnostic imaging technique that produces depth-resolved, high-resolution images of the retinal microvascular system without the injection of dye. By using built-in automatic OCT angiography software, OCT angiography instruments can easily assess retinal blood flow based on various retinal microvascular parameters, such as vessel density (VD) and foveal avascular zone (FAZ). Vessel density has been found to be lower in diabetics versus non-diabetics and correlates with DR severity and worse visual acuity (72, 73). Diabetes and hypertension can cause maculopathy related vision loss and also contribute to other retinal vascular visual morbidity.

e. Diabetic- and hypertensive retinopathy related morbidity

The leading cause of blindness worldwide is cataract (33%), followed by uncorrected refractive errors (21%) and macular degeneration (7%). The leading causes for retinal vascular blindness are DR and retinal vein occlusions (RVO). Diabetes remains the leading cause of acquired vision loss in the middle age economically active group and it is estimated that the number of people with DR and vision threatening DR (which can include severe NPDR, PDR and macular oedema), will rise to 191 million and 56.3 million people respectively by the year 2030 (48). Approximately one tenth of people living with diabetes will develop a vision threatening form of the disease. The proportion of blindness cases attributable to DR has increased from 2.1% in 1990 to 2.6% in 2010 (74). Hypertension is one of the major risk factors for branch retinal vein occlusion (BRVO) which has a worldwide prevalence of 0.4% (75, 76). Knowing the underlying microvascular severity of diabetes and hypertension and how this correlate with macrovascular disease will further our understanding to better counsel our patients, in particular about the association between DR and CVD (77).

f. Association between retinopathy and cardiovascular disease

Klein et al in the ARIC study describes the prevalence of retinopathy in diabetics and its association with other vascular risks (78). This study found that the severity of DR was not associated with CAD but after controlling for age, hard exudates was associated with serum low-density lipoprotein. Klein et al also investigated DR severity and the incidence of CAD morbidity in an evaluation of 996 patients followed up over 20 years in Wisconsin counties. This study suggested that microvascular complications precede macrovascular disease in diabetes. Interestingly the 20-year incidence of angina and myocardial infarction was twice as high in the early NPDR group compared to the no retinopathy group and up to 4 times higher in the moderate to severe NPDR and PDR group compared to the no retinopathy group (66). In the Japanese diabetes complications cohort study, it was concluded that DR increases the risk of CVD including CAD and stroke. In 1620 patients the incidence rate of CAD per 1000-person years were found to be 7.54 in the no-DR group and 12.46 and 13.61 in the mild NPDR and moderate NPDR groups respectively (79).

The association of DR with CVD and CAD is well reported in a large review of 13 cohort studies. In type 2 diabetes those with DR had a 1.81-fold increased risk of having CVD. The relative risk was even higher among type 1 diabetes with regards to CAD. The review showed that patients with DR had an increased risk of developing CAD compared to those without DR (80).

Interestingly, a number of studies have looked at retinopathy across known diabetic and non-diabetic patients. The term “any retinopathy” or “retinopathy” was then used. In all these studies the retinopathy was classified according to the ETDRS diabetic retinopathy classification system irrespective of their underlying systemic condition. Ojaimi et al looked at the prevalence of retinopathy in 6176 patients between the ages 45 and 84 years all of whom did not have diabetes (81). The prevalence was found to be 12.5% and retinopathy had a strong association with hypertension, smoking and increased internal carotid intima media thickness. Similarly in the Handan study the prevalence of retinopathy was found to be 13.6% in 6830 non-diabetic patients and independent risk factors associated with retinopathy was male gender, increased systolic, -diastolic blood pressure and age (82) .

There is also a strong association between any retinopathy and mortality (83-85). Fisher et al looked at mortality in older persons with retinopathy and concomitant health conditions. Of the 4966 patients 503 had diabetes and 614 had retinopathy. They concluded that even minimal retinopathy, irrespective of the diagnosis of diabetes, was a significant predictor of all-cause mortality and CVD related mortality. The Beijing eye study and the Blue Mountains eye study also found that mortality was significantly higher in those subjects with diabetic-like retinopathy than those without and DR was an independent predictor of CAD related death. It is clear that retinopathy defined either as non-diabetic or DR classified according to the ETDRS is a valuable prognostic factor for cardiovascular related morbidity and mortality.

As mentioned earlier, HR and its association with CAD has not been extensively researched as is the case with DR. A small study of 655 hypertensive patients has shown that low grade HR was not associated with other cardiovascular risk factors (57).

In a larger study of 2172 non-diabetic patients with hypertension, grade 3-4 HR was significantly associated with left ventricular hypertrophy, carotid intima media thickness and carotid artery plaques (58). A recent review of HR in 2017 concludes that signs of HR are commonly seen in the general adult population and are associated with both subclinical and clinical measures of CVD (86). Persons with moderate HR are more likely to have a stroke and HR predicts a doubling in the risk of CAD events in high-risk men with hyperlipidemia (55, 87).

Retinopathy and its relationship with angiographically detectable CAD have also not been widely reviewed. Most studies have been small with patient numbers ranging from 69-371 subjects in diabetic patients to 437 subjects in hypertensive subjects. In one study the prevalence of DR in diabetic CAD patients was found to be 39% in 90 subjects (88). Two hundred and twenty-three diabetics with multivessel CAD were followed up for eleven years after undergoing coronary artery bypass graft (CABG). Of those with DR, 60.8% died and of those without DR only 18.8% died leading the authors to conclude that DR increases your mortality rate after CABG (89). In a Turkish study of 69 type 2 diabetes patients undergoing coronary angiography, 45% had DR. Those with DR had 2.3 coronary vessels with more than 50% stenosis versus 1.3 vessels in the non-DR group. Only 6.5% had normal coronary angiograms in the DR group compared to the 36.8% in the non-DR group (90). In a Japanese study proliferative DR was found in 12.4 % of 371 Japanese type 2 diabetes at baseline. This was significantly associated with those patients having single vessel CAD over a median of 2.8 years of follow up (91).

With regards to HR and CAD the prevalence of left ventricular hypertrophy and CAD has been shown to be significantly higher in the group with grade 2 HR than those with grade 1 and no HR (92). In Romania the prevalence of HR was found to be 35% in 600 patients with hypertension. The prevalence increased to 66% in those with hypertension and CAD (93). In a cross-sectional study involving 370 patients with hypertension looking at the association between HR and angiographically detectable CAD, the authors found significant association between HR and severity of CAD (94).

Rationale for this study

The increase of NCDs, in particular diabetes and hypertension, is of major concern in the South African context since the prevalence of hypertension is almost 33%. These systemic diseases are associated with a high incidence of morbidity and mortality due to the underlying micro- and macrovascular complications such as CAD. Hypertension and diabetes are major risk factors for CAD. The prevalence of retinopathy in subjects with CAD and how this relates to other predictors of retinopathy and CAD have not been researched in South Africa.

Furthermore most studies looking at the correlation between retinopathy and CAD describe the prognostic value of retinopathy and the prospective outcomes of CVD or CAD events. There is also no conclusive evidence that there is a direct correlation between the severity of retinopathy and the CAD severity.

The study therefore aims to investigate the prevalence of retinopathy and maculopathy in CAD patients and describe the profile of patients with CAD who have retinopathy. It further aims to correlate the presence of retinopathy with the severity of CAD patients.

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CHAPTER 2

The Prevalence and Severity of Retinopathy in Patients with Coronary Artery Disease at a Tertiary Hospital in Durban, South Africa.

Prepared according to the Instructions for the Authors for submission to the Cardiovascular Journal of Africa

Abstract

Aim

The study determined the prevalence of retinopathy in CAD patients and its association with the severity of CAD.

Methods

Over a ten-month period 121 patients underwent coronary angiography (109 CAD, 12 controls) and fundal examination.

Results

The prevalence of any form of retinopathy was 66% in the CAD group and 33% in the control group (p=0.026). Patients with CAD and hypertensive retinopathy were more likely to be between the ages of 55-64 years (41.9%, p=0.016), to be smokers (p=0.034) and have the metabolic syndrome (p=0.004). Diabetes was strongly associated with having CAD and any form of retinopathy (OR = 0.238, CI = 0.109-0.517, p<0.001). Subjects with double vessel disease (DVD) were more likely to have any form of retinopathy (77.8%) compared to those with single vessel disease (65.2%) and triple vessel disease (59.2%) (p=0.027). Patients with CAD and diabetic retinopathy (DR) were more likely to have microalbuminuria compared to those without CAD and DR

(p=0.014). An irregular foveal avascular zone (FAZ) was more frequent in CAD subjects with diabetes (21.3% vs 2.9%, p=0.013).
Conclusion
Retinopathy is common in subjects with CAD. Diabetic retinopathy, microalbuminuria and foveal abnormalities suggest the presence of underlying microvascular disease.

Keywords: Retinopathy; diabetic retinopathy; hypertensive retinopathy; coronary artery disease.

Introduction

The global burden of non-communicable diseases (NCDs) is well described. In 2016 NCDs accounted for 71% of deaths worldwide (1). It is projected that the number of deaths from NCDs will overtake infectious deaths in sub-Saharan Africa by 2035 (2). Hypertension is a major component of the NCDs and is a major risk factor for coronary artery disease (CAD). According to a systematic analysis of 90 countries the prevalence of hypertension differs among low-, middle- and high-income countries. The prevalence in high income countries is 28.5% and slightly higher (31.5%) in low- and middle income countries (3). This is even more prominent in Africa where the prevalence ranges between 54% and 60% (4, 5). Hypertension frequently accompanies and complicates diabetes. Nearly two thirds of the global diabetic population lives in urban environments and 79% live in low- and middle-income countries (6). The prevalence of diabetes has almost doubled between the years 2000 and 2009 from five and half to nine percent in South Africa (7). Hypertension and diabetes frequently coexist in subjects with CAD. The ACCESS registry found that 55.6% of South African patients with CAD had hypertension and 23.9% had diabetes (8).

Coronary artery disease is the leading cause of cardiovascular disease (CVD) mortality worldwide. The CAD mortality rate doubled from 1990 to 2020, with approximately 82% of the increase attributable to the developing world (9). It is estimated that both the prevalence of CAD risk factors and the resultant CAD mortality will continue to rise in

developing countries and will be accompanied by an increase in related micro- and macrovascular complications including retinopathy and renal disease. Longitudinal studies have long established that blood pressure and fasting plasma glucose are major risk factors for microvascular complications such as nephropathy and proliferative retinopathy in type 2 diabetes (10). The prevalence of hypertensive retinopathy (HR) varies according to the population sampled. Ong et al found the prevalence to be 51% in 2907 American hypertensive patients (11). The Evaluation of Target Organ Damage in Hypertension (ETODH) study found a much higher prevalence of 78% in European patients (12). Elevated blood pressure determines the macrovascular complications such as stroke and cardiovascular disease in type 2 diabetes, while high total cholesterol increases the risk of coronary artery disease and proliferative retinopathy (10).

A systematic review in 2012 estimated the global prevalence of diabetic retinopathy (DR) at 34.6% (13). This prevalence is very similar (35%) in developing countries (14). In South Africa (SA) the prevalence ranges from 39% to as high as 56% (15, 16). Knowledge of the underlying microvascular disease and its severity in hypertension and diabetes might help predict and possibly prevent further macrovascular manifestations (17). Klein et al suggested that microvascular complications precede macrovascular disease in diabetes mellitus (18). Studies looking at the correlation between retinopathy and CAD have described the prognostic value of retinopathy and the prospective outcomes of CVD and/or CAD events (19-21). In a meta-analysis of 13 cohort studies representing 17611 patients, DR was associated with an increased risk of CVD (relative risk: 2.72) (22). Gemino-Orna et al. found the incident CVD rates were 30.7 per 1,000 patient-years in patients with a normal fundus, 56.7 in patients with non-proliferative diabetic retinopathy (NPDR), and 90.7 in patients with proliferative diabetic retinopathy (PDR) over a mean follow up time of 6.7 years (21). Similarly, persons with moderate HR are more likely to have a stroke and the presence of HR predicts a two-fold increase in the risk of CAD events in high risk patients (23).

Limited data are available on the prevalence of retinopathy amongst patients with established CAD. A Romanian study reported that the prevalence of HR nearly doubled in individuals with hypertension and CAD compared to those with hypertension alone

(24). Several studies at the turn of the century reported an association between DR and the abnormalities in the coronary circulation (25) and defects on thallium scans (26). In individuals with angiographically detectable CAD the prevalence of DR was found to be 39% and 45% in two studies with sample sizes of 90 and 69 respectively (27, 28). South African studies have reported a high prevalence of diabetes and hypertension in Asian Indian subjects with CAD but none have reported the prevalence of retinopathy and how it relates to other predictors of CAD (29).

The current study examines the associations of retinopathy and maculopathy in patients with CAD. The specific objectives of the study were (1) to investigate the prevalence and severity of retinopathy, (2) to determine the central macular- and retinal nerve fibre layer thickness and examine macular perfusion and macular vessel density in patients with established coronary artery disease. (3) The study also determined the factors associated with the presence of retinopathy in subjects with CAD and correlated the presence of retinopathy with the angiographic severity of CAD.

Methods

i. Design and setting of the study

A cross sectional prospective study was undertaken of patients admitted to the cardiology and cardiothoracic wards at Inkosi Albert Luthuli Central Hospital (IALCH) during the period January 2019 to October 2019 for evaluation of CAD. The study included consenting patients who had undergone a recent coronary angiogram and fasting blood chemistry at IALCH. Patients were excluded if they had a history of narrow angle glaucoma or if both eyes were not eligible for fundus assessment. Retinopathy was assessed after pharmacological pupillary dilatation with tropicamide 1%. Five to seven wide-field photographs were obtained using the Visucam 500 fundus photography camera (Zeiss, Germany). Further retinal macular evaluation was assessed with the Cirrus 5000 high definition optical coherence tomography (OCT) scanner (Zeiss, Germany). This was used to assess central macular thickness, the presence of cystoid macular changes and retinal nerve fibre layer and ganglion cell layer thickness.

The macular capillary network was assessed by OCT angiography looking at the foveal avascular zone, the vascular capillary network vessel density (mm/mm^2) and vessel perfusion (%). Only images with a signal strength >7/10 were retained. The vessel density and vessel perfusion parameters were further described based on the Early Treatment Diabetic Retinopathy Study macular grid. The central zone describes a 1mm diameter with the fovea at its centre. The inner zone describes a circular band with a 1 mm radius surrounding the central zone. The outer zone describes a circular band with a 1mm radius surrounding both the central and inner zones. The full macular zone therefore describes all three zones with a diameter of 6mm.

ii. Definitions

Any form of retinopathy included either DR, HR or other retinopathy not defined elsewhere. The latter included patients with signs of retinal vascular changes but not diagnosed with either diabetes or hypertension. Diabetic retinopathy, macular oedema and clinical significant macular oedema were classified according to the modified Airlie House Early Treatment in Diabetic Retinopathy study (ETDRS) classification (30). Hypertensive retinopathy was graded according to the Keith-Barker-Wagener classification system (31). Hypertensive patients with venous tortuosity and/or arterial straightening were classified as pre-clinical hypertensive retinopathy (32).

Coronary artery disease was defined using the criteria from the 2013 American College of Cardiology Foundation/American Heart Association Task Force (ACCF/AHA) (33). The term ACS as outlined in the Third Universal Classification of Myocardial Infarction, encompasses ST segment elevation MI (STEMI), non-ST segment elevation MI (NSTEMI), and unstable angina (UA). Angiographic obstructive CAD was defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery and multivessel CAD was defined as ≥50% luminal diameter stenosis in ≥2 epicardial coronary arteries. The remaining subjects were classified as normal or non-obstructive coronary disease at coronary angiography. Angiographic findings of obstructive coronary disease were further grouped into single-vessel disease (SVD), double-vessel disease (DVD) and triple-vessel disease (TVD).

Hypertension was defined as blood pressure ≥140/90 mmHg or self-reported use of antihypertensive medication or previously documented diagnosis from medical records. Diabetes mellitus was diagnosed in patients who were on chronic anti-hyperglycaemic drugs, or self-reported or had a documented HbA1c ≥6.5% or previously documented diagnosis of diabetes mellitus from medical records. Dyslipidaemia was diagnosed in patients who were on chronic anti-lipid drugs, or self-reported, or previously documented diagnosis from medical records. Metabolic syndrome was defined according to the modified NCEP-ATP III criteria (34) as the presence of any three of the following five factors: abdominal obesity (defined as a waist circumference in men ≥102 cm and in women ≥88 cm); hypertriglyceridaemia (TG ≥1.7 mmol/L or drug treatment for elevated triglycerides); low HDL cholesterol (HDL-C ≤1.03 mmol/L for men and ≤1.3 mmol/L for women or drug treatment for low HDL-C); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or current use of antihypertensive drugs); impaired fasting glucose (fasting plasma glucose ≥5.6 mmol/L or drug treatment for elevated blood glucose).

iii. Statistical analysis

Results were first captured in MS Excel and transposed to Stata 14 (35) for statistical analysis. Descriptive statistics were used to summarise the demographics, risk factors, metabolic factors and biochemical factors. The categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as means ± standard deviation (SD). Sample characteristics were disaggregated by patients who have CAD and those who do not have CAD, diabetics and non-diabetics and retinopathy vs no retinopathy. Tests of association were conducted in the second part of the analysis which tested whether there was any association between those who had CAD and various retinopathies and the different risk factors. For this analysis the chi square test at a 95% level of significance ($p < 0.05$) was used. Using Chi square tests, associations between clinical categories of CAD and the presence of various retinopathies and macular changes were tested. Lastly, associations between CAD severity and the presence of retinopathy severity was also tested. Bivariate and multivariate analyses were performed to ascertain the predictors for CAD and retinopathy.

Results

The sample comprised 121 patients who underwent coronary angiography for suspected coronary artery disease. All but three patients had their angiogram performed within the last six months prior to their ophthalmological assessment. Male patients comprised the majority of the sample (n=89, 73.5%) with a male: female ratio of 3:1. Among those sampled, 77 (63.6%) were smokers, 93 (76.9%) had hypertension, 76 (62.8%) had diabetes mellitus and 100 (81.9%) had dyslipidaemia.

Demographic and risk factor profile of the study group

Of the 121 subjects, 109 patients had confirmed angiographic coronary artery disease and comprised the study group; the remaining 12 had normal coronary angiograms and served as the control group. Of those with CAD, 83 (76.2%) were male and 90 patients (82.6%) were of Indian ethnicity. Forty-six patients (38%) were between the ages 55-64 years with only 14 patients younger than 44 years and four patients older than 75 years. The frequency of metabolic syndrome (74.3% vs 58.3%, p=0.238), dyslipidaemia (88.6% vs 87.5%, p=0.927) and hypertension (77.1% vs 75%, p=0.872) was similar in the CAD and control groups. Sixty five (65.7%) patients with CAD had a positive family history of CAD compared to six (50%) in the control group (p=0.286) (table 1). Compared to the 12 with normal angiograms, subjects with CAD had more frequent diabetes (67.9% vs 16.7% p<0.001).

Metabolic and biochemical factors

The risk factor profile of the CAD and control groups was similar. There was no difference in the mean body mass index [27.35±4.66 (CI 26.40 - 28.29) vs 27.72±7.58 (CI 22.29 - 33.14) kg/m^2] and blood pressures between CAD and control subjects respectively (table 1). There was also no difference in the mean serum cholesterol [4.16±1.08 (CI 3.93 - 4.39) vs 4.50±0.52 (CI 4.07 - 4.94) mmol/litre] and serum triglyceride level [2.03±1.11 (CI 1.80, 2.26) vs 1.61±0.40 (CI 1.28, 1.94) mmol/litre] between the CAD and control groups respectively. The serum high density lipoprotein level was found to be abnormally low in 76% of patients in the CAD group compared to 62% in the control group (p=0.372). The mean HbA1C was 7.34% ±1.64 (CI 7.02 -

7.67) and 6.23% ±1.05 (CI 5.56 - 6.90) in the CAD and control group respectively (p=0.180) (table 2).

Coronary artery disease

In the study group 97 (89%) patients had a history of acute coronary syndrome (ACS) and the remaining 12 had chronic stable angina. The majority of patients (n=58, 53.2%) were classified as ST segment elevation myocardial infarction (STEMI), 30 patients (27.5%) had non-ST segment elevation myocardial infarction (NSTEMI), nine patients (8.3%) had unstable angina (UA). Atypical chest pain was more frequent in the control group compared to the CAD group (41% vs 5.5%, p<0.001). Among patients with CAD coronary angiography revealed that 23 (21%) had single vessel disease (SVD), thirty six (33%) had double vessel disease (DVD), forty nine (44.9%) had triple vessel disease (TVD) and one patient showed severe diffuse disease. Triple vessel disease was more frequent in the diabetic (n=33) compared to the non-diabetic (n=16) group (43.4% vs 35.6%, p=0.004). Severe angiographic disease as assessed by the presence of multivessel involvement (DVD and TVD) was more frequent in the diabetic (n=60) compared to the non-diabetic (n=26) group (78.9% vs 57.8%, p=0.002).

The left ventricular ejection fraction was impaired (EF 40-49%) in 41.9% of CAD patients and severely reduced (EF <40%) in 19.1% of CAD patients, compared to 16.7% and 8.3% respectively in the control group (p=0.058).

Prevalence of Retinopathy

Fundus photography was performed in 121 patients. One patient was excluded due to poor visibility of the fundus secondary to cataracts. The prevalence of any form of retinopathy was 66% (n=72) in the CAD group and 33% (n=4) in the control group (p=0.026) (table 2). Across the different categories of CAD (STEMI vs UA vs CSA vs NSTEMI) there was no difference in the prevalence of retinopathy [71% vs 55% vs 75% vs 56% (p=0.085)], the prevalence of DR [34% vs 11% vs 25% vs 33% (p=0.196)] and the prevalence of HR [44% vs 22% vs 50% vs 41% (p=0.292)] respectively.

Hypertensive retinopathy was present in 43 (40.2%) subjects in the CAD group and three (25%) in the control group (p=0.306). More than 60% of the CAD patients with

HR had grade 2 retinopathy; only one CAD subject had grade 3 HR. Diabetic retinopathy was present in 34 subjects (31.2%) in the CAD group and one subject (8.3%) in the control group (p=0.097). The majority of CAD patients with DR had non-proliferative diabetic retinopathy (NPDR) (n=29, 85.3%) and five (14.7%) had proliferative diabetic retinopathy (PDR). Clinically significant macular oedema (CSMO) was present in three patients in the CAD group as opposed to none in the control group (p=0.768). Seven (6.4%) patients in the CAD group without known diabetes or hypertension were found to have retinal vascular changes compared to none in the control group (p=0.366) (table 2).

Macular evaluation

Retinal measurements showed no difference in the mean central macular thickness (CMT) [245.6±29.2 (CI 239.9 - 251.2) μm vs 250±22.2 (CI 235.9 - 264.1) μm], the mean retinal nerve fibre layer (RNFL) [80.2±26.9 (CI 74.9 - 85.3) μm vs 79±31.3 (CI 59.1 - 98.9) μm] and the mean ganglion cell layer (GCL) [75.0±11.2 (CI 72.6 - 77.4) μm vs 78.6±8.4 (CI 73.2 - 83.9) μm] in the CAD vs control group respectively. Similarly there was no difference in the macular vessel density and the macular perfusion density between the CAD and control group. The foveal avascular zone was irregular in sixteen (15.5%) patients in the CAD group compared to one (8.3%) patient in the no CAD group (p=0.506) (table 2).

The mean thickness of the CMT, RNFL thickness and ganglion cell layer (GCL) were similar across the different clinical categories of CAD. The macular perfusion density was lower in patients with CSA compared to those patients with UA, NSTEMI and STEMI. The macular perfusion density in the central zone measured 9.4% (CI 4.6 - 14.1) in the CSA group compared to 17.4% (CI 8.2 - 26.5), 14.1% (CI 10.6 - 17.7) and 15.7% (CI 13.5 - 18.0) in the UA, NSTEMI and STEMI groups respectively (Fig 2). An abnormal foveal avascular zone was present in one (12.5%), six (21.4%), nine (16.4%) and none (0%) in the UA, NSTEMI, STEMI and CSA groups respectively (p=ns).

The foveal avascular zone was more frequently abnormal in diabetics compared to non-diabetics (21.13% vs 4.55%, p=0.015). The average CMT [245.0 (CI 237.7 - 252.3) μm

vs 247.6 (CI 240.7 - 254.5) μm], GCL [75.9 (CI 73.4 - 78.4) μm vs 74.6 (CI 70.3 - 78.9) μm] and RNFL [78.9 (CI 72.3 - 85.8) μm vs 81.9 (CI 74.4 - 89.5) μm] thickness was similar in the diabetic vs non-diabetic patients.

Predictors of coronary artery disease and retinopathy

Bivariate analysis showed that female gender (OR = 0.354, 95% CI 0.129 - 0.973, p=0.044), patients of African ethnicity (OR = 0.234, 95% CI 0.063 - 0.868, p=0.030) and non-diabetic subjects (OR = 0.238, 95% CI 0.109 - 0.517, p<0.001) were the least likely to have CAD associated with any form of retinopathy.

Bivariate analysis showed a significant association between abnormal urine albumin levels and the presence of CAD with diabetic retinopathy (DR) (OR = 6.896, CI 1.302 - 36.534, p=0.023), but this relationship fell away on multivariate analysis (OR = 3.032, CI 0.041 - 223.406, p=0.613). There appeared to be an association between elevated total cholesterol (OR 3.323, CI 0.956-11.552, p=0.059) and CAD without diabetic retinopathy but this was not significant in multivariate regression (OR 2.248, CI 0.372-13.572, p=0.377). Similarly, a severely abnormal ejection fraction tended to be associated with CAD and DR (OR = 2.812, CI 0.982 - 8.053, p=0.054) but this relationship was not significant in multivariate analysis (OR = 6.775, CI 0.926 - 49.597, p=0.060).

Patients with CAD and hypertensive retinopathy (HR) were more likely to be between the ages of 55-64 years (p=0.016), to be smokers (p=0.034) and have the metabolic syndrome (p=0.004) compared to those with CAD and no HR. Patients with CAD and DR were more likely to have microalbuminuria compared to those without CAD and DR (p=0.014).

Association between retinopathy type and severity of coronary artery disease

We also examined whether the presence of retinopathy was associated with more severe CAD as assessed by the number of vessels involved on angiography. Retinopathy was more frequent in subjects with DVD compared to SVD and TVD (77.8% vs 65.2% vs 59.2%, p=0.027) respectively.

Across the angiographic groups (SVD vs DVD vs TVD) we found no difference in the prevalence of DR (21.7% vs 36.1% vs 32.7%, p=0.257) and HR (48.5% vs 47% vs 34%, p=0.206) respectively. Multivessel disease (DVD + TVD) was a more frequent finding than SVD in subjects with DR (33.7% vs 21.7%, p=0.068) and HR (43.5% vs 39.3%, p=0.597) but these differences were not significant. There was also no significant association between the severity of retinopathy and angiographic severity of CAD. (Table 3)

Retinal assessment in CAD with diabetes (table 4)

In a further analysis we compared patients with CAD and diabetes (n=74) vs CAD and no diabetes (n=35). There was no difference between CAD with diabetes vs CAD and no diabetes in the prevalence of STEMI, NSTEMI, CSA and UA (p=0.298), number of vessels involved (p=0.324) and multivessel involvement (81.1% vs 74.3%, p=0.417). Macular assessment revealed that 15 patients (21.3%) with CAD and diabetes had an irregular foveal avascular zone compared to only one (2.9%) in the CAD and no diabetes group (p=0.013). There was no difference in the macular layer thickness profiles (CMT and RNFL) between the two groups. The CMT was 244.9±31.4 (CI 237.6 – 252.6) μm vs 246.8±24.2 (CI 238.5 – 255.1) μm (p=ns) and the RNFL was 78.6±29.1 (CI 71.8 – 85.4) μm vs 83.6±21.3 (CI 76.1 – 91.1) μm (p=ns) in the CAD and diabetes vs the CAD and no diabetes groups respectively.

Discussion

This study reports the overall prevalence of any form of retinopathy in patients with CAD and has shown that retinopathy is a frequent finding in predominantly ACS subjects with angiographically confirmed CAD. The prevalence was found to be 66% for any form of retinopathy, 40.2% for HR and 31.2% for DR. Boruga et al reported a 35% prevalence of HR in a hypertensive population which nearly doubled to 66% in subjects who developed CAD over a 3 year period (24). Previous studies have found a 39% - 45% prevalence of DR in CAD patients (27, 28).

In a systematic review in 2012 which excluded countries from the Middle East, Africa, and South America, the overall global prevalence of DR was 34.6% (13). In developing countries the prevalence of DR was found to be over 35% (14). Local South African studies have shown a 29%- 32% prevalence of DR at primary care level (36, 37), increasing to 39% at tertiary care level (15) and up to 56% in hospitalised patients who have had type 1 diabetes for more than 10 years (16).

Our study findings show a significant association between retinopathy and CAD (p=0.026). However, we found no significant association between the type of retinopathy (any form, HR or DR) and the clinical categories of CAD (CSA, UA, NSTEMI or STEMI). There was no significant association between any form of retinopathy severity and the CAD severity. Although the presence of any form of retinopathy was more frequent in subjects with DVD (77.8%) this was not the case in those CAD subjects with TVD (65.2%). This difference in frequency was furthermore less apparent when classifying CAD into SVD (65%) and MVD (66%). This is most likely due to the small sample size in our study and possibly because HR was a more frequent finding in those subjects with SVD (44%) as opposed to those with MVD (39%). Furthermore our classification based on the number of major vessels involved, was more an indication of the extent of coronary involvement rather than the severity of the coronary vessel stenosis. We did not determine disease severity using the SYNTAX score which would have given a more accurate indication of the severity of stenosis in CAD subjects.

In our study the prevalence of DR among subjects with CAD (n=109) was 31.2% and in our subgroup of CAD patients with diabetes (n=74) it was 46%. This high prevalence of DR in patients with angiographically confirmed epicardial disease suggests that these patients might also have underlying coronary microvascular disease and places them at a higher risk for coronary events. Studies have shown that the presence of any retinopathy, HR or DR increase the risk for CVD and CAD related morbidity and mortality. In individuals 67 – 96 years Fisher et al (38) found that even minimal retinopathy was a significant predictor of increased mortality irrespective of diabetes status concluding that retinopathy may serve as a biomarker for structural or functional abnormalities in the systemic microvasculature. The Beijing eye study (39) also found a

higher mortality rate over 5 years in those patients with retinopathy at baseline compared to those without retinopathy. Persons with moderate HR compared to those with no HR are more likely to have a stroke (11) and the presence of HR is associated with a two-fold higher risk of CAD events over a median of 7.8 years (23).

In a large meta-analysis Guo et al found that DR was associated with an increased risk for cardiovascular disease in diabetes (22). In 2007 the ARIC study (40) reported that DR was associated with a two-fold increased risk of CAD in both men and women. The presence of diabetic retinopathy was associated with a two-fold higher risk of incident CAD events [hazard rate ratio (HR) 2.07 (95% CI 1.38-3.11)] and a three-fold higher risk of fatal CAD [3.35 (1.40-8.01)]. This association was independent of glycaemic levels, cardiovascular risk factors, and large vessel atherosclerosis and appeared to be graded with retinopathy severity, leading the authors to conclude that microvascular disease may contribute to the development of CAD in type 2 diabetes. Our findings (Fig 1) of an association between any retinopathy and DVD are in keeping with Norgaz et al. who found that the presence of DR was associated with more severe and diffuse CAD (28). However, we found no difference in the prevalence of DR between patients with multivessel involvement (DVD + TVD) vs SVD (p=0.068) (table 3). The severity of retinopathy has been associated with more severe CAD (41, 42). Cheng et al (43) describes different retinal findings including DR, hypertensive retinopathy and retinal venular calibre and its association with angiographic detectable CAD. It found that the presence of retinal haemorrhages, moderate microvascular retinopathy and PDR were associated with a higher Leaman score. It also found that venular calibre was increased with TVD as compared to those with normal angiograms and the presence of DR correlated with an increased TIMI blush score. This might indicate that there is some correlation between retinopathy and CAD severity but larger trials looking at retinopathy severity classification and how this correlate with CAD severity is needed. In our study we did not analyse retinal venular calibre or evaluate the Leaman score. Habib et al found that a higher grade of hypertensive retinopathy was associated with a higher angiographic severity of CAD as judged by the SYNTAX score (44). We did not show a direct relationship between the severity of retinopathy and the severity of CAD (table 3), possibly due to our small sample size, the absence of subjects with more

severe proliferative retinopathy, and the fact that we assessed severity by the number of vessels involved and not the SYNTAX score.

This is the first study to report the macular OCT findings in patients with angiographic CAD. There was no difference in mean CMT between the CAD group and control groups. Literature supports the notion of thinning of certain macular layers in patients with diabetes and DR compared to normal individuals (45, 46) and lower microvascular density in diabetics compared to non-diabetics (47, 48). Oshitari et al. found that macular thickening was present in diabetics, and increased with increasing stages of diabetic retinopathy (45). In our analysis we found no difference in the CMT and retinal nerve fibre layer (RNFL) thickness between subjects with CAD and diabetes vs CAD without diabetes. We also described the macular perfusion in CAD patients and found the macular perfusion density (%) to be lower in the CSA group as compared to the UA, NSTEMI and STEMI groups but this finding was not significant (p=ns). Only two studies have examined the macular vessel density in patients with ACS (49, 50) and findings suggest that the inner vessel density is lower in the ACS group (49). Of importance we found that the foveal avascular zone (FAZ) was more frequently irregular in the subgroup of CAD with diabetes (n=15) compared to the CAD without diabetes (n=1) group (21.3% vs 2.9%, p=0.013).

In our study we showed a significant association between abnormal urine albumin levels and the presence of CAD with DR (p=0.014). The literature supports the relationship between diabetes, chronic kidney disease (CKD) and CVD related morbidity (51-54). Kim et al (51) found a higher incidence of CAD in the group with microalbuminuria and no DR. The Chronic Renal Insufficiency Study (CRIC) (52) study has shown that the presence and severity of retinopathy is associated with an increased risk of cardiovascular disease events in CKD patients suggesting that microvascular pathology in diabetes may serve as a marker for the presence of macrovascular disease.

Strengths and limitations

There are significant limitations to our study, among them being the small sample size and the small number of control subjects. A significant limitation was the cross-sectional design without follow up data to determine outcome events in our subjects, and so we were unable to determine the prognostic implications of our findings. Also we did not determine disease severity using the SYNTAX score which would have given a more accurate indication of coronary disease severity. However, the majority of our subjects had already sustained a recent coronary event, presenting with ACS, supporting the predictive association of retinopathy with acute cardiac events. Of importance we included a small number of subjects as controls, who had normal angiograms prior to undergoing valve replacement surgery. This is of clinical importance as 12.5-13.6% of the general population have been shown to have retinopathy lesions (55, 56), the prognostic significance of which is unclear.

Furthermore the use of wide field fundus photography to detect retinopathy lesions in our study enable us to accurately document the lesions since it is known that clinicians using a direct ophthalmoscope may miss up to 50% of these lesions (57) and as many as one third of cases may go undetected with non-mydriatic fundus photography (58). We used a standardised protocol for photographic capture of both retinas after pharmacological pupillary dilation and grading was performed by the researcher masked to participants' clinical information. Only a single photograph was ungradable, avoiding the underestimation of retinopathy and misclassification. Also retinopathy was categorised into HR and DR enabling us to determine associations with the type of retinopathy. We avoided selection bias distorting the associations by performing fundal assessment and serum chemistry during the same admission in a group of all consenting subjects admitted for coronary angiography over a ten month period. We also examined HbA1c levels and electrolytes so that undiagnosed diabetes could be detected and also any confounding effects of undiagnosed diabetic nephropathy unlikely to distort the associations.

Conclusion

In conclusion, this study shows a high prevalence of both hypertensive and diabetic retinopathy in a sample of predominantly ACS patients undergoing coronary angiography. Retinopathy was associated with clustering of the major risk factors. The presence of DR, microalbuminuria and foveal abnormalities in diabetic subjects with epicardial CAD suggest that this high risk group might also have underlying coronary microvascular disease which may contribute to future cardiovascular events and calls for careful surveillance for CAD as well as appropriate ophthalmological follow up to prevent DR related vision loss in these patients.

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Table 1. Clinical and biochemical characteristics of the CAD and control (no CAD) groups

	CAD (n = 109)			No CAD (n = 12)			
	n	(%)	Mean (SD)	n	(%)	Mean (SD)	P value
Demographics							
Average age (years)			57.36 (9.3)			53.50 (11.9)	
Age 45-54	29	(26.6)		5	(41.7)		
55-64	45	(41.3)		1	(8.3)		
65-74	20	(18.4)		3	(25.0)		0.151
Female	26	(23.9)		6	(50.0)		
Male	83	(76.2)		6	(50.0)		0.051
African	8	(7.3)		3	(25.0)		
Mixed race	1	(0.9)		1	(8.3)		
Indian	90	(82.6)		7	(58.3)		
Caucasian	10	(9.2)		1	(8.3)		0.044
Risk Factors							
Smoking	72	(66.1)		5	(41.7)		0.096
Hypertension	84	(77.1)		9	(75.0)		0.872
Diabetes	74	(67.9)		2	(16.7)		0.000
Dyslipidaemia	93	(88.6)		7	(87.5)		0.927
Fam Hx of CAD	65	(65.7)		6	(50.0)		0.286
Metabolic Syndrome	81	(74.3)		7	(58.3)		0.238
Metabolic Factors							
BMI (kg/m2)	95		27.35 (4.7)			27.57 (7.6)	
Underweight + normal	28	(29.5)		5	(50.0)		
Overweight + above	67	(70.5)		5	(50.0)		0.184
Heart rate (bpm)	109		74.96 (16.1)			76.76 (12.1)	
<77	67	(61.5)		9	(75.0)		
≥77	42	(38.5)		3	(25.0)		0.357
Systolic BP (mm/Hg)	109		131.4(19.5)			124.84 (19.8)	
Normal	55	(50.5)		8	(66.7)		
Elevated	54	(49.5)		4	(33.3)		0.286
Diastolic BP (mm/Hg)	109		78.29 (11.6)			70.17 (14.3)	
Normal	76	(69.7)		9	(75.0)		
Elevated	33	(30.3)		3	(25.0)		0.704
Biochemical Factors							
Cholesterol (mmol/L)	90		4.16 (1.1)			4.50 (0.5)	
Normal	74	(82.2)		7	(87.5)		
Elevated	16	(17.8)		1	(12.5)		0.706
Triglycerides (mmol/L)	90		2.03 (1.1)			1.61 (0.4)	
Normal	40	(44.5)		4	(50.0)		
Elevated	50	(55.6)		4	(50.0)		0.762
HDL (mmol/L)	90		0.97 (0.2)			1.07 (0.2)	
Normal	21	(23.3)		3	(37.5)		
Elevated	69	(76.7)		5	(62.5)		0.372
LDL (mmol/L)	89		2.26 (0.8)			2.69 (0.6)	
HBA1C (%)	99		7.34 (1.6)			6.23 (1.1)	
Normal	6	(6.1)		2	(16.9)		
Elevated	93	(93.9)		10	(83.3)		0.180
Haemoglobin (g/dL)	109		13.44 (1.9)			12.19 (2.2)	
Creatinine (umol/L)	109		89.96 (20.5)			77.50 (13.7)	
Urine Albumin (mg/L)	37		57.06 (200.2)			24.25 (36.7)	
Normal	31	(83.8)		3	(75.0)		
Elevated	6	(15.2)		1	(25.0)		0.657

There were no significant differences in the demographics, risk factors, metabolic factors and biochemical factors between the CAD and control (no CAD) groups.

n: number, SD: standard deviation

CAD: coronary artery disease, Fam Hx: Family history, BMI: body mass index, bpm: beats per minute, BP: blood pressure, HDL: high density lipoproteins, LDL: low density lipoproteins

Table 2. Retinal assessment in the CAD and control (no CAD) groups

	CAD (n = 109)			Control (No CAD) (n = 12)			
	n	**(%)**	**Mean (SD)**	**n**	**(%)**	**Mean (SD)**	**P value**
Retinopathy							
Visual acuity R (decimal)	106		0.83(0.4)	12		0.81(0.8)	
Visual acuity L (decimal)	106		0.92 (0.4)	12		0.78(0.8)	
IOP right	86		15.28 (2.4)	10		15.40 (2.2)	
IOP left	86		15.23 (2.5)	10		15.40 (2.3)	
Any retinopathy	72	(66.1)		4	(33.33)		0.026*
Diabetic retinopathy	34	(31.2)		1	(8.33)		0.097
NPDR	29	(85.3)		1	(100)		0.679
Very mild to moderate	25	(86.2)		1	(100)		
Severe to very severe	4	(13.8)		0	(0.00)		0.690
PDR	5	(14.7)		0	(0.00)		0.697
Hypertensive Retinopathy	43	(40.2)		3	(25.00)		0.306
Pre-clinical to Grade 2	42	(97.7)		3	(100)		
Grade 3-4	1	(2.3)		0	(0.00)		0.789
Retinopathy not classified	7	(6.4)		0	(0.00)		0.366
CSMO	3	(4.2)		0	(0.00)		0.768
Macular Assessment							
CMT	107		245.56 (29.2)	12		250.00 (22.2)	
RNFL	106		80.15 (26.9)	12		79.00 (31.3)	
GCL	88		75.01 (11.2)	12		78.58 (8.4)	
FAZ regular	87	(84.5)		11	(91.67)		
FAZ irregular	16	(15.5)		1	(8.33)		0.506
Vessel Density (mm/mm2)							
Central	91		8.18 (3.6)	10		9.11 (2.9)	
Inner	83		15.99 (2.6)	12		16.40 (1.9)	
Outer	82		16.92 (1.6)	12		17.31 (1.7)	
Full	82		16.48 (1.7)	12		16.78 (1.7)	
Perfusion Density (%)							
Central	82		14.91 (7.9)	12		14.58 (7.9)	
Inner	82		39.01 (5.7)	12		39.40 (5.1)	
Outer	82		42.37 (4.2)	12		43.18 (4.6)	
Full	82		40.85 (4.4)	12		41.56 (4.5)	

*Retinopathy was a more frequent finding in the CAD group. The other retinal characteristics were similar between the CAD and no CAD groups.

n: number, SD: standard deviation, CAD: coronary artery disease, R: right, L: left

IOP: intra ocular pressure, NPDR: non proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy, CSMO: clinical significant macular oedema, CMT: central macular thickness, RNFL: retinal nerve fibre layer, GCL: ganglion cell layer, FAZ: foveal avascular zone

Table 3. Association between coronary angiographic severity and retinal findings

	SVD (n = 23)		DVD (n = 36)		TVD (n = 49)			Mild CAD (SVD) (n = 23)		Severe CAD (MVD) (n = 85)		
	n	(%)	n	(%)	n	(%)	p-value	n	(%)	n	(%)	P value
Any Retinopathy	15	(65)	28	(77.8)	29	(59)	0.027*	15	(65)	57	(66)	0.216
Diabetic retinopathy	5	(22)	13	(36)	16	(33)	0.257	5	(22)	29	(34)	0.068
Mild DR	3	(13)	10	(28)	11	(22)	0.413	3	(13)	21	(24)	0.218
Severe DR	2	(8)	3	(8)	4	(8)	0.413	2	(9)	7	(8)	0.218
Hypertensive retinopathy	10	(48.5)	17	(47)	16	(34)	0.206	10	(44)	33	(39)	0.597
Mild HR	10	(48.5)	16	(44)	16	(34)	0.172	10	(44)	32	(38)	0.745
Severe HR	0	(0)	1	(3)	0	(0)		0	(0)	1	(1)	
FAZ regular	19	(86)	27	(79)	40	(87)	0.256	19	(86)	68	(84)	0.555
FAZ irregular	3	(14)	7	(21)	6	(13)	0.256	3	(14)	13	(16)	0.555

* There was no significant association between the different types of retinopathy severity and the CAD severity. Although any form of retinopathy was more frequent in DVD, this was not seen in CAD subjects with TVD. This difference in frequency was furthermore less apparent when classifying CAD into SVD and MVD.

n: number, CAD: coronary artery disease, SVD: single vessel disease, DVD: double vessel disease, TVD: triple vessel disease, MVD: multi-vessel disease, DR: diabetic retinopathy, HR: hypertensive retinopathy, FAZ: foveal avascular zone

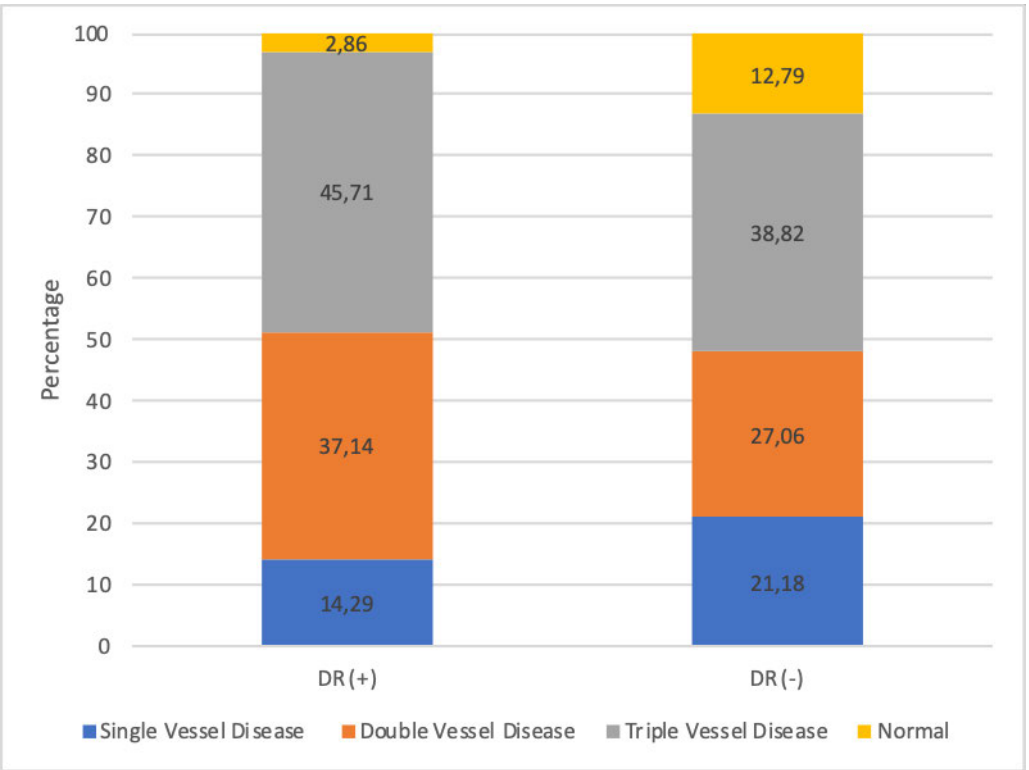
Table 4. Angiographic and retinal findings in CAD subjects with and CAD subjects without diabetes

	CAD with DM (n = 74)		CAD with no DM (n = 35)		
	n	Mean/(%)	n	Mean/(%)	p-value
Age	74	57.55 (SD 9.5)	35	56.94 (SD 9.1)	
Male	52	(70.3)	31	(88.6)	
female	22	(29.7)	4	(11.4)	
CAD type					
UA	5	(6.8)	4	(11.4)	
STEMI	43	(58.1)	15	(42.9)	
NSTEMI	17	(22.9)	13	(37.1)	
CSA	9	(12.2)	3	(8.6)	0.298
Angiogram classification					
SVD	14	(18.9)	9	(25.7)	
DVD	27	(36.5)	9	(25.7)	
TVD	33	(44.6)	16	(45.7)	0.324
Diffuse disease	0	(0)	1	(2.9)	
Angiogram severity					
Mild	14	(18.9)	9	(25.7)	
Severe/multiple	60	(81.1)	26	(74.3)	0.417
Macular assessment					
CMT	72	244.97 (SD 31.4)	35	246.79 (SD 24.2)	
RNFL	73	78.60 (SD 29.1)	33	83.59 (SD 21.3)	
GCL	62	75.66 (SD 9.9)	26	73.46 (SD 13.9)	
FAZ regular	54	(78.3)	33	(97.1)	
FAZ irregular	15	(21.7)	1	(2.9)	0.013*
Vessel Density (mm/mm2)					
Full	56	16.45 (SD 1.7)		16.55 (SD 1.9)	
Perfusion Density (%)					
Full	56	40.83 (SD 4.4)		40.90 (SD 4.6)	

*Macular OCT assessment revealed that patients with CAD and diabetes had an increased irregular foveal avascular zone compared to those with CAD and no diabetes.

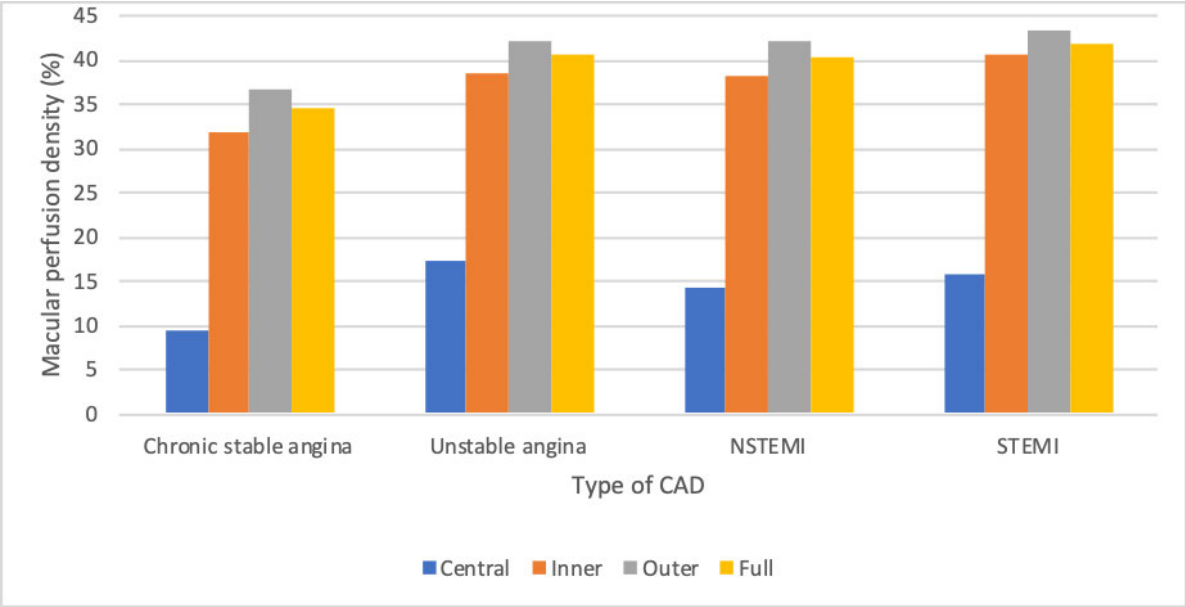
n: number, SD: standard deviation, CAD: coronary artery disease, UA: unstable angina, STEMI: ST segment elevation myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, CSA: chronic stable angina, SVD: single vessel disease, DVD: double vessel disease, TVD: triple vessel disease, MVD: multivessel disease, CMT: central macular thickness, RNFL: retinal nerve fibre layer, GCL: ganglion cell layer, FAZ: foveal avascular zone, OCT: Optical coherence tomography

Figure 1: Bar graph showing vessel involvement in subjects with CAD with and without diabetic retinopathy.



There was no difference in disease severity between subjects with vs without diabetic retinopathy. DR(+) vs DR(-).

Figure 2. Bar graph showing the macular perfusion across the types of CAD



There was no difference in macular perfusion across the clinical categories of CAD

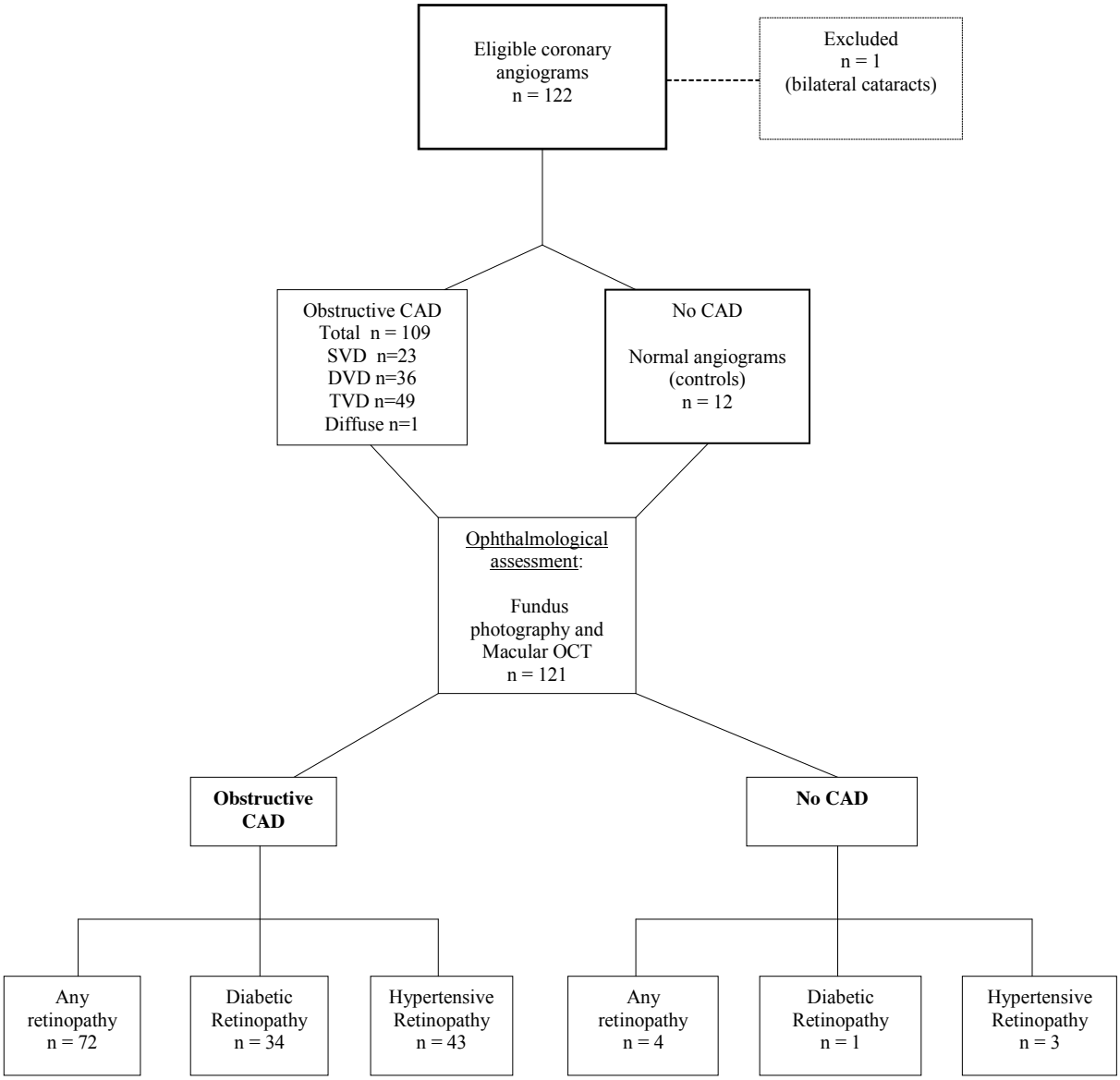


Figure 3. Flow diagram of patients enrolled for the study. Showing the cohort and control groups, the different types of retinopathy of each of these groups and the coronary angiographic classification of the cohort group. It furthermore illustrates the subgroup analysis of those with CAD and diabetes and those with CAD and no diabetes.

APPENDIX I

Research Protocol

Title of study

The Prevalence and Severity of Retinopathy in Patients with Coronary Artery Disease (CAD) at a Tertiary Hospital in Durban, South Africa.

Aim of study

The study aims to investigate the prevalence of retinopathy in CAD patients. It further aims to correlate the severity of retinopathy with the severity of CAD.

Specific objectives

1. To determine the prevalence of retinopathy in CAD.
2. To classify the degree of retinopathy using fundus photography
3. To identify macular oedema on OCT
4. To compare retinopathy in diabetic and non-diabetic patients with CAD who are undergoing coronary angiograms.
5. To identify predictors of retinopathy
6. To correlate the severity of CAD with the presence and severity of retinopathy.

Background and Literature

Retinopathy represents any disease or condition that effects the retina. In retinal vascular disease retinopathy relates to the microvascular damage of underlying systemic

disease. The main contributors to retinal vascular disease are atherosclerosis, hypertension and diabetes mellitus.

Diabetes mellitus is a worldwide pandemic with an estimated 628 million people affected by the year 2045, imposing a potentially large burden of retinopathy with its consequences. Africa has the highest percentage (69.2%) of people with undiagnosed diabetes, estimated at 10.7 million people (1). In Africa, delayed diagnosis often leads to the development of diabetic complications including retinopathy (2).

A review of 12 surveys for sub-Saharan Africa showed that the single-country prevalence of diabetes ranged from 2% to 14%, with a median prevalence of 5%, rising to 9% in the age group of 55-64 (2). The SANHANES survey for South Africa in 2012, showed a much higher prevalence of 15% in subjects over 55 years of age (3). In another study in black South Africans a prevalence of 36% was recorded in the age group 65 – 74 (4).

The high prevalence of diabetes in South Africa is accompanied by diabetic related systemic involvement manifesting as large and small vessel disease such as diabetic retinopathy (DR) (5, 6).

According to a systematic review in 2012 the overall global prevalence of any DR is 34.6% excluding countries from Middle East, Africa, or South America (7). The prevalence ranges between 10-50% depending on method used, age, population (hospital vs population based) and duration of diabetes (8). A recent review estimated that the number of people with DR and vision threatening DR will rise to 191 million and 56.3 million respectively by 2030 (9). DR prevalence in developing countries was found to be over 35% (10).

Ophthalmoscopy based studies in African patients have shown a 15-17% prevalence of DR (8). A South African multiethnic photography-based study has shown higher prevalence across ethnic groups (Black African 37%, Europeans 41%, and Indians 37%); severe retinopathy was more frequent in African and Indians (11). In contrast, in a hospital based South African population study, Motala et al. found a much higher prevalence of 56% for any DR and 17% for proliferative DR. Black patients showed a

DR prevalence of 55.6% and Indian patients (45.5%) in those with Type 1 diabetes for longer than 10 years (6).

The DR prevalence varies depending on the population sample. A randomised trial at a primary care level in the Tshwane district, South Africa documented a prevalence of 29% for any DR and 26% for maculopathy amongst referred diabetics. This study however, found that the screening for diabetes related complications was suboptimal with only 8.2% diabetics referred (12). A similar cross sectional study in the Western Cape found a slightly higher prevalence of 32% with 8.9% having sight-threatening DR (13). At the tertiary care level the prevalence of any DR was found to be 39% (14).

Amongst the major sequelae of DR are its association with visual loss and major organ involvement such as nephropathy and cardiac disease. Although DR accounts for less than 5% of all causes of moderate to severe visual impairment worldwide it is the leading cause of vision loss in the working-age adults between 20 and 65 years of age. Approximately one tenth of people living with diabetes will develop a vision threatening form of the disease. The proportion of blindness cases attributable to DR has increased from 2.1% in 1990 to 2.6% in 2010 (15).

People with diabetes are two to three times more likely to have CVD than people without diabetes. Every year 14 – 47 per 1000 middle-aged people with diabetes between the ages 50 – 69 living in high to low-income countries have a CVD event. Of these 2 -26 per 1000 are CAD (Coronary Artery Disease) events (16). Among older people (51-69 years) with type 1 and type 2 diabetes, the prevalence of coronary artery disease ranged from 12% to 31.7% (1).

Patients with diabetes are known with premature CAD, greater severity and extent of the disease, and higher associated morbidity and mortality. To what extent this is related to the macro-vascular disease alone, or concomitant micro-vascular disease is not clear.

The association of DR with cardiovascular disease (CVD) has only recently been described (17). Several studies show that the presence of retinopathy (diabetes and non-diabetes) increases the risk of a CAD event and the CAD mortality (17-21).

In mild DR the risk for CVD is increased (22). Moderate retinopathy conveys a 6.7-fold

increased risk of CAD event in diabetic patients and a 2.3-fold increased risk of CAD event in non-diabetic patients (18).
The Wisconsin Epidemiological Study of Diabetic Retinopathy found that the hazard ratio for CAD mortality ranges from 1.5 to 2.07 depending on the severity of DR (21). Approximately 25% of patients with diabetic retinopathy receiving ophthalmologic care as outpatients have significant stenotic coronary artery disease (23).

It is well known that patients with advanced DR have a poor life expectancy. The 5-year mortality rate for patients with proliferative DR (PDR) is 45%. Another prospective study of 709 patients with Type 2 diabetes on insulin followed up over 13 years showed a 5 year mortality rate of 44% in patients with PDR (21). Fifty percent of patients with CAD undergoing vitrectomy died within three years and those without CAD had a five year survival rate of 90% (24).

Similarly in chronic kidney disease (CKD) patients, the presence and severity of retinopathy were associated with the increased risk of developing any CVD. The prevalence of retinopathy in CKD patients was found to be 11% and associated with an increased rate of all-cause mortality and CVD-mortality (25, 26). It is significantly associated with mortality and even more significantly with CVD related mortality (27, 28). The prevalence of retinopathy in non-diabetic patients ranges from 9 – 12 % and are three times higher in diabetic patients globally (7, 18, 29).

The clinical correlates of retinopathy in CAD have not been examined in detail. Whether it is due to associated risk factors or a reflection of microvascular disease in the myocardium is not clear (30).

Although DR is associated with CAD the presence of DR is the only independent predictor of CAD severity (20, 31). A retrospective cohort study in Tokyo Japan found a relationship between PDR and single vessel CAD but not between PDR and multi vessel CAD (19). Limited literature is available on the prevalence of retinopathy in diabetes and non-diabetes in CAD.

A study in Tokyo, Japan found the prevalence of DR to be 39% in 90 CAD patients with Type 2 diabetes (32). Klein et al. investigated the prevalence of DR using Intima Media wall Thickness (IMT) as a surrogate for atherosclerosis (17). Both these studies

looked at the fundus through an non-dilated pupil and a recent systematic review found that as many as one third of retinopathy cases may go undetected using a single view image (as through a no-dilated pupil) (33).

In the proposed study the researcher will firstly investigate the prevalence of retinopathy in patients with CAD. Secondly the researcher will attempt to link the severity of DR with the severity of CAD by examining the fundus after pharmacologically dilating the pupils.

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Study design

Quantitative cross-sectional study

Study population

Patients undergoing Coronary Angiograms at Inkosi Albert Luthuli Central Hospital, Durban, South Africa.

Sampling strategy - Statistical planning (variables / confounders)

The sampling method is purposive because patients are pre-selected for coronary angiogram according to cardiology related indications. The sampling is also convenient rather than random as all patients going for coronary angiography will be included for

retinopathy screening.

The study will investigate the relationship and presence of coronary artery disease and retinopathy.

Other confounding variables include age and the presence of hypertension, diabetes mellitus, dyslipidemia and micro-albuminuria.

Sample size

The study aims to include 120 to 140 patients.

Inclusion / exclusion criteria

Inclusion:

All diabetic and non-diabetic patients undergoing coronary angiography with consent to take part in the study.

Exclusion:

1. Patients with no view of the fundus in both eyes.

2. Patients with pupils who do not dilate well enough for an optimal fundus view.

3. Patients known with Narrow Angle Glaucoma.

Data collection methods and tools

All patients scheduled for coronary angiography will be approached for consent either on the day of consultation at the cardiology clinic or on the day of admission at Inkosi Albert Luthuli Tertiary hospital.

Consented patients will be escorted to the Eye Clinic where both eyes will be dilated with tropicamide eye drops. Where after fundus photos will be taken. Retinopathy will be graded according to Early Treatment Diabetic Retinopathy study classification.

Information regarding patient age, gender, race, co-morbidities and degree of coronary artery disease will be collected post angiography from the Inkosi Albert Luthuli electronic patient information system.

Data analysis techniques

In order to understand the prevalence we will be using descriptive analysis, chi-square testing to highlight relationships between variables and regression analysis to highlight determinants of retinopathy in patients with coronary artery disease.

Study location

The study will take place at the Cardiology and Ophthalmology departments of Inkosi Albert Luthuli Central Hospital, Durban, South Africa.

Study period

Data collection will take place from July 2018 to December 2018. However, the period might be extended depending on the number of patients acquired at the end of the study period.

Limitations to the study

The sample size is limited due to the period of the study and the limited time available

to collect data. The study is limited to a region of and does not represent the South African population

Ethical considerations

Informed consent will be done with all potential patients. There will be no rewards for patients enrolling in the study. The benefits will include helping future patients with a similar problem to be treated more effectively and any retinopathy diagnosed that needs treatment will be referred appropriately.

All information obtained during the study will be kept anonymous. Patients will be made aware of temporary visual discomfort for the duration of the dilating eye drops' effect. As all study patients will take part in the study one day prior to their angiography procedure all efforts will be made to not disturb their pre-procedure rest and comfort.

APPENDIX II

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_201809_017

Dear Dr JF de Jager
UKZN

Approval of research

1. The research proposal titled **'The prevalence and severity of retinopathy in patients with Coronary Artery Disease (CAD) at a tertiary hospital in Durban, South Africa'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.
   c. Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 09/10/18

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APPENDIX III

Approval letter from the Biomedical Research Ethics committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

15 October 2018

Dr JF de Jager (217078222)
School of Clinical Medicine
College of Health Sciences
frikdejager@yahoo.com

Protocol: The prevalence and severity of retinopathy in patients with Coronary Artery Disease at a tertiary hospital in Durban. Degree: MMed **BREC Ref No: BE398/18**

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 09 July 2018.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 09 October 2018 to BREC letter dated 10 September 2018 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 15 October 2018. Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from **15 October 2018.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on **13 November 2018.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc postgraduate administrator
Supervisor: naidood@ukzn.ac.za

Biomedical Research Ethics Committee
Professor V Rambiritch (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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APPENDIX IV

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Office of The Medical Manager
IALCH

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@.ialch.co.za
www.kznhealth.gov.za

Reference: BE 398/18
Enquiries: Medical Management

29 August 2018

Dr J F de Jager (217078222)
School of Clinical Medicine
College of Health Sciences

Dear Dr de Jager

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **The prevalence and severity of retinopathy in patients with Coronary Artery Disease at a tertiary hospital in Durban.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

Dr N Tathiah
Acting Medical Manager

APPENDIX V

Research Data Collection sheet Date:
KZ number
Age Gender Race

Smoking (yes/no)
Hypertension (yes/no)
Diabetes (yes/no)
Dyslipidemia (yes/no)
Family history of ischaemic heart disease (yes/no)
Acute coronary syndrome (yes/no). Type: UA STEMI NSTEMI
Chronic stable angina: yes/no Arrythmia yes/no
Chest pain (typical or atypical)

Height weight BMI
Pulse Systolic BP Diastolic BP
Heart failure (yes/no) History of previous CVA

Total Cholesterol Triglyceride level
High density lipoprotein level Low density lipoprotein level
Fast glucose level HbA1C level
Urine-albumin level Urine-creatinine level Serum Creatinine

Eject fraction(%)
Date of angiogram
Reason for admission
Angiographic findings

Visual acuity R (VAR)	Visual acuity L (VAL)
VAR with pinhole	VAL with pinhole
R fundus	**L fundus**
R any retinopathy	L any Retinopathy
R Hypertensive retinopathy Y/N	L Hypertensive retinopathy Y/N
R Hypertensive retinopathy grade	L Hypertensive retinopathy grade
R Diabetic retinopathy (DR)	L Diabetic retinopathy
R non-proliferative DR Y/N Grade:	L non-proliferative DR Y/N Grade:
R Proliferative DR. Y/N Grade:	L Proliferative DR Y/N Grade:
R Clinical significant macula oedema	L Clinical significant macula oedema
R Cystoid macular oedema	L Cystoid macular oedema
R Central macular thickness	L Cystoid macular oedema
R Retinal nerve fibre layer	L Retinal nerve fibre layer
R Intraocular pressure	L Intraocular pressure
R Foveal avascular zone regular/irregular	L FAZ regular/irregular

Other retinal findings:

APPENDIX VI

Table 1

	Logit regression estimating the odds of having cad with no retinopathy						Logit regression estimating the odds of having cad with retinopathy					
	Bivariate			Multivariate			Bivariate			Multivariate		
	OR	CI	p value	OR	CI	p value	OR	CI	p value	OR	CI	p value
35-44	1.070	0.319-3.585	ns	1.274	0.190-8.545	ns	0.454	0 139-1.476	ns	0.489	0.569-4.198	ns
45-54	0.689	0.265-1.791	ns	0.307	0.064-1.464	ns	0.839	0 342-2.053	ns	2.096	0.468-9.399	ns
65-74	0.840	0.294-2.403	ns	1.092	0.189-6.309	ns	0.763	0 281-2.073	ns	0.918	0.182-4.618	ns
75+	0.205	0.010-4.054	ns	0.340	0.012-9.745	ns	5.339	0 271-105.217	ns	4.916	0.200-120.96	ns
Female	0.354	0.129-0.973	0.044**	0.282	0.047-1.695	ns	1.398	0.610-3.202	ns	1.721	0.324-9.160	ns
African	2.063	0.611-6.964	ns	3.935	0.304-50.917	ns	0.234	0.063-0.868	0.030**	0.024	0.001-1.058	0.054*
Coloured	0.488	0.023-10.480	ns	0.408	0.008-19.722	ns	0.568	0.057-5.667	ns	1.822	0.381-87.073	ns
White	1.463	0.420-5.093	ns	0.840	0.130-5.451	ns	0.671	0 201-2.246	ns	1.223	0.191-7.851	ns
Non-smoker	0.559	0.243-1.285	ns	0.442	0.105-1.869	ns	1.122	0 530-2.375	ns	2.617	0.603-11.367	ns
No HTN	1.674	0.702-3.992	ns	1.618	0.403-6.498	ns	0.607	0 262-1.404	ns	0.424	0.105-1.703	ns
No DM	1.984	0.908-4.335	0.086*	1.548	0.370-6.467	ns	0.238	0 109-0.517	0.000***	0.328	0.741-1.447	ns
No Dyslipid	0.998	0.302-3.304	ns	0.418	0.040-4.385	ns	0.993	0 316-3.118	ns	5.454	0.468-63.571	ns
No FHx ofCAD	1.153	0.506-2.629	ns	0.544	0.142-2.083	ns	0.681	0 314-1.480	ns	1.598	0.424-6.030	ns
BMI ≥25	0.766	0.326-1.804	ns	1.490	0.392-5.666	ns	1.755	0.771-3.994	ns	1.337	0.313-5.713	ns
Heartrate≥77	0.754	0.337-1.685	ns	0.722	0.192-2.717	ns	1.597	0.748-3.410	ns	2.155	0.601-7.732	ns
SBP≥130	0.767	0.355-1.657	ns	1.230	0.246-6.140	ns	1.606	0.776-3.323	ns	0.693	0.157-3.066	ns
DBP≥85	0.571	0.236-1.385	ns	0.329	0.071-1.525	ns	1.797	0.794-4.063	ns	3.012	0.680-13.340	ns
Elev TChol	1.033	0.341-3.130	ns	3.574	0.539-23.705	ns	1.104	0 382-3.185	ns	0.270	0.044-1.668	ns
Elev TG	1.476	0.617-3.534	ns	1.720	0.403-7.345	ns	0.759	0 335-1.717	ns	0.702	0.167-2.945	ns
HbA1C>6.5	0.622	0.152-2.539	ns	2.384	0.373-15.226	ns	2.566	0.634-10.379	ns	0.620	0.069-5.570	ns
EF impaired	1.022	0.433-2.414	ns	2.354	0.616-8.999	ns	1.709	0.758-3.852	ns	1.192	0.303-4.684	ns
EF severely reduced	1.185	0.409-3.435	ns	0.935	0.136-6.406	ns	1.468	0 530-4.068	ns	1.571	0.228-10.813	ns

	Logit regression estimating the odds of having cad with no DR						Logit regression estimating the odds of having cad with diabetic retinopathy					
	Bivariate			Multivariate			Bivariate			Multivariate		
	OR	CI	p value	OR	CI	p value	OR	CI	p value	OR	CI	p value
35-44	0.850	0.253-2.860	ns	1.356	0.183-10.051	ns	0.448	0 101-1.993	ns	0.399	0.036-4.473	ns
45-54	0.552	0.224-1.357	ns	1.050	0.256-4.280	ns	1.097	0.429-2.803	ns	0.481	0.087-2.650	ns
65-74	0.751	0.271-2.081	ns	2.054	0.334-12.636	ns	0.833	0 279-2.482	ns	0.456	0.071-2.947	ns
75+	1.148	0.154-8.544	ns	1.192	0.098-14.457	ns	0.961	0 129-7.172	ns	1.761	0.130-23.87	ns
Female	0.856	0.380-1.935	ns	1.300	0.314-5.373	ns	0.668	0 264-1.693	ns	0.454	0.093-2.213	ns
African	0.765	0.229-2.553	ns	0.124*	0.011-1.443	0.095	0.556	0 130-2.383	ns	3.622	0.241-54.468	ns
Coloured	0.647	0.064-6.449	ns	0.332	0.006-19.366	ns	0.422	0.020-9.057	ns	5.050	0.072-352.03	ns
White	2.459	0.576-10.49	ns	3.881	0.226-66.548	ns	0.302	0.052-1.757	ns	0.189	0.008-4.329	ns
Non-smoker	0.956	0.450-2.032	ns	1.144	0.326-4.018	ns	0.665	0 287-1.540	ns	0.861	0.214-3.468	ns
No HTN	1.118	0.472-2.652	ns	1.040	0.262-4.128	ns	0.844	0 329-2.165	ns	0.528	0.103-2.708	ns
No Dyslip	2.954	0.711-12.283	ns	3.043	0.448-20.682	ns	0.253	0.044-1.447	ns	0.431	0.052-3.554	ns
No FHx ofCAD	1.197	0.540-2.653	ns	1.850	0.467-7.336	ns	0.575	0 233-1.422	ns	0.271	0.051-1.435	ns
BMI ≥25	1.227	0.530-2.838	ns	2.350	0.545-10.138	ns	1.171	0.463-2.966	ns	0.911	0.205-4.048	ns
Heartrate≥77	0.755	0.357-1.595	ns	1.362	0.371-4.992	ns	1.769	0.797-3.927	ns	1.037	0.259-4.144	ns
SBP≥130	1.526	0.732-3.181	ns	1.249	0.292-5.343	ns	0.813	0 370-1.786	ns	0.704	0.143-3.463	ns
DBP≥85	1.313	0.586-2.940	ns	0.538	0.129-2.248	ns	0.820	0 343-1.958	ns	2.389	0.494-11.56	ns
Elev TChol	3.323	0.956-11.552	0.059*	2.248	0.372-13.572	ns	0.287	0.070-1.176	0.083*	0.258	0.361-1.833	ns
Elev TG	1.805	0.804-4.054	ns	2.173	0.615-7.682	ns	0.563	0 241-1.314	ns	0.441	0.116-1.678	ns
HbA1C>6.5	0.579	0.128-2.623	ns	0.869	0.095-7.901	ns	7.386	0.414-131.93	ns	3.302	0.145-75.08	ns
EF impaired	2.012	0.857-4.720	ns	2.391	0.609-9.384	ns	0.886	0 347-2.262	ns	1.425	0.345-5.885	ns
EF severely reduced	0.665	0.244-1.817	ns	0.338	0.060-1.917	ns	2.812*	0 982-8.053	0.054	6.775	0.926-49.597	0.060*
Abn u-album	0.146	0.027-0.785	0.025**	exclud			6.896	1 302-36.534	0.023**	exclud		

*** p<0.01, ** p<0.05, * p<0 1

Reference categories: age 55-64, male, Indian, smokers, hypertension, dyslipidaemia, + family history of CAD, BMI < 25, heart rate <77, normal systolic BP, normal diastolic BP, normal urine albumin, normal total cholesterol, normal triglycerides, normal HBA1C, normal ejection fraction

Abnormal urine albumin was only present in 27 patients. The regression analysis for this smaller sample yielded no statistical significance.

Abbreviations: OR: odds ratio, CI: confidence interval, DR: diabetic retinopathy, ns: not significant, HTN: hypertension, CAD: coronary artery disease, Dyslipid: dyslipidaemia, FHX: family history, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TChol: total cholesterol, TG: triglycerides, EF: ejection fraction, ABN: abnormal, u-album: urine-albumin, exclude: excluded

APPENDIX VII

Table 2. Association between the CAD category and retinopathy

	Chronic stable angina			Unstable angina			NSTEMI			STEMI		
	n	(%)	P value	n	(%)	P value	n	(%)	P value	n	(%)	P value
Any retinopathy	9	(75.00)	0.375	5	(55.56)	0.640	17	(56.67)	0.422	41	(70.69)	0.085
DR	3	(25.00)	0.752	1	(11.11)	0.221	10	(33.33)	0.539	20	(34.48)	0.196
NPDR	3	(100)	0.640	1	(100)	0.679	9	(90.00)	0.647	16	(80.00)	0.265
PDR	0	(0.00)	0.460	0	(0.00)	0.679	1	(10.00)	0.647	4	(20.00)	0.265
HR	6	(50.00)	0.395	2	(22.22)	0.292	12	(41.38)	0.729	23	(4.35)	0.716
Pre-clin to grade 2	6	(50.00)	0.333	2	(22.22)	0.334	12	(40.00)	0.713	22	(37.93)	0.871
Grade 3-4	0	(0.00)	0.739	0	(0.00)	0.776	0	(0.00)	0.564	1	(1.72)	0.295
FAZ regular	12	(100)		7	(87.50)		22	(78.57)		46	(83.64)	
FAZ irregular	0	(0.00)	0.127	1	(12.50)	0.850	6	(21.43)	0.255	9	(16.36)	0.647

n: number, DR: diabetic retinopathy, NPDR: non proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy, HR: hypertensive retinopathy, Pre-clin: pre-clinical, FAZ: foveal avascular zone

There was no difference in the prevalence and characteristics of retinopathy across the clinical categories of CAD.

APPENDIX VIII

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Frik De Jager

a complété avec succès - has successfully completed

Introduction to Research Ethics

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

September 28, 2017
CID : [illegible]

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

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Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Frik De Jager

a complété avec succès - has successfully completed

South Africa

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

March 9, 2018
CID : [illegible]

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

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[REV : 20170310]

APPENDIX IX

UKZN BIOMEDICAL RESEARCH ETHICS COMMITTEE

APPLICATION FOR ETHICS APPROVAL
For research with human participants (Biomedical)

Information Sheet and Consent to Participate in Research

Date:

Dear sir/madam
My name is Dr Johannes Frederik de Jager.

I am currently specializing in Ophthalmology at the University of Kwazulu-Natal. I am working full time at McCord Provincial Eye Hospital as a Registrar in Ophthalmology.

My contact number: 079 934 0865, work: 031 268 5700
My email address: frikdejager@yahoo.com

You are being invited to consider participating in a study that involves taking patients with possible heart vessel disease/narrowing of the heart vessels and taking pictures of the back of there eye (called the 'retina'). The aim and purpose of this research is to determine whether these patients have any problem with the retina and to what degree they have this problem and whether there is any correlation/relationship with the heart. The study is expected to enroll 120 to 140 patients here at Inkosi Albert Luthuli Hospital. It will involve you being escorted to the eye clinic on the day of admission to the hospital where the eye-clinic staff will test your eyes, put drops in your eyes and pictures of both your eyes will be taken. The duration of your participation if you choose to enroll and remain in the study is expected to be 2 hours.

The study may involve you having mild blurry vision for a few hours. We hope that the study will create the following benefits:

1. If any problem with the back of your eye (retinopathy) is diagnosed further treatment will be offered to you. This might prevent you from future vision loss.
2. The study hope to reveal the close relationship between problems of the heart and problems of the eye and how these problems can be prevented in the future.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee (approval number_____).

In the event of any problems or concerns/questions you may contact the researcher at 079 934 0865 or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

Participation in this research is voluntary. As a participant it is your right to withdraw from the study at any point in time and that in the event of refusal/withdrawal of participation you will not incur penalty or loss of treatment or any other benefit to which you are normally entitled.
Withdrawing from the study might mean that you will not know the condition of your own retina depending at which point in time you withdraw. Any decision of withdrawal must be reported to the relevant nursing staff at hand.
There will be no costs involved to you for taking part in this study.
All information that will be acquired during this study will be kept confidential on electronic systems that are password protected. All the information retracted from these systems for further analytical interpretation will be kept safe in my position on a data disc (flash drive) and my personal computer.

CONSENT

I (Name)_____ have been informed about the study entitled 'The Prevalence and Severity of Retinopathy in Patients with Coronary Artery Disease (CAD) at a Tertiary Hospital in Durban, South Africa.' by Dr Johannes Frederik de Jager.

I understand the purpose and procedures of the study.

I have been given an opportunity to ask questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

I have been informed about any available compensation or medical treatment if injury occurs to me as a result of study-related procedures.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher at 079 934 0865

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

_____ _____
Signature of Participant **Date**

_____ _____
Signature of Witness **Date**
(Where applicable)

_____ _____
Signature of Translator **Date**
(Where applicable)

APPENDIX X

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

26 June 2018

Prof DP Naidoo
Department of Cardiology

Dear Prof Naidoo

MMED PROTOCOL: "The prevalence and severity of retinopathy in patients with Coronary Artery Disease at a tertiary hospital in Durban, South Africa"
Student: Dr JF De Jager, Student Number: 217078222 (Department of Ophthalmology)

I am pleased to inform you that the abovementioned protocol has been approved.

Please note:

- The Academic Leader: School Research must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

Postgraduate Administrator

CC Dr de Jager

Biomedical Research Ethics Committee
Westville Campus

Postgraduate, Higher Degrees & Research
School of Clinical Medicine, NRMSM Campus
Postal Address: P/Bag X3, Congella, Durban, 4013, South Africa
Telephone: +27 (0) 31 260 4416 **Facsimile:** +27 (0) 31 260 4723 **Email:** konar@ukzn.ac.za **Website:** www.ukzn.ac.za

APPENDIX XI

Plagiarism:

DECLARATION

I.....Johannes Frederik de Jager.....declare that
(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

(iv) This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

a) their words have been re-written but the general information attributed to them has been referenced;

b) where their exact words have been used, their writing has been placed inside quotation marks, and referenced.

(v) Where I have reproduced a publication of which I am an author, co-author or editor, I have indicated in detail which part of the publication was actually written by myself alone and have fully referenced such publications.

(vi) This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the References sections.

Signed: Date: 1 September 2021

APPENDIX XII

ARTICLE SUBMISSION

All categories of manuscripts for the Cardiovascular Journal of Africa must be submitted on-line to Editorial Manager. You will be assigned your own password and user name. This will allow complete interaction between the editor and authors. Internally, reviewers will be approached to review material in their field of expertise and assigned with similar interaction. All information will be entirely protected and confidential.

All submissions should be written in a clear and succinct manner, following the style of the Journal. Title page should include a descriptive title; authors' surname and forename, address of each author and full address, telephone, fax and e-mail contacts for the corresponding author. In text: tables and figures are either inserted as part of sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (**download off-line document**). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to **info@clinicscardive.com**

All images MUST be at or above intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi Image files also must be cropped as close to the actual image as possible.

Preferred Image Format		**Alternative Image Format**	
Image Format	.tif	**Image Format**	.jpg
Image Width	Greater than or equal to intended display size	**Image Width**	Greater than or equal to intended display size

Colorspace	RGB	**Colorspace**	RGB
DPI	500+	**DPI**	500+
Alpha Channels	None	**Compression Quality**	Maximum
Layers	Flattened		

References numbered in the order of appearance in the text, according to Vancouver style. For articles: Author AB, Author C, Author M. The title of the article. Abbreviated journal title 1999; 14: 172–183. For book chapters: Author AB, Author CD. The title of the chapter. In: Editor A, Editor BC, ed. Title of the book, 2nd edn. Location: Publisher, 1999: 133 –139. DOI Numbers / PMID (Pubmed ID / PMC ID) must be added to all references to facilitate tagging for PubMed Central.

Original articles: Title page as above. Abstract (150 words) a short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results and the main conclusion. Keywords: maximum of six keywords for indexing. Introduction: concise description of background, sufficient for the non-specialist to appreciate the context of the work. Clear statement of the purpose of the study. Methods: a brief description of study design, procedures, analytical techniques and statistical evaluation. Results: a clear account of the study findings using quantitative language where possible and cross-referenced to tables and figures. Discussion: an interpretation of the study placed within the context of current knowledge, leading to specific conclusions where possible. Acknowledgements. References, figures and tables as above.

Reviews

Title page as above. Abstract (150 words) setting out the scope, key messages and conclusions of the review. Body of text liberally partitioned with headings and subheadings leading to a synopsis with conclusions at the end. Key messages in a separate box itemising two to five short principal statements. Acknowledgements,

references, tables and figures as above.

Other articles should adopt a concise style consistent with similar articles previously published in the journal. Manuscripts should include a title page, and appropriate subheadings for text. Style of tables, figures and references as above.

Figures be sent to us in a high resolution JPEG format, but they MUST be sent separately from the Word document. If not in high resolution JPEG, then PowerPoint will do.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (**download off-line document**). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to **info@clinicscardive.com**

The status of progression of the peer-review system will be directly accessible by authors. The Editorial Manager system is particularly useful to authors and reviewers as there is a direct link to PubMed for viewing all related articles on the subject matter.

Submitted manuscripts must be supplied with a covering letter with any additional information that may be helpful to the editor, such as the type or format of article that the manuscript represents. If the manuscript has been submitted previously to another journal, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Copies of any permission to reproduce published material, to use illustrations or report information about identifiable people, or to name people for their contributions must accompany the manuscript.

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APPENDIX XIII

Table 5. Angiographic and retinal findings in subjects with vs without diabetes

	Diabetic group (n = 76)		Non-Diabetic group (n = 45)		
	n	(%) / mean	n	(%) / mean	p-value
Age	76	57.46 (SD 9.6)	45	56.16 (SD 9.4)	
Male	52	(68.4)	37	(82.2)	
female	24	(31.6)	8	(17.8)	0.096
CAD type					
UA	5	(6.6)	4	(8.9)	
STEMI	43	(56.6)	15	(33.3)	
NSTEMI	17	(22.3)	13	(28.9)	
CSA	9	(11.8)	3	(6.7)	0.004
Vessel involvement					
SVD	14	(18.4)	9	(20.0)	
DVD	27	(35.5)	9	(20.0)	
TVD	33	(43.4)	16	(35.6)	0.004*
Diffuse disease	0	(0)	1	(2.2)	
Normal	2	(2.6)	10	(22.2)	
Angiographic severity					
SVD	14	(18.4)	9	(20.0)	
MVD	60	(78.9)	26	(57.8)	0.002*
Macular assessment					
CMT	74	245.0 (SD 31.5)	45	247.6 (SD 22.9)	
RNFL	75	78.9 (SD 28.7)	33	81.9 (SD 24.5)	
GCL	64	75.9 (SD 9.9)	36	74.6 (SD 12.7)	
FAZ regular	56	(78.9)	42	(95.5)	
FAZ irregular	15	(21.1)	2	(4.6)	0.015**

* Severe angiographic disease as assessed by the presence of multivessel involvement (DVD and TVD) was more frequent in the diabetic compared to the non-diabetic group. **The foveal avascular zone was more frequently abnormal in diabetics compared to non-diabetics.

n: number, SD: standard deviation, CAD: coronary artery disease, UA: unstable angina, STEMI: ST segment elevation myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, CSA: chronic stable angina, SVD: single vessel disease, DVD: double vessel disease, TVD: triple vessel disease, MVD: multi vessel disease, CMT: central macular thickness, RNFL: retinal nerve fibre layer, GCL: ganglion cell layer, FAZ: foveal avascular zone