Outcomes of Myocardial Perfusion Imaging (MPI) using Single Photon Emission Computer Tomography (SPECT) in Diabetic Chronic Kidney Failure (CKF) patients

Dr A Hassim-Sakoor

Student number: 219095428

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School of Clinical Medicine

College of Health Sciences

University of KwaZulu-Natal.

Dr A Hassim-Sakoor

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DECLARATION

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Prof A. ASSOUNGA, Supervisor [redacted]

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DEDICATION

To my dad to whom I owe everything and my spouse, Rabia, without whom I would be nothing.

Contents

CHAPTER 1

Introduction

Background

Cardiovascular disease remains the leading cause of death in patients with chronic kidney failure (CKF). A successful kidney transplant reduces mortality and improves the quality of life compared to maintenance dialysis. With the increasing burden of CKF, the high prevalence of cardiovascular disease and increasing organ transplant waiting time, the need for an effective screening strategy has become imperative.

At the Inkosi Albert Luthuli Central Hospital (IALCH) renal unit, all diabetic CKF patients being assessed for transplantation are subject to a single photon emission computer tomography myocardial perfusion imaging (SPECT-MPI) study as part of cardiac surveillance. Patients must first be assessed at the cardiac clinic before undergoing a SPECT-MPI study (with inputs from both a cardiology and nuclear medicine physician). Those with normal MPI scans are then waitlisted for transplantation, with its inherent organ wait times. Findings of myocardial perfusion defects equate to higher cardiovascular risk and these patients are excluded from the transplant waiting list. Since the inception of the use of SPECT-MPI in cardiovascular risk stratification at the renal unit, an audit of the imaging perfusion outcomes and burden of coronary artery disease (CAD) in diabetic CKF patients being assessed for transplant eligibility has not been undertaken.

Objectives

This study aims to assess the burden of coronary artery disease using MPI with SPECT in diabetic CKF patients being assessed for transplant eligibility at the IALCH, a quaternary nephrology referral centre in Kwa-Zulu Natal. Furthermore, the study will analyse the demographic characteristics and cardiovascular risk factor profile in these patients. In addition, if a statistically significant correlation between an abnormal perfusion study and the pre-transplant cardiovascular evaluation can be established, then the hypothesis to use clinical criteria as a

gatekeeper for initial risk stratification and further non-invasive testing, as suggested by current research, may be advanced in our setting.

Problem statement

After kidney transplantation, cardiovascular death remains the most common cause of mortality. Therefore, in CKF patients being assessed for kidney transplant eligibility, cardiac surveillance is paramount, and attempts to identify patients at high risk of cardiovascular events and flow-limiting CAD. Patients with CKF are more likely to be asymptomatic, owing to uremic or diabetic neuropathy, and present a challenge in diagnosing CAD. Moreover, the traditional clinical risk assessment tool using Framingham risk scores has limited value in dialysis patients, as it does not include kidney function as a significant predictor for cardiovascular mortality. Over and above this, dobutamine stress echocardiography and myocardial perfusion imaging (MPI) have moderate sensitivity and specificity in detecting obstructive CAD in chronic kidney disease (CKD)patients. In this population, with an overall lack of randomised clinical trial evidence, clinicians face the dilemma of coalescing evidence from observational studies with its inherent potential for bias, expert opinion, and extrapolation from the general population to provide care to this complex and clinically distinct cohort.

Therefore, the most appropriate approach to the investigation of CAD is the subject of considerable discussion.

Literature Review

CKF and cardiovascular disease are inextricably linked.

In patients with CKD, CVD is far more common when compared to those without CKD[1].Indeed, cardiovascular morbidity and mortality remain high in those with CKF, and this holds true after renal transplantation, as the high cardiovascular risk carries over into the post-transplant period. Patients with CKF are eight times more likely to die[2].Mortality from cardiovascular disease after stratification for age is approximately five fold higher in dialysis patients, even at the extremes of age, compared to the general population [3].Approximately half of the deaths occurring within thirty days post-transplant are due to acute myocardial infarctions.

In addition, in patients with functioning kidney allografts, cardiovascular death is the most common cause of mortality at all times after transplantation, coming to pass in 36% of patients within ten years of transplantation. In this high-risk pre-transplant population therefore, cardiac risk stratification remains critical[4], particularly in the setting of a scarcity of donor organs.

Cardiovascular risk factors in CKF patients

In patients with CKF, cardiovascular disease risk factors include diabetes mellitus, hypertension, dyslipidaemia, smoking, family history, and sedentary lifestyle. In addition, there exist non-traditional risk factors such as elevated inflammatory markers, endothelial dysfunction, fluid overload, anaemia, and dialysis. Furthermore, risk prediction tools used to assess cardiovascular risk, such as the Framingham and Atherosclerotic Cardiovascular Disease (ASCVD) may underestimate risk by as much as 50% and do not account for the high event rates in CKF patients [4].

Burden of DM and HT and CKF on the rise

The burden of CKF is increasing worldwide, driven by the rising prevalence of two major risk factors: diabetes and hypertension. The prevalence of diabetes and hypertension over the next decade will rise significantly and a concomitant increase in the incidence of CKF is foreseen[5], posing a major public health and economic burden on the fiscus. In the majority of developing regions fewer than a quarter of patients projected to develop CKF related to diabetes and hypertension ever access renal replacement therapy. Based on the population of adults living in developing regions, this translates into at least 1.2 million patients with diabetes or hypertension dying prematurely due to lack of access to therapy and over 3 million premature deaths due to all causes of CKF and lack of renal replacement therapy[5].When considering it is projected that 70% of patients reaching CKF in 2030 will be residents of low-income countries[6], this statistic becomes even more ominous.

Kidney transplantation advantageous

Africa is faced with increasing rates of non-communicable diseases such as hypertension and diabetes previously described, a high burden of infectious diseases (such as HIV), pregnancy-related diseases, trauma-related complications, environmental toxins and rapid urbanisation. This dual burden of communicable and non-communicable diseases has led to a consequential rise in the number of people affected by CKD on the continent[6].Of the aforementioned diseases ,the major risk factors in Sub-Saharan Africa (SSA) include hypertension, diabetes, HIV and glomerulonephritis[7].

Stanifer et al.[8] and Kaze et al. [9], in their systematic reviews, estimated the population prevalence of CKF to be 13.9 % and 15.8%, respectively, and report that the bulk of the CKF burden is borne by SSA.

Kidney replacement entails either chronic dialysis or kidney transplantation, both of which are lifesaving. The concept of organ donation in the annals of history dates back tithe 4th century BC, wherein the hearts of two soldiers were exchanged by the Chinese surgeon, sin Yue-Jen. The innovative experimentation in skin transplants of Medawar and Merrill et al. in the 1940s laid the foundation in the field of transplantation immunology. In 1954 Joseph Murray, MD, performed the first successful kidney transplant between identical twins, ushering in the era of solid-organ transplantation. A succession of firsts followed these, all outstanding technical accomplishments: the first successful lung transplant undertaken by James Hardy, MD, in 1963, the first successful pancreas transplant performed by Richard Lillehei, MD, in 1966, the first successful liver transplant undertaken by Thomas Starzl,MD,in1967,as well as the first successful heart transplant by Christiaan Barnard, MD, in 1967[10].

The field of transplantation has made tremendous progress since the first successful kidney transplant. Currently, kidney transplantation is preferred over dialysis due to improved quality of life and health-related outcomes [11].In addition, kidney transplantation can lead to substantial cost savings. Jarl et al. reported a saving of between 66–79% of the expected dialysis health care costs over ten years through kidney transplantation. Savings were the highest for successful transplantations, but on average the treatment was cost-saving for patients who returned to dialysis after failed kidney transplantation[11].

Kidney replacement therapy

In SSA kidney replacement therapy for CKF is markedly limited or non-existent. In South Africa, inparticular, with a resource-limited public health care sector and budget constraints, chronic dialysis slots are rationed, in general favouring the most suitable candidates, while others are denied such lifesaving therapies [7].

In the public health care sector, the incidence of kidney replacement therapy is only 4.4 per million population (pmp), compared to 139 pmp in the private sector, which serves the 16% of South Africans with medical insurance[6].The concept of rationing dialysis is an unwelcome one. South Africa has 2.1 nephrologists pmp as compared with 16 nephrologists pmp in the United States[7]. As available resources dictate therefore, the public health sector in South Africa has and will continue to ration care. Given that kidney transplantation can potentially lead to substantial cost savings, all patients selected for chronic dialysis must be transplantable as well[11].

This incorporation of transplantation as a pre-requisite for treating patients has contributed to the success of dialysis programs in South Africa. The principle of utilitarianism is applied, which refers to allocating a scarce resource (donor's kidney) in such a way that society will derive a maximum benefit from such an allocation. As a result, patients with characteristics that are less favourable, for example, habitual non-adherence with any medical treatment, alcohol abuse, illicit drug abuse, mental illness with diminished functional capacity or morbid obesity, are turned down for kidney transplantation. Furthermore, there are medical exclusion criteria as well, such as active malignancy and advanced irreversible, progressive disease of vital organs. On this basis, patients at high risk for a cardiac event are excluded from the transplant programme[7].Regrettably this is the cost of maintaining a kidney replacement program in a resource-limited setting.

Cardiac Surveillance and risk stratification

Clinical risk stratification for CAD in CKF oftentimes entails a clinical assessment using traditional cardiovascular risk factors, non-invasive structural imaging, as well as functional stress testing using SPECT for MPI, the use of cardiovascular biomarkers, and coronary angiography[12]. Of note however is that coronary angiography remains an invasive test with procedure-related complications and a high risk of contrast nephropathy in advanced CKF patients[13], such that the administration of contrast in these patients may tip them over into dialysis dependence[14].Consequently, SPECT-MPIa noninvasive pharmacological stress test with acceptable diagnostic accuracy, is widely used in screening for coronary artery disease in this patient population.

Assessing clinical variables such as hypertension, dyslipidaemia, tobacco use, and left ventricular hypertrophy is usually the initial clinical step when attempting to stratify patients into low and high-cardiovascular risk groups and in some centres, to further direct testing in higher risk patients [12]. Further non-invasive testing in this setting using SPECT MPI has provided incremental prognostic value to the clinical data [4].As alluded to previously, recipients of kidney transplants are a population at high risk of cardiovascular disease and often demonstrate the presence of several cardiovascular risk factors [3].Many regulatory agencies and scientific societies recommend non-invasive cardiovascular assessment of transplant candidates with multiple risk factors or diabetes, to identify patients at high risk of cardiovascular events to ensure that graft survival is not limited by premature death.

In the general population, the premise regarding non-invasive stress testing is to pursue exercise (treadmill) testing when appropriate, which gives added information relating to exertional symptoms and functional status. However, there remains a greater likelihood of non-diagnostic exercise tests in the CKF population due to the high prevalence of exercise intolerance and an inability to attain the age-predicted target heart rate. Against this backdrop, pharmacologic stress tests like MPI have been extensively studied and are well validated among CKF patients[15]. MPI is a functional evaluation of coronary arteries with a good negative predictive value and is cost-effective in the pre-transplant work up[15].

Several MPI studies have attempted to identify patients at risk for cardiovascular disease. In a study by Kim et al., patients were stratified into low and high-risk groups. The high-risk group patients had diabetes for more than ten years, were above fifty years of age, had a prior history of CAD, an abnormal electrocardiogram, a left ventricular ejection fraction (LVEF) of less than 40%, or a regional wall motion abnormality on echocardiography. Additionally, this high-risk group had two or more traditional CAD risk factors such as hypertension, dyslipidaemia, smoking, left ventricular hypertrophy, or family history of premature CAD. Patients were subsequently followed up for adverse cardiac events (cardiac death, non-fatal myocardial infarction, and heart failure).In the high-risk group, compared with baseline clinical data, the addition of echocardiography data improved prediction of cardiac events, and the addition of MPS data further improved the prognostic capability[12].

The American Heart Association (AHA) recommends aggregating CAD risk factors to target screening of patients with the highest pre-test likelihood of prognostically significant CAD. The presence of greater than and equal to three risk factors (DM, prior cardiovascular disease, dialysis duration more than a year, left ventricular hypertrophy, age, smoking, hypertension, and dyslipidaemia) are considered to be a reasonable indication for further non-invasive testing[16]. These risk factors proposed by the AHA were recently validated and further confirmed that MPI was predictive of obstructive CAD in patients with three or more risk factors but not in lower risk patients (two or less risk factors),and in this setting provided incremental value as a cardiovascular prognosticator [17].

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References

1. Saran, R., et al., US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis, 2017. 69(3 Suppl 1): p. A7-a8.

2. Fathala, A., M. Alqattan, and R. Alsalloum, The diagnostic accuracy of stress myocardial perfusion scintigraphy in patients with end-stage renal disease. Am J Cardiovasc Dis, 2021. 11(2): p. 246-252.

3. Sarnak, M.J., et al., Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation, 2003. 108(17): p. 2154-69.

4. Golzar, Y. and R. Doukky, Stress SPECT Myocardial Perfusion Imaging in End-Stage Renal Disease. Curr Cardiovasc Imaging Rep, 2017. 10(5).

5. Anand, S., A. Bitton, and T. Gaziano, The Gap between Estimated Incidence of End-Stage Renal Disease and Use of Therapy. PLoS ONE, 2013. 8(8): p. e72860.

6. Jardine, T., et al., Survival of South African patients on renal replacement therapy. Clin Kidney J, 2020. 13(5): p. 782-790.

7. Kilonzo, K.G., et al., Disparities in dialysis allocation: An audit from the new South Africa. PLoS One, 2017. 12(4): p. e0176041.

8. Stanifer, J.W., et al., The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health, 2014. **2**(3): p. e174-81.

9. Kaze, A.D., et al., Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. BMC Nephrology, 2018. 19(1): p. 125.

10. Rana, A., et al., Survival benefit of solid-organ transplant in the United States. JAMA Surg, 2015. 150(3): p. 252-9.

11. Jarl, J., et al., Do kidney transplantations save money? A study using a before-after design and multiple register-based data from Sweden. Clin Kidney J, 2018. 11(2): p. 283-288.

12. Shroff, G.R. and T.I. Chang, Risk Stratification and Treatment of Coronary Disease in Chronic Kidney Disease and End-Stage Kidney Disease. Semin Nephrol, 2018. 38(6): p. 582-599.

13. Cai, Q., V.K. Mukku, and M. Ahmad, Coronary artery disease in patients with chronic kidney disease: a clinical update. Curr Cardiol Rev, 2013. 9(4): p. 331-9.

14. Cheng, X.S., et al., Coronary Computed Tomography Angiography in Diagnosing Obstructive Coronary Artery Disease in Patients with Advanced Chronic Kidney Disease: A Systematic Review and Meta-Analysis. Cardiorenal Med, 2021. 11(1): p. 44-51.

15. Delville, M., et al., Prevalence and predictors of early cardiovascular events after kidney transplantation: evaluation of pre-transplant cardiovascular work-up. PLoS One, 2015. 10(6): p. e0131237.

16. Lentine, K.L., et al., Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. Circulation, 2012. 126(5): p. 617-63.

17. Doukky, R., et al., Validation of a clinical pathway to assess asymptomatic renal transplant candidates using myocardial perfusion imaging. J Nucl Cardiol, 2018. 25(6): p. 2058-2068.

Chapter 2

Outcomes of Myocardial Perfusion Imaging (MPI) using Single Photon Emission Computer Tomography (SPECT) in Pre-Transplant Diabetic Chronic Kidney Failure (CKF) patients

Prepared according to the instructions for authors of the African Journal of Nephrology

Abstract

Background

In patients with CKF, cardiovascular disease remains the leading cause of death, and this holds true after kidney transplantation as well. In addition, diabetic patients bear a high burden of coronary artery disease and are at an increased risk for cardiovascular disease. Compared to chronic dialysis, kidney transplantation offers the advantages of reduced mortality, improved quality of life and significant cost savings. Hence all patients accepted onto the chronic renal programme must be suitable transplant candidates.

On this backdrop and in the face of scarcity of donor organs, at the IALCH nephrology unit, all diabetic patients with CKF undergo cardiovascular risk stratification with a myocardial perfusion imaging (MPI) study.

Objectives

To evaluate the prevalence and clinical cardiovascular predictors of myocardial perfusion abnormalities in pre-transplant diabetic chronic kidney failure patients undergoing SPECT-MPI.

Method

A retrospective chart review of 82 diabetic CKF candidates being assessed for transplantation. The results of the work including clinical data, electrocardiogram, echocardiography, and myocardial perfusion testing, were analyzed.

Results

The prevalence of myocardial perfusion defects as determined by MPI, consistent with previous studies was significant at 20%. Most patients in the cohort were of advanced age, black African ethnicity, female gender and were hypertensive. More patients in the group with abnormal MPI had evidence of left ventricular hypertrophy, impaired left ventricular function and a history of smoking. Although the direction of the differences noted was expected, this did not reach statistical significance.

Conclusion

The evaluation of CAD in patients with CKF poses a major challenge. MPI has at best moderate diagnostic accuracy in this specific patient population. Nonetheless, it is relatively well established that perfusion defects in MPS predict cardiac events in CKF patients, and to date remains a valuable non-invasive modality in cardiovascular risk stratification. To determine optimal strategies for CAD investigation, needs well conducted randomized controlled trials.

Introduction

CKF and cardiovascular disease inextricably linked

It is well established that kidney dysfunction is a significant independent risk factor for cardiovascular events. In South Africa(SA),kidney disease accounts for a startling 1 000 deaths pmp and has become one of the leading causes of death[18].Patients with CKF are at an increased risk of cardiovascular morbidity and mortality with more than 40% of deaths being attributed to cardiovascular causes[4].This increased cardiovascular risk relates primarily to CAD[19].

Kidney replacement therapy

Kidney replacement therapy in patients with CKF is two pronged, consisting of either chronic dialysis or kidney transplantation. Since the first successful kidney transplant in 1954,and the first kidney transplant on the African continent undertaken by Thomas Starzl and Bert Myburgh in Johannesburg, South Africa (SA), in 1966[18],the field of kidney transplantation has hitherto made tremendous progress, and provides an improved quality of life as well as a robust advantage in terms of survival when compared to chronic dialysis[11].

In addition, kidney transplantation presents a substantial cost saving compared to chronic dialysis, as outlined by a study in Sweden which showed a 75% lower than the expected cost at six years[11].

Given the advantages that kidney transplantation presents, all patients selected for chronic dialysis at the IALCH renal unit, must be transplantable as well.

Of note though, even after kidney transplantation, the atherosclerotic process previously alluded to remains high, with hyperlipidaemia, hypertension and hyperglycemia often aggravated by immunosuppressant therapy (corticosteroids, calcineurin inhibitors)[19].The high cardiovascular

risk aforementioned, therefore, remains the leading cause of death post kidney transplantation, with as much as half of the deaths occurring within thirty days after transplant being attributed to acute myocardial infarctions[4].

CKF remains a global public health problem and it is estimated that the majority of dialysis patients, in the region of 80%,reside in the developed world countries, i.e. Europe, Japan and the USA[6]. For the majority of South Africans, in terms of access to kidney replacement therapy, there has been no real growth over the past two and a half decades[6].Importantly, present reports need to account for the substantial proportion of patients who die without ever accessing care. Hence the true burden of Cafes underestimated.

The availability of human organs for transplantation remains scarce the world over, and this holds true for SSA[11].In South Africa, with a resource-constrained public health care sector, kidney replacement therapy and dialysis slots are strictly rationed. Hence guidelines priorities selection of patients based on suitability for transplantation[7].

Cardiac Surveillance

In patients with CKF the high prevalence of CAD is largely attributable to the clustering of typical atherosclerotic risk factors such as hypertension, diabetes mellitus, dyslipidaemia, family history, sedentary lifestyle and tobacco use. The uremic milieu and the inflammatory state of CKF, with high levels of C-reactive protein and pro-inflammatory cytokines, further contribute to the accelerated progression of plaque formation and CAD[20].Furthermore , CKF patients who have developed CAD are frequently asymptomatic due to impaired capacity to exercise or due to diabetic or uremic neuropathy [2]. Consequently, these patients are more likely to present with an acute coronary syndrome as the first manifestation of CAD, as opposed to angina that is typically seen in patients without kidney disease[20]. Atherosclerosis in addition, is further driven by the high oxidative stress and endothelial dysfunction which are exacerbated in the setting of an activated renin–angiotensin–aldosterone system in CKF[20]. Given the high cardiovascular risk that patients with CKF pose, and to further ensure that graft survival is not limited by premature cardiovascular death, screening for cardiovascular disease therefore becomes imperative when assessing the eligibility for kidney transplantation[21].

Non-invasive Imaging to assess CAD

Identifying coronary artery disease, in patients with CKF presents a challenge[22], and in kidney transplantation candidates, centre specific guidelines aim to guide cardiovascular evaluation. The overarching goal and objective are to identify the subset of patients who may maximally benefit from renal transplantation. Noninvasive testing with an electrocardiogram (ECG), transthoracic echocardiogram, pharmacological stress echocardiography, and nuclear imaging SPECT are suggested in investigating for the presence of CAD. However there remains no universal consensus regarding the optimal noninvasive test modality[20].

The cardiovascular evaluation in patients with CKF differs from the general population in that these patients represent a fragile cohort. For an exercise stress test to be diagnostic and adequate, 85% of the maximal predicted heart rate needs to be achieved. The vast majority of patients cannot fulfill this target due to systemic illnesses that limit their mobility, or in instances where the baseline electrocardiogram is abnormal such as with a paced rhythm, Wolff Parkinson White (WPW) syndrome, left bundle branch block (LBBB), left ventricular hypertrophy(LVH), or ST-segment depression greater than 1mm[23].Therefore, due to the aforementioned reasons, in this patient population , exercise electrocardiogram is not recommended[19].

Coronary angiography with its procedure-related complications, further presents the risk of contrast nephropathy and may potentiate the premature initiation of dialysis[14].Additionally, CT angiography is frequently hampered by high rates of coronary calcification[19]. Contrast-enhanced cardiovascular magnetic resonance (CMR) is another established and validated modality for the assessment of CAD, allowing evaluation of both myocardial perfusion defects and infarct burden. However, the administration of gadolinium-based contrast is contraindicated in patients with advanced kidney disease due to the risk of nephrogenic systemic fibrosis[22].

A baseline transthoracic echocardiogram, performed at dry weight can help identify impaired left ventricular function and wall motion abnormalities and provide evidence of prognostically significant CAD and therefore forms part of the pre-transplant diagnostic work up at IALCH [19]. In patients with CKF the role of MPS in predicting cardiac events is relatively well-established. In addition, many studies have demonstrated the prognostic value of MPS in patients with CKF[2]. An abnormal stress MPI is associated with a clear increase in the risk of

cardiac ischemic events, and conversely, a fairly good outcome is predicted with a normal stress MPI in patients with CKF[19].Kidney transplant candidates with diabetes mellitus represent a high-risk group for coronary artery disease. Consequently, in addition to transthoracic echocardiography, the IALCH transplant unit utilizes myocardial perfusion SPECT imaging in the cardiac surveillance of all diabetic CKF patients.

Technical Aspects of MPI- SPECT

The principal tenet behind stress testing is to assess the ability of the coronary circulation to augment blood flow, reflecting coronary flow reserve [23]. Stress imaging attempts to identify ischemic myocardial tissue, by comparing hemodynamics at rest and during hyperaemic stress. This hyperaemic stress state, is induced via coronary artery vasodilators such as adenosine, regadenosonor dipyridamole[24], which exert their effect on coronary flow reserve directly by increasing the coronary flow[23].

In the setting of flow-limiting coronary stenosis, stress testing induces hypoperfusion ,and in turn diagnoses coronary artery disease (CAD)[23]. Indeed, stress imaging can detect pre-symptomatic stenoses[24] and, as mentioned previously, has been recognised as a successful predictor of major adverse cardiovascular events.

Myocardial perfusion SPECT imaging presents the advantages of being relatively simple to perform and analyze, particularly in the setting of the increasing number of patients for whom echocardiography or MRI is contraindicated or unreliable, as seen in atrial fibrillation and other rhythm disturbances, as well as in the presence of a poor acoustic window, certain metallic implants or a pacemaker [19].

At the IALCH nuclear medicine department the radio isotope tracer employed is an isonitrile compound labelled with technetium -99m: Sestamibi, and the MPI SPECT scan undertaken is often colloquially referred to as a MIBI scan. The tracer above mentioned distributes proportionally to regional blood flow. It has a low washout after entering myocardial cells, allowing the acquisition of perfusion images up to two hours post injection of radio isotope. A double injection is required to compare myocardial perfusion after stress and at rest , and the two studies are performed on separate days. SPECT refers to the tomographic or three-dimensional

acquisition of images and is performed with dual-headed gamma cameras allowing good visualization of the left ventricle.

A homogenous uptake of tracer inside the left ventricular wall occurs in normal subjects during stress and rest, appearing as an orange yellow colour in Figure 1. Perfusion defects are detected when there is a lack of tracer uptake. The presence of reversible perfusion defects i.e., during stress with normalization during rest is an expression of transient ischemic changes (Figure 2). Lastly the expression of fixed defects in both stress and rest images implies myocardial infarction (Figure 3). Nuclear physician and cardiologist concurred with a <5% interobserver variability. An abnormal MPI study was defined as evidence of infarction, ischemia, or both.

Method

a. Study design

A retrospective descriptive chart review of diabetic CKF patients being assessed for transplant eligibility. Patients were selected for this study by using the ICD 10 coding system to identify all diabetic patients diagnosed with CKF and referred for MPS imaging as part and parcel of pre-transplant cardiac surveillance at the IALCH kidney unit.

b. Study setting

IALCH is an 842-bed quaternary referral centre. The study source is the entire area that refers patients to the nephrology unit which includes KwaZulu Natal and part of the Eastern Cape.

c. Study population

All diabetic CKF patients being assessed for transplant eligibility at the IALCH nephrology unit between 1 January 2014 and 31 December 2018.

d. Sampling strategy

The sampling technique employed was non-probability convenience sampling. All patients that fulfilled the criteria during the specified time were included in the study.

e. Inclusion criteria

All diabetic CKF patients,13years and older being assessed for kidney transplant eligibility.

f. Exclusion criteria

Patients with appeals and reassessments, and patients that were transitioned back to dialysis following failed transplantation. Patients with inconclusive scan reports. Appeals and reassessments refers to those candidates deemed unsuitable for kidney transplantation, who displayed other transplant exclusion criteria, for example active malignancy or psychiatric illness. Over the study period; however, no files with appeals and reassessments were identified.

g. Data collection

The IALCH electronic database (Speedminer) was used to access patient records. Patients diagnosed with chronic kidney failure (on dialysis or glomerular filtration rate <15 mL/min/1.73 m^2)were identified using the ICD 10 coding system. Hospital electronic medical records including clinician notes, demographic data, and results of all investigations performed were accessed from this database.

Clinical data were retrospectively tabulated via detailed chart review and entered into a Microsoft excel spreadsheet. Demographic data collected included age, gender, ethnicity, and time spent on dialysis. In addition, data were collected on cardiovascular variables including hypertension, tobacco use, dyslipidaemia, and prior CVD (CAD, heart failure, peripheral arterial disease, and cerebrovascular disease).

Diabetes was defined as individuals with a medical history of diabetes, taking anti-diabetic agents (oral hypoglycemic agents, insulin, or a combination). Hypertension was defined as a medical history of high blood pressure with subjects taking blood pressure-lowering medication or a blood pressure level of 140/90 mmHg or higher at admission. The definition of dyslipidaemia was a medical history of dyslipidaemia with subjects taking lipid-lowering medication, or with the following abnormal lipid cut-off levels (total cholesterol ≥5.18 mmol/L, triglycerides ≥1.7 mmol/L, low-density lipoprotein cholesterol ≥2.59 mmol/L, and high-density lipoprotein cholesterol,<1.3 mmol/L in females or,<1.0 mmol/L in males).

Smoking was defined as those individuals with a past or active smoking history as documented in the electronic medical records.

Electrocardiographic LVH was diagnosed following Sokolow-Lyon criteria when the voltage amplitude sums of either SV1 + RV5 or SV1 + RV6 at baseline was equal to/or above 3.5 mV. Echocardiography results were classified as normal, impaired left ventricular function (a left ventricular ejection fraction of <40%), or regional wall motion abnormality (RWMA).

In the MPI study, infarction was defined as a fixed reduction in myocardial tracer uptake in both stress and rest images. Ischemia was defined as a reversible stress-induced reduction in myocardial tracer uptake (reversal by more than 10% with rest). A fixed and reversible reduction in myocardial tracer uptake could occur in different areas of the left ventricle in the same patient.

h. Statistical Analysis

STATA version 17 was used to analyse the data. Descriptive statistics were used to summarise the data. Numbers and percentages are used for all the categorical data, and medians and interquartile ranges for the continuous variables of age and dialysis duration. Fisher's exact test was used to compute the p values for comparisons on the categorical variables. The Mann-Whitney U test was used to compare the subgroups on the continuous variables of age and dialysis duration. A p value <0.05 was considered statistically significant for the variables being evaluated.

i. Ethical considerations

The study is retrospective, hence subjects were not exposed to any harm or intervention. As no identifiable personal data was utilised, anonymity and confidentiality were ensured. Patient personal information was used by the involved researchers with no personal information being transferred to third parties. Relevant gatekeeper and hospital permissions were obtained. The study was approved by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu Natal (BREC/00000954/2020), the IALCH hospital board and the KwaZulu Natal Department of Health. A copy of the study protocol is attached.

Results

Spanning a period of 5 years from 1 January 2014 to 31 December 2018, 82 patients with diabetes and CKF, were referred for a SESTAMIBI myocardial perfusion study to determine eligibility for kidney transplantation and the chronic kidney programme. From this group, all of the 82 files retrieved by the search criteria, had adequate clinical assessments and clinical notes and were selected for the study. Over this same period, none of the patients had inconclusive SESTAMIBI scan reports.

Description of the total sample of patients in the study (Table 1)

The ages of the patients in the total study population ranged between 22 and 73 years, with approximately half of the patients aged 59 years or older. Forty eight patients (59%) were female and of black African ethnicity.

Sixteen patients (20 %) showed abnormal MPS (reversible or fixed defect) with the remaining 66 patients (80%) having normal MPI scans reported.

Table 1 Demographic characteristics of the total study group

		Abnormal MPI Ischemia or Infarction						Fisher's exact test (*p*)
		No		Yes		Total		
Total patients		66	80%	16	20%	82	100%	
Demographics								
Age in years: Median (Interquartile range)		59.0 (11.0)		58.5 (10.5)		59.0 (11.0)		0.935*
Sex	Female	40	61%	8	50%	48	59%	0.573
	Male	26	39%	8	50%	34	41%	
Race	Asian	21	32%	6	38%	27	33%	0.937
	African	39	59%	9	56%	48	59%	
	White	2	3%	0	0%	2	2%	
	Coloured	4	6%	1	6%	5	6%	

The cardiovascular evaluation (Table 2) showed that of the total study group, twenty one (26%) demonstrated electrocardiographic evidence of left ventricular hypertrophy. Echocardiography was normal in seventy four (90%) patients with the remaining eight patients (10%) having impaired left ventricular function. None of the patients demonstrated regional wall motion abnormalities.

Indicators of prior cardiovascular disease were not statistically significant. One patient presented with a history of previous heart failure and another patient had a history of peripheral artery disease (both in the abnormal MPI study group). None of the patients in the total group had a prior history of coronary artery disease or a cerebrovascular accident..

The cardiovascular risk factor indicators showed that hypertension was very common and present in eighty patients (98 %) of the total study group. In addition, forty three (52%) of subjects had dyslipidaemia; eight (10%) were smokers, and only seven (9%) patients had a positive family history of premature coronary artery disease.

Concerning the dialysis vintage, nineteen (29%) subjects had been on dialysis for up to 6 months, a further nineteen (29%) had been on dialysis for 7 to 12 months and the remaining 13 (20%) received dialysis for longer than a year. Ten patients (15%) had been on dialysis for 24 months, one patient for 36 months and one other for 60 months. Less than a quarter 18 (22%) of subjects were being prepared for initiation of dialysis. Of the 64 patients on dialysis, the median dialysis duration was 7.5 months with an interquatile range of 8 months. The median dialysis vintage of the total study sample was six months with an interquatile range of ten months.

Subgroup characteristics and comparison

Table 2 also provides the non-directional Fisher's exact test *p* values for comparisons of the normal versus abnormal MPI subgroups. Fisher's exact test was more appropriate than the Pearson Chi square test for comparisons on categorical variables as most of the comparisons involved small cell sizes and low expected frequencies which went against Chi square test assumptions. The age distribution was significantly negatively skewed at -1.05 ($p<.001$), and the dialysis duration distributions were significantly positively skewed ($p<.001$) with skewness values of 1.13 and 2.17 excluding patients not initiated on dialysis, and including these patients,

respectively. Correlations between pairs of other indicators were either non-significant or based on variables with insufficient variability for reliable results.

Table 2: Description and comparisons of patients without versus with ischemic lesions, and total group (n=82)

		Abnormal MPI Ischemia or Infarction						Fisher's exact test (*p*)	Odds Ratios p
		No		Yes		Total			
Total patients		66	80%	16	20%	82	100%		
Cardiovascular evaluation									
Left ventricular hypertrophy	Yes	13	20%	4	25%	17	21%	0.732	1.36 p=.64
	No	53	80%	12	75%	65	79%		
Echocardiography normal	Yes	60	91%	14	88%	74	90%	0.650	0.70 p=.68
	No	6	9%	2	13%	8	10%		
Impaired left ventricular function	No	59	89%	14	88%	73	89%	1.000	0.83 p=.83
	Yes	7	11%	2	13%	9	11%		
Regional wall motion abnormality	No	66	100%	16	100%	82	100%		
Prior Cardiovascular Disease									
Coronary artery disease	No	66	100%	16	100%	82	100%		
Heart failure	No	65	98%	16	100%	81	99%	1.000	0.76 p=.87
	Yes	1	2%	0	0%	1	1%		
Peripheral artery disease	No	65	98%	16	100%	81	99%	1.000	0.76 p=.87
	Yes	1	2%	0	0%	1	1%		
CVA	No	66	100%	16	100%	82	100%		
Cardiovascular risk factors									
Ht	Yes	64	97%	16	100%	80	98%	1.000	1.28p=.88
	No	2	3%	0	0%	2	2%		
Lipid	Yes	36	55%	7	44%	43	52%	0.578	0.65 p=.44
	No	30	45%	9	56%	39	48%		
Smoking	No	61	92%	13	81%	74	90%	0.183	0.36 p=.19
	Yes	5	8%	3	19%	8	10%		
Family history	No	60	91%	15	94%	75	91%	1.000	1.5p=.72
	Yes	6	9%	1	6%	7	9%		
Dialysis duration (months) for 64 patients on dialysis: Median (Interquartile range)		8.5 (9.0) n=52		4.5 (6.0) n=12		7.5 (8.0) n=64		0.012*	

**p* value for Mann Whitney U test

Discussion

Diabetic patients are at high risk for cardiovascular disease development and bear a greater burden of coronary artery disease[25]. In addition, patients with CKF are at a considerably increased risk of cardiac events. This double bullet of diabetes and CKF places transplant candidates at a heightened cardiovascular risk and is relevant concerning the scarcity of available organs. This forms the basis of the rationale adopted by the IALCH renal department in referring all diabetic CKF patients for cardiac risk stratification using MPI. Our results show a prevalence of myocardial perfusion abnormalities of 20% in diabetic CKF patients being assessed for transplant eligibility. In the setting of resource constraints, the harsh reality is that these high-risk patients with perfusion defects will effectively be excluded from the transplant waiting list and the chronic renal programme. The alternative is private medical care and if this is not feasible, a palliative care plan for these non-selected patients will then be implemented.

The prevalence of perfusion defects with MPI in CKF that we report in this study, is comparable to previous research where Hase et al. in 2004 reported perfusion defects in 27% of subjects, and Momose et al. in 2009 reported frequencies of myocardial ischaemia and resting perfusion defects, to be 22 and 20% respectively. In addition, in a recent study using MPS in 2021 by Bautz et al.,a 16% prevalence of myocardial perfusion defects using MPI in CKF was reported [26].

In our study cohort, the median age was 59 years, in keeping with the shift noted in kidney transplant waitlist toward older adults. The ethnic distribution showed that most patients were black (59%).An audit in the Western Cape by Kilonzo et al, report a black ethnic distribution of 43%[7].This trend, in keeping with the present government's policy to provide equitable access to healthcare, is promising ,given the covert discrimination in access to chronic dialysis in our historically unequal past. To this end, the IALCH renal department has adopted guidelines and prioritization criteria, wherein selection for the chronic renal programme is based on suitability for transplantation. These rationing guidelines are formally adhered to and can be defended on a moral, legal and ethical basis.

In the group with abnormal perfusion scans, 44 % demonstrated electrocardiographic evidence of LVH versus 21% in those with normal MPI scans. In this same group with perfusion defects,13% demonstrated impaired left ventricular function compared to 9% in the normal MPS group.

Hypertension confers a two-fold risk of coronary heart disease and is the leading attributable risk factor for heart disease and premature death worldwide [14].In South Africa, about 45% of men and 48% of women older than 15 years have hypertension [15]. The high prevalence of hypertension in patients with CKF is exemplified in this study, with almost all patients (98%) presenting with hypertension in the total study group. Hypertension was prevalent in all patients in the group with perfusion defects and in most patients (97%) in the group with normal Pisceans.

More subjects in the normal study group had dyslipidaemia (55 %) compared to the group with perfusion defects (44 %). A past or active smoking history was more prevalent in the ischemia–infarction group (19 %) versus 8 % in those with a normal MPI study. The presence of prior cardiovascular disease did not reach statistical significance, with 98% of patients having no prior cardiovascular disease.

The relationship between a family history of premature coronary artery disease in first-degree relatives and increased risk of atherosclerotic cardiovascular disease is well described [27].The age-adjusted odds ratio of cardiovascular events is estimated to be approximately two and a half times greater among individuals with a family history of premature coronary artery disease [28].This risk of premature cardiovascular events increases linearly with an increase in the number of affected family members[29]. Herein we report a positive family history of premature coronary artery disease in 9% of subjects with normal perfusion scans versus 6 % in those with abnormal perfusion scans. This contrasts with other studies that have reported a higher prevalence of perfusion defects in those with a family history of premature cardiovascular disease. One possible explanation could relate to the collection of data when taking a family history and underscores the importance of collecting a family history beyond the parental history of cardiovascular disease when attempting to risk stratify patients.

The dialysis vintage in this study was longer for patients without perfusion defects versus those with perfusion defects (U=167,Z=2.49,p=.012) with median values of 8.5 and 4.5 months, respectively. The American Heart Association and the American College of Cardiology, in addition to traditional cardiovascular risk factors, consider a dialysis vintage greater than a year an additional risk factor for coronary artery disease in the transplant population[30].Previous research reports an association between abnormal MPS and a longer duration of dialysis. Bautz et al., in a larger study of 229 patients, reported a median dialysis duration of 19 months. Furthermore, in this same study, the median dialysis duration was 27 months in those with abnormal MPS compared to 16 months in those with normal MPS. In addition, a longer duration of dialysis was found to be a strong predictor of adverse cardiovascular events[26].

The findings in our study, of a relatively short duration of dialysis (median duration of 7.5 months) could be attributed to a relatively common occurrence wherein patients present late to the nephrology service with advanced stages of disease and uremic symptoms. This is in contrast to patients in developed world centres, who commence dialysis earlier and therefore exhibit cardiovascular disease after a longer period of dialysis. In addition, other causes of mortality could account for the shorter period of dialysis.

Conclusion

Our results show that the prevalence of myocardial perfusion defects as determined by MPS in diabetic kidney transplant candidates was significant at 20%. Of the risk factors for coronary artery disease, left ventricular hypertrophy, echocardiographic evidence of impaired left ventricular function as well as a past or current history of smoking was noted more in the group with perfusion defects when compared to the normal MPI study group. Although the direction of the differences noted are expected, this did not reach statistical significance given the study sample size. In addition, our findings were not consistent with current literature of an association between a longer dialysis vintage and abnormal stress perfusion.

In summary therefore, there is insufficient evidence in this study to claim any significant differences between patients without, versus with perfusion defects on the indicators considered for demographics, cardiovascular evaluation, prior cardiovascular disease, and cardiovascular risk factors. It is important to bear in mind however that “absence of evidence is not evidence of absence”[31].

Cardiac risk stratification in CKF remains a challenge due to the limitations of available imaging modalities. The diagnostic accuracy of SPECT-MPI, though imperfect in kidney transplantation candidates, remains a valuable non-invasive imaging protocol for pre-transplant cardiovascular stratification in CKF in our setting.

Limitations

The retrospective nature of the study serves as a limitation. The highly selective and convenient sample population risks selection bias. Another limitation is that this is a single centre study

Competing interests

The authors of this study declare no competing interests.

Author contributions

Dr A Hassim-Sakoor, Prof A Assounga (supervisor) and Prof R Bhimma (co-supervisor) contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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Data availability

The data supporting this study's findings are not openly available due to patient confidentiality and are available upon reasonable request.

Disclaimer

The views expressed in this article are those of the authors and not an official position of the institution.

APPENDICES

Images

Key:

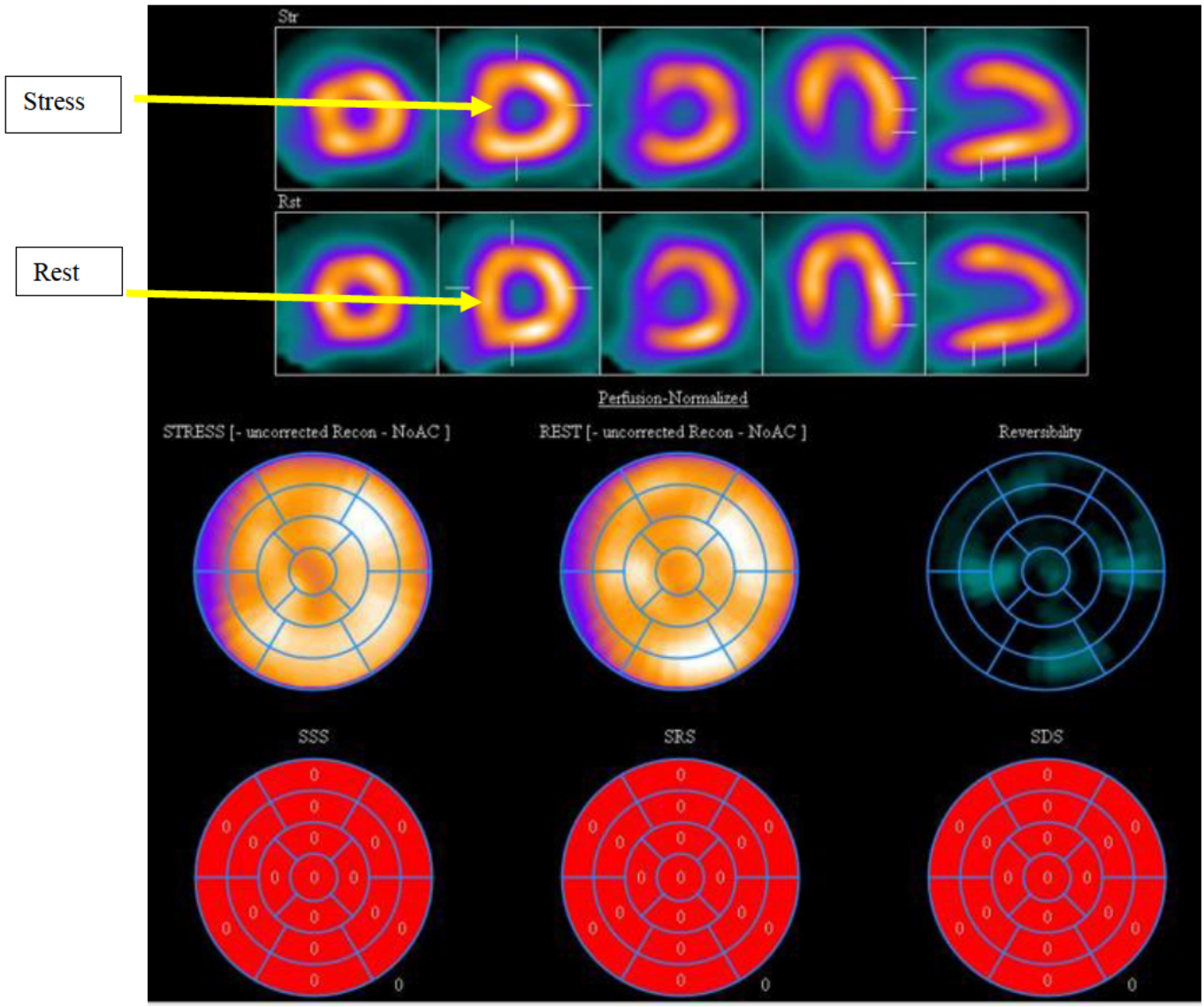

Figure1:A homogenous uptake of tracer inside the left ventricular wall during stress and rest

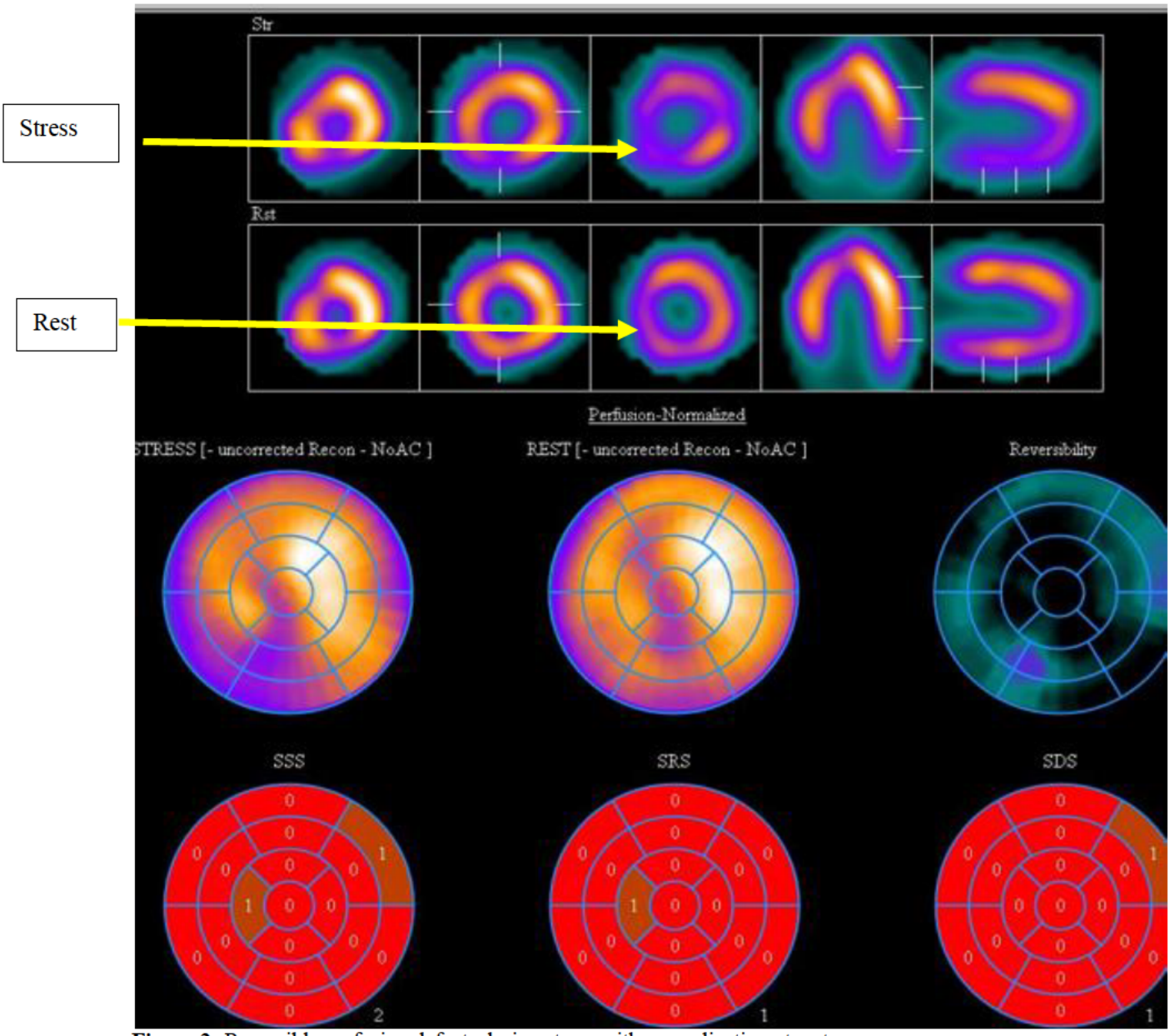

Figure 2: Reversible perfusion defects during stress with normalization at rest

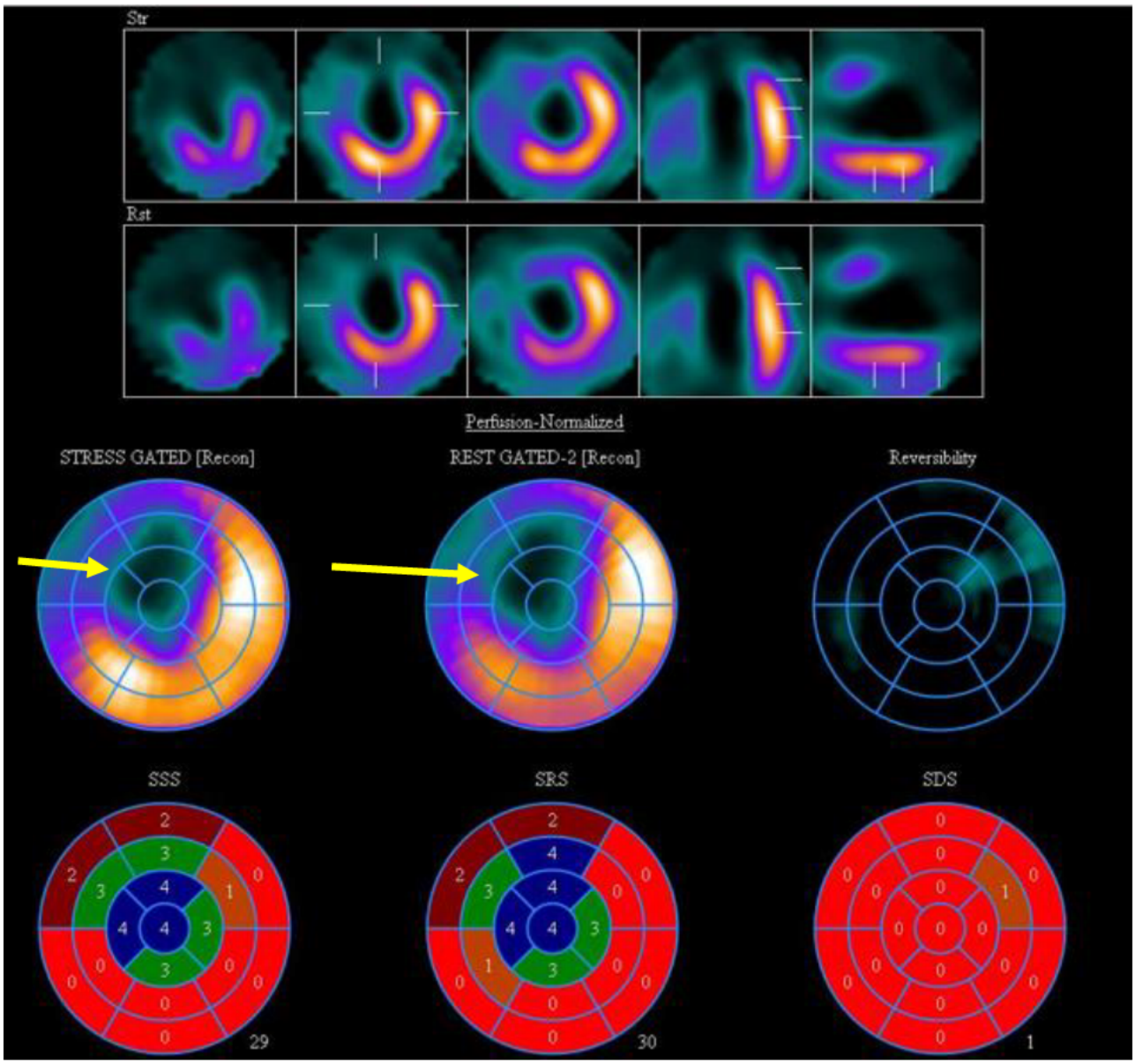

Figure 3: Transmural infarct showing fixed defects in both stress and rest

References

1. Saran, R., et al., US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis, 2017. 69(3 Suppl 1): p. A7-a8.

2. Fathala, A., M. Alqattan, and R. Alsalloum, The diagnostic accuracy of stress myocardial perfusion scintigraphy in patients with end-stage renal disease. Am J Cardiovasc Dis, 2021. 11(2): p. 246-252.

3. Sarnak, M.J., et al., Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation, 2003. 108(17): p. 2154-69.

4. Golzar, Y. and R. Doukky, Stress SPECT Myocardial Perfusion Imaging in End-Stage Renal Disease. Curr Cardiovasc Imaging Rep, 2017. 10(5).

5. Anand, S., A. Bitton, and T. Gaziano, The Gap between Estimated Incidence of End-Stage Renal Disease and Use of Therapy. PLoS ONE, 2013. 8(8): p. e72860.

6. Jardine, T., et al., Survival of South African patients on renal replacement therapy. Clin Kidney J, 2020. 13(5): p. 782-790.

7. Kilonzo, K.G., et al., Disparities in dialysis allocation: An audit from the new South Africa. PLoS One, 2017. 12(4): p. e0176041.

8. Stanifer, J.W., et al., The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health, 2014. 2(3): p. e174-81.

9. Kaze, A.D., et al., Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. BMC Nephrology, 2018. 19(1): p. 125.

10. Rana, A., et al., Survival benefit of solid-organ transplant in the United States. JAMA Surg, 2015. 150(3): p. 252-9.

11. Jarl, J., et al., Do kidney transplantations save money? A study using a before-after design and multiple register-based data from Sweden. Clin Kidney J, 2018. 11(2): p. 283-288.

12. Shroff, G.R. and T.I. Chang, Risk Stratification and Treatment of Coronary Disease in Chronic Kidney Disease and End-Stage Kidney Disease. Semin Nephrol, 2018. 38(6): p. 582-599.

13. Cai, Q., V.K. Mukku, and M. Ahmad, Coronary artery disease in patients with chronic kidney disease: a clinical update. Curr Cardiol Rev, 2013. 9(4): p. 331-9.

14. Cheng, X.S., et al., Coronary Computed Tomography Angiography in Diagnosing Obstructive Coronary Artery Disease in Patients with Advanced Chronic Kidney Disease: A Systematic Review and Meta-Analysis. Cardiorenal Med, 2021. 11(1): p. 44-51.

15. Delville, M., et al., Prevalence and predictors of early cardiovascular events after kidney transplantation: evaluation of pre-transplant cardiovascular work-up. PLoS One, 2015. 10(6): p. e0131237.

16. Lentine, K.L., et al., Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. Circulation, 2012. 126(5): p. 617-63.

17. Doukky, R., et al., Validation of a clinical pathway to assess asymptomatic renal transplant candidates using myocardial perfusion imaging. J Nucl Cardiol, 2018. 25(6): p. 2058-2068.

18. Moosa, M., The state of kidney transplantation in South Africa. South African Medical Journal, 2019. 109(4): p. 235-240.

19. Marie, P.-Y. and P. Rossignol, Stress myocardial perfusion gated-SPECT imaging in advanced chronic kidney disease. Journal of Nuclear Cardiology, 2019. 26(6): p. 1971-1973.

20. Bhatti, N.K., et al., Diagnosis and Management of Cardiovascular Disease in Advanced and End‐Stage Renal Disease. Journal of the American Heart Association, 2016. 5(8): p. e003648.

21. Bestetti, A., et al., Diagnostic and Prognostic Role of Myocardial Perfusion Scintigraphy in Kidney Transplant Candidates: Narrative Review. Heart International, 2016. 11(1): p. heartint.500023.

22. Poli, F.E., et al., The reliability and feasibility of non-contrast adenosine stress cardiovascular magnetic resonance T1 mapping in patients on haemodialysis. J Cardiovasc Magn Reson, 2020. 22(1): p. 43.

23. Elkholy, K.O., et al., Regadenoson Stress Testing: A Comprehensive Review With a Focused Update. Cureus, 2021. 13(1): p. e12940.

24. Weyers, J.J., et al., Myocardial blood flow is the dominant factor influencing cardiac magnetic resonance adenosine stress T2. NMR in Biomedicine, 2022. 35(3): p. e4643

25. Shmendi, A., et al., Myocardial perfusion imaging for evaluation of suspected ischemia and its relationship with glycemic control in South African subjects with diabetes mellitus. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 2014: p. 545.

26. Bautz, J., et al., Prognostic implication of myocardial perfusion and contractile reserve in end-stage renal disease: A direct comparison of myocardial perfusion scintigraphy and dobutamine stress echocardiography. J Nucl Cardiol, 2021.

27. Khera, A. and E. Ajufo, Family History of Premature Atherosclerotic Cardiovascular Disease, in Cardiovascular Risk Assessment in Primary Prevention, M.D. Shapiro, Editor. 2022, Springer International Publishing: Cham. p. 149-175.

28. Osadnik, T., et al., Family History of Premature Coronary Artery Disease (P-CAD)—A Non-Modifiable Risk Factor? Dietary Patterns of Young Healthy Offspring of P-CAD Patients: A Case-Control Study (MAGNETIC Project). Nutrients, 2018. 10(10): p. 1488.

29. Chacko, M., et al., Family history of cardiovascular disease and risk of premature coronary heart disease: A matched case-control study. Wellcome Open Res, 2020. 5: p. 70.

30. Bhatti, N.K., et al., Diagnosis and Management of Cardiovascular Disease in Advanced and End-Stage Renal Disease. Journal of the American Heart Association, 2016. 5(8): p. e003648.

31. Altman, D.G. and J.M. Bland, Absence of evidence is not evidence of absence. Bmj, 1995. 311(7003): p. 485.

Research Protocol submitted to BREC

Title

Outcomes of Myocardial Perfusion Imaging (MPI) using Single Photon Emission Computer Tomography (SPECT) in Diabetic Chronic Kidney Failure (CKF) patients

Aim of the study

To determine the burden of myocardial ischemia in diabetic CKF patients being assessed for transplant eligibility at Inkosi Albert Luthuli Central Hospital

Specific objectives

1. To assess the demographic profile of pre-transplant diabetic end-stage kidney disease patients
2. To determine the burden of coronary artery disease using MPI with SPECT in diabetic end-stage kidney disease patients being assessed for transplant eligibility
3. To evaluate the cardiovascular risk factor profile in pre-transplant diabetic end-stage kidney disease patients

Background and literature

Cardiovascular disease remains the leading cause of death in patients with CKF and a successful kidney transplant reduces mortality and improves quality of life when compared to maintenance dialysis. Due to the scarcity of donor organs, cardiovascular evaluation has become of paramount importance. Cardiac surveillance attempts to identify patients at high risk of cardiovascular events and flow-limiting coronary artery disease. This oftentimes entails a clinical assessment using traditional cardiovascular risk factors, non-invasive evaluation with functional stress testing using single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), the use of cardiac biomarkers, as well as invasive coronary angiography. The

extent of cardiac evaluation is centre specific and across the board, societal recommendations vary in this regard. Whereas a coronary angiogram will provide morphological information of the coronary arteries, non-invasive MPI will provide a functional state of coronary stenosis. Studies have shown that non-invasive MPI provides additional diagnostic and prognostic value when integrated with clinical assessment tools that use cardiovascular risk factor scores. With the increasing burden of ESKD, the high prevalence of cardiovascular disease and increasing organ transplant waiting time, the need for an effective screening strategy has become imperative. Atthe Inkosi Albert Luthuli Central Hospital (IALCH) renal unit, all diabetic CKF patients being assessed for transplantation are subject to a SPECT MPI study as part of cardiac surveillance. Patients must first be assessed at the cardiac clinic before being booked for a SPECT MPI study (with inputs from both a cardiology and nuclear medicine physician), prior to being waitlisted for transplantation, with its inherent organ wait times. Findings of myocardial perfusion defects equate to higher cardiovascular risk and these patients are excluded from the transplant waiting list. Since inception of the use of SPECT MPI, an audit of the imaging perfusion outcomes has not been undertaken.

This study will attempt to evaluate the burden of coronary artery disease (CAD) as determined by SPECT MPI, as well as evaluate the demographic and cardiovascular risk factor profiles in diabetic ESKD patients assessed for transplant eligibility at IALCH.

Technical aspects of SPECT MPI

At IALCH, the radioisotope tracer used is an isonitrile compound labeled with technetium-99m: Sestamibi. This tracer distributes proportionally to regional blood flow and has a low washout after entering myocardial cells, allowing the acquisition of perfusion images up to 2 hours post-injection.

To compare myocardial perfusion after stress and at rest, a double injection is required; the two studies are performed on separate days. SPECT refers to the tomographic acquisition of images and is performed with dual-headed gamma cameras allowing good visualization of the left ventricle. A homogenous uptake of tracer inside the left ventricular wall occurs in normal subjects. Perfusion defects are detected when there is a lack of tracer uptake. The presence of

reversible perfusion defects is an expression of transient ischemic changes and the presence of fixed defects in both stress and rest images implies myocardial infarction or severe ischemia

Literature Review

In patients with end-stage kidney disease (ESKD), cardiovascular morbidity and mortality remain high [1,2], and this holds after renal transplantation, as the high cardiovascular risk carries over into the post-transplant period as well [2]. The prevalence of diabetes and hypertension over the next two decades will rise significantly and a concomitant increase in the incidence of ESKD is foreseen [4], posing a major public health and economic burden on the fiscus.

In developing counties such as South Africa with resource limitations and budget constraints, lifesaving chronic dialysis slots are rationed, favoring the most suitable candidates, while others are denied such therapies [5]. Kidney transplantation can potentially lead to substantial cost savings [6], therefore all patients selected for chronic dialysis have to be transplantable. The principle of utilitarianism is applied which refers to the allocation of a scarce resource (donor's kidney) in such a way that society will derive a maximum benefit from such an allocation. As such, patients at high risk for a cardiac event are excluded from the transplant programme.

Clinical variables such as hypertension, dyslipidemia, tobacco use, and left ventricular hypertrophy have been used to stratify patients into low and high-risk groups and in turn further direct testing in patients at high risk [8]. Further non-invasive testing in this setting using SPECT MPI has been shown to provide incremental prognostic value to clinical data [2]. Recipients of kidney transplants are a population at high risk of cardiovascular disease and often demonstrate the presence of several cardiovascular risk factors [3]. Many regulatory agencies and scientific societies recommend non-invasive cardiovascular assessment of transplant candidates with multiple risk factors or diabetes, to identify patients at high risk of cardiovascular events in an attempt to ensure that graft survival is not limited by premature death [6].

Due to the high prevalence of exercise intolerance in patients with ESKD, and the subsequent inability to achieve age-predicted target heart rates, there is a higher likelihood of non-diagnostic exercise (treadmill) testing. On this backdrop, pharmacologic stress tests like myocardial

perfusion imaging have been extensively studied [8]. Of all non- invasive testing, SPECT MPI is well validated for ESKD patients [9].

In the pre-transplant population, several MPI studies have attempted to identify patients at risk for cardiovascular disease. In a study by Kim et al, patients were stratified into low and high risk groups based on the following variables (age; diabetes mellitus; prior history of coronary artery disease or an abnormal electrocardiogram, impaired left ventricular function or regional wall motion abnormality on echocardiography; and traditional coronary artery disease (CAD) risk factors such as hypertension, dyslipidemia, smoking, left ventricular hypertrophy, or family history of premature CAD. Patients were subsequently followed up for adverse cardiac events (cardiac death, non-fatal myocardial infarction, and heart failure). On the follow-up, the high-risk group with perfusion defects had a higher rate of development of cardiac events (46% per person-years), versus the high-risk group without perfusion defects (15%) versus the low-risk group (4.5%). Also, myocardial imaging was not justified in the low-risk group as the cardiac event rate here was low [10].

The American Heart Association (AHA) recommends aggregating CAD risk factors to target screening of patients with the highest pre-test likelihood of prognostically significant CAD. The presence of greater than and equal to three risk factors (DM, prior cardiovascular disease, dialysis duration more than a year, left ventricular hypertrophy, age, smoking, hypertension, and dyslipidaemia) is considered to be a reasonable indication for further non-invasive testing [11].

These risk factors proposed by the AHA were recently validated and further confirmed that having three or more of these risk factors is associated with an increased risk of obstructive CAD, and myocardial perfusion imaging provided incremental value as a cardiovascular prognosticator in this setting. [12]

Study design

A retrospective cross-sectional descriptive study.

Study population

All diabetic ESKD patients being assessed for transplant eligibility at Inkosi Albert Luthuli Central Hospital between 1 January 2014 and 31 December 2018

Sampling strategy

All diabetic ESKD patients 13 years and above, presenting to the IALCH nephrology department being assessed for the transplant waitlist will have data extracted from the computerized records at IALCH for the period 1 January 2014 to 31 December 2018.

Statistical planning

Statistical planning will be undertaken by a professional statistician

Sample size Inclusion / exclusion criteria

Inclusion criteria

All dialysis-dependent, diabetic CKF patients,13 years and above who are awaiting kidney transplant eligibility.

Exclusion criteria

Patients with appeals and reassessments, and

Patients that were transitioned back to dialysis following failed transplantation

Patients with inconclusive SPECT MPI reports

Data collection methods and tools

1. The data collection period is between 01 January 2014 and 31 December 2018
2. Hospital numbers will be used to identify patients that meet the inclusion criteria
3. The imaging study(MPI using SPECT) is uploaded in a picture archiving communication system (PACS).
4. Information relating to patients' socio-demographic profiles, age, sex, cardiovascular profile, and traditional cardiovascular risk factors will be collected from the chart history recorded as computer data on the hospital information system (HIS) at IALCH, which provides a link to the picture generated from the MPI using SPECT.

Data analysis technique

The data collected will be captured and subsequentlyanalysed in SPSS version 26 by a professional statistician.

Statistical analysis

Descriptive statistics such as frequencies and percentages will be used to estimate the prevalence of myocardial perfusion defects and cardiovascular risk factors as well as describe the demographic profile of the study sample. Central tendency and dispersion of data will be measured using means and standard deviations for age if it is normally distributed variables and medians and interquartile ranges will be reported if age is skewed. The results will be presented in tables and graphs.

Data Sheet

(Appendix 1)

Abbreviations

(Appendix 2)

Definitions

(Appendix 3)

Study location

Inkosi Albert Luthuli Central Hospital, Durban, South Africa

Study period

01 January 2014 to 31 December 2018

Limitations to the study

The study is retrospective in design.

Patients having incomplete data.

Ethical considerations

No ethical considerations as this is a descriptive, retrospective study with no consent necessary

References

1. United States Renal Data System USRDS. Cardiovascular Disease in Patients with CKD. 2016.

2. Yasmeen Golzar,R Doukky Curr Cardiovascular Imaging Rep May 2017:10(5) Stress SPECT Myocardial perfusion Imaging in End-stage renal Disease

3. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. Kidney international. 2000; 57(1):307–13.

4. Suchi Anand, Asaf Bitton et al [2013] The Gap between Estimated Incidence of End-Stage Renal Disease and Use of Therapy PLOS One, Volume 8, Issue 8, e 72860

5. Kajiru G.Klionzo, Erika SW, Jones et al Disparities in dialysis allocation: An audit from the new South Africa.April 18, 2017, PLOS One 12[4;e 0176041]

6. Johan Jarl, Peter. Do kidney transplants save money? A study using a before and after design and multiple register-based data from Sweden. Clinical kidney journal volume 11, Issue 2, April 2018, Pages 283–288,

7. Alberto Bestetti, Antonella Cappozaet al Diagnostic and prognostic role of myocardial perfusion scintigraphy in kidney transplant candidates. Heart International 2016:11[1]e 50 e55

8. Gautam R, Shroff, Tara I Chang, Risk stratification and treatment of coronary artery disease in chronic kidney disease and end-stage kidney disease. Seminars in Nephrology 2018 582-599

9. Delville M, Sabbah L et al,[2015] Prevalence and predictors of early cardiovascular events after kidney transplantation: Evaluation of pre-transplant cardiovascular work up PLOS One June 24; 2/12

10. Kim JK, Kim SG et al Cardiac risk assessment by gated Pectin asymptomatic end-stage renal disease patients at the start of dialysis. Journal of nuclear cardiology 2012:19 438-47

11. Lentine KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. Circulation. 2012; 126(5):617–63.

12. Doukky R, Fughhi I, Wassouf M, Vuj A, Campagnoli T, Kharouta M, et al. A Clinical Pathway to Assess Asymptomatic Renal Transplant Candidates Using Myocardial Perfusion Imaging. Journal of Nuclear Cardiology. 2016; 23(4):916–7.

Appendix 1:

DATA SHEET

STUDY NUMBER: ----------

Section 1 **Demographics**	
Age at time of SPECT MPI Study	
Sex	
Race	

Clinical Data Dialysis duration **Cardiovascular evaluation**	
Electrocardiogram	Left ventricular hypertrophy
Echocardiography	1.normal 2. Impaired left ventricular function (ejection fraction<40%) 3.Regional wall motion abnormality

Section 2	
Prior Cardiovascular Disease Coronary Artery Disease Heart Failure Peripheral Artery disease Cerebrovascular accident	1.Prior history of myocardial infarction 2.Coronary artery bypass grafting 3.Percutaneous coronary intervention 4.Known coronary stenosis >50%

Section 3 **Cardiovascular risk factors**	
Hypertension	
Dyslipidaemia	
Smoking	
Family history of premature coronary artery disease	

Appendix 2: Abbreviations

AHA - American Heart Association

CAD - Coronary artery disease

CKF - Chronic kidney failure

EGFR - Estimated glomerular filtration rate

ESKD - End stage kidney disease

HIV - Human Immunodeficiency Virus

IALCH -Inkosi Albert Luthuli Central Hospital

LDL - Low-density lipoprotein

LVH - Left ventricular hypertrophy

MPI - Myocardial perfusion Imaging

MPS - Myocardial perfusion scintigraphy

Appendix 3 Abbreviations

PACS -Picture archiving communication system

PMP -per million population

SPECT -Single-photon emission computed tomography

SPECT -MPI -Single photon emission computed tomography myocardial perfusion imaging

SSA -Sub-Saharan Africa

Appendix 4

Definitions

End-stage kidney disease	an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m and/or on chronic dialysis
Hypertension	a past medical history of high blood pressure or a blood pressure level of 140/90mmHg or higher at admission
Diabetes	a past medical history of diabetes or glycated hemoglobin above 6.5% (HBA1c) at admission
Dyslipidaemia	a past medical history of dyslipidemia or an LDL cholesterol level >2.6mmol/l at inclusion
Electrocardiographic left ventricular hypertrophy	Sokolow Lyon criteria voltage amplitude sum of either SV1 +RV5 or SV1 +RV6 at baseline was equal to /or above 3.5 mV
Family history of premature coronary artery disease	A fatal or nonfatal myocardial infarction and/or coronary angioplasty/coronary artery bypass surgery that occurred before the age of 55 years in male relatives and before 65 years of age in female relatives.

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Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
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Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

ahmed hassim-sakoor

a complété avec succès - has successfully completed

Research Ethics Evaluation

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

[redacted]

Release Date: 2019/05/05
CID : ZyGTWxg18S

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

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[REV : 20170310]

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/3189/3122 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_202005_014

Dear Dr Ahmed Hassim-Sakoor
(UKZN)

Approval of research

1. The research proposal titled '**Outcomes of Myocardial Perfusion Imaging (MPI) using Single Photon Emission Computer Tomography (SPECT) in Pre Transplant Diabetic End-Stage kidney disease patients (ESKD)**' was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   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. *All research conducted in KwaZulu Natal must comply with government regulations relating to Covid 19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *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.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *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*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

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

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 22/06/2020

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

13 December 2020

Dr Ahmed Hassim-Sakoor (219095428)
School of Clinical Medicine
Medical School

Dear Dr Hassim-Sakoor,

Protocol reference number: BREC/00000954/2020
Project title: Outcomes of Myocardial Perfusion Imaging (MPI) using Single Photon Emission Computer Tomography (SPECT) in Pre Transplant Diabetic End-Stage Kidney Disease (ESKD) patients
Degree: MMed

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 13 December 2020. Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is subject to national and UKZN lockdown regulations dated 10th November 2020, see (http://research.ukzn.ac.za/Libraries/BREC/BREC_Lockdown_Level_1_Guidelines.sflb.ashx). Based on feedback from some sites, we urge PIs to show sensitivity and exercise appropriate consideration at sites where personnel and service users appear stressed or overloaded.

This approval is valid for one year from 13 December 2020. 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 09 February 2021.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X06, Mayville, 4058
Tel: 0312401059 Fax: 0312401059 Email: cmsulanum@ialch.co.za
www.kznhealth.gov.za

Office of The Medical Manager
IALCH

Reference: BREC/00000954/2020
Enquiries: Medical Management

6 May 2020

Dr A Hassim-Sakoor (219095428)
School of Clinical Medicine
Medical School

Dear Dr Hassim-Sakoor

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: **Outcomes of Myocardial Perfusion Imaging (MPI) using Single Photon Emission Computer Tomography (SPECT) in Pre Transplant Diabetic End-Stage Kidney Disease (ESKD) patients.**

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

[redacted]

pp **Dr L P Mtshali**
Medical Manager

DR. A. Harrichandpaul
Clinical Care Manager