NUTRITIONAL STATUS AND QUALITY OF LIFE IN HIV POSITIVE PRE- AND POST- KIDNEY TRANSPLANT RECIPIENTS, FROM HIV POSITIVE DONORS

By

CLAIRE JULIET MARTIN

Submitted in fulfilment of the
requirements for the degree of
Doctorate of Philosophy (Dietetics)
Dietetics and Human Nutrition,
School of Agricultural, Earth and Environmental Sciences
College of Agriculture, Engineering and Science
University of KwaZulu-Natal
Pietermaritzburg

April 2019

DECLARATION

I, Claire Juliet Martin declare that:-

a) This thesis has not been submitted for a degree at any other institution.

b) The work contained within this thesis is my own, original work. The work of other authors are acknowledged and referenced.

Signed  Date 26 August 2019

Claire Juliet Martin

Signed  Date 26 August 2019

Supervisor: Dr Susanna Maria Kassier

Signed  Date 26 August 2019

Co-supervisor: Prof Frederick Johannes Veldman

ABSTRACT

Background: Kidney transplantation from a HIV-positive donor to a HIV-positive recipient is now a treatment option available for patients with ESRD. Impairments in nutritional status are common, and increase the risk of adverse clinical and health-related quality of life (HRQOL) outcomes. Therefore Optimising nutritional status is therefore an important adjunct of medical care that begins with a nutritional status assessment.

Aim: To describe the nutritional status and HRQOL of HIV-positive kidney transplant recipients from a HIV-positive donor and candidates on the waiting list to receive one.

Objectives: To determine nutritional status through the assessment of body composition, bone mineral density (BMD), dietary intake, biochemical indicators and gastrointestinal symptoms (GIS). To determine HRQOL based on the patient's perception of their health.

Methods: The frequency and severity of GIS was determined using a previously validated questionnaire; the gastrointestinal symptom rating scale (GSRS). BMD and body composition were measured by dual-energy x-ray absorptiometry (DEXA). Dietary intake was evaluated using a 24-hour recall. Biochemical indicators of albumin, prealbumin fasting glucose, lipids and serum 25-hydroxyvitamin D [25(OH)D] were analysed. Adiposity and musculature were determined through anthropometric indices of weight, body mass index (BMI), waist circumference (WC) and mid-arm muscle circumference (MAMC). HRQOL was assessed using a validated questionnaire; the Short form-36 (SF-36) and semi-structured interviews. With the exception of DEXA, all other assessments were done at baseline and at six months.

Results: The study sample consisted of 76 participants (n=22 transplant recipients, n=54 transplant candidates), who were predominantly black (93.4 %) and male (60.5%), with a mean age of 43.6 ± 8.1 years. The frequency of GIS was high for both groups. Indigestion was a frequent and severe GIS. Amongst transplant candidates, females had significantly higher GSRS severity scores for selected subscales and the overall global mean score (p=0.030) compared to males. Age and duration of treatment correlated with selected subscales in transplant candidates. WC correlated positively with constipation amongst transplant recipients. BMD was assessed in 56 participants. Osteoporosis was more prevalent amongst transplant recipients (20.0%), while osteopenia was more prevalent amongst transplant candidates (27.8%). T-scores strongly correlated with lean mass at the BMD of the spine ($r = 0.707$, $p = 0.007$), and moderately with

each side of the total hip (r = 0.455, p = 0.007 and r = 0.420, p = 0.007). Serum 25(OH)D vitamin D levels was low for the group as a whole, with a mean of 22.04 ±12.74 ng/ml, and was not related to BMD. There was a significant positive association between dietary calcium and all BMD sites for transplant recipients. In a subset of participants (n = 34), there was a significant positive association between anthropometry and DEXA derived indices of adiposity. These were BMI and percent body fat (%BF) (r = 0.773, p < 0.001), WC and truncal fat (TF) (r = 0.799, p = 0.00) and visceral adipose tissue (VAT) (r = 0.885, p < 0.001). The indicator of muscularity (MAMC) correlated with appendicular lean mass index (ALMI) (r = 0.511, p = 0.011), establishing these anthropometric indices as suitable proxy measures of overall and regional adiposity (including visceral adipose tissue) as well as musculature. The majority of transplant candidates were overweight (38.5%), or had normal BMI (36.5%) At six months, 62.7% had a statistically significant weight loss t (50) = 2.072, p = 0.043). Metabolic syndrome (MetS) was present in 47.5% and 51.0% of candidates at baseline and six months respectively. The mean daily energy and protein intake were below recommendations for dialysis. The majority of transplant recipients had a normal BMI (71.4%). At six months, 52.4% showed a weight gain trend and a significant increase in WC (t (14) = -2.861, p 0.013). MetS was present in about 35% of transplant recipients. At baseline, weight correlated with total protein (r = 0.609, p = 0.003), animal (r = 0.513, p = 0.017) and plant protein (r = 0.534, p = 0.013) intake. At six months, WC correlated with animal protein (r = 0.517, p = 0.028) intake. 68 patients completed the SF-36 at baseline and 6 months. Transplant candidates had lower HRQOL than recipients. The main mental stressors were income, employment and waiting for a donor. Physical health complaints were body pain and fatigue. In transplant recipients, the composite physical and mental scores were above the average for the general population. Prealbumin, BMI, albumin and MAMC showed positive correlations with selected SF-36 domains.

Conclusion: A series of studies showed altered nutritional status and HRQOL in a substantial proportion of transplant candidates and some transplant recipients. These results can be used to improve nutritional status and hence optimise graft and patient outcomes.

ACKNOWLEDGEMENTS

With sincere gratitude I would like to acknowledge all those who have supported me with this research. Firstly, thank you to Dr S M Kassier and Professor F Veldman who supervised my research. Suna, your personal and professional commitment to your students is astounding, and it was a privilege working with you as my supervisor. Professor D Labadarios, thank you for your ongoing support, expertise and encouragement in pursuing this degree in this exceptionally interesting field.

Heartfelt appreciation to Professor E Muller, and the transplant team at Groote Schuur Hospital. Thank you for allowing me access to your programme, without which, this research would not have been possible. It was a wonderful opportunity to work with such dedicated professionals and your special patients. In particular, I am very grateful to Sister P Michaels whose assistance in all patient and clinic related matters was invaluable.

Thank you to my dietetic colleagues for assistance with data collection, and to all the patients who participated in this research.

The financial assistance from the National Research Foundation, the Sugar Association of South Africa and the Halley Stott grant is highly appreciated, and made this national project possible.

Finally, to my friends and family, thank you so very much for your kindness love and support. Joshua and Cairenn, my very special cheerleaders whom I love dearly, this thesis is dedicated to you.

TABLE OF CONTENTS

APPENDICES

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1
INTRODUCTION

1.1 Study background

Global estimates of people living with human immunodeficiency virus (HIV), average 36.9 million (1), with the majority (71%) residing in Sub-Saharan Africa (2). About 1.8 million were newly infected and 940 000 died of Acquired Immunodeficiency Syndrome (AIDS) - related causes in 2017 (1). South Africa (SA) bears one of the heaviest healthcare burdens (3), with a HIV prevalence of 7.5 million or 13.1% of the population (4), and is currently running the largest antiretroviral (ART) programme in the world (3). By 2018, the estimated number of adults and children on ART was in excess of 4.3 million (3).

ART has significantly reduced morbidity and mortality, such that HIV is now regarded as a chronic condition with a greater life expectancy (5). As a result, corresponding increases in the number of comorbidities affecting the ageing HIV population have been observed (6,7). The attention originally placed on infectious complications has broadened to the management of non-communicable diseases (NCD) such as cardiovascular disease, diabetes mellitus, osteoporosis, and renal disease increasing the burden of the disease on the individual and the health system (8,9,10,11,12).

Renal disease, both chronic and acute, is a co-morbid, non-AIDS-defining condition of increasing prevalence in the HIV population (13,14) with some form of renal dysfunction identified in as many as 30% of the HIV-positive population (15). In sub-Saharan Africa, the prevalence of kidney disease in the HIV-positive population is reportedly between 6% and 48.5% (16). HIV-associated nephropathy (HIVAN) is however the most frequent aetiology in chronic kidney disease (CKD) (17), responsible for 27% to 62% of CKD in patients of black ethnicity (18,19). Early prevalence studies listed HIVAN as the third leading cause of end stage renal disease (ESRD) amongst African Americans (20), and the foremost aetiology in patients of African descent in South Africa (18,21). Based on early United States (US) HIVAN prevalence, statistical projections for Africa were that as many as 3.1 million people will eventually develop HIVAN, placing an even greater health, economic and social burden on the continent (22).

HIVAN is thought to be caused by direct viral infection of the kidney cells, presenting with excessive proteinuria and collapsing focal and segmental glomerular sclerosis on histology. CD4 counts of < 200 cells/mm^3 and elevated viral loads are considered predisposing risk factors (13,23). Without treatment, prognosis is bleak, with patients developing ESRD within months (18). In South Africa, State hospitals have limited dialysis resources and patients can only access dialysis if they are eligible for a transplant. Therefore, for HIV-positive state patients, a renal transplant remains the most favourable treatment option (24).

A HIV-positive status was formerly contraindicated for kidney transplantation (25), and an exclusion criterion for being placed on transplant waiting lists (26). However, over time, many centres across the globe have published their experience, demonstrating the viability of kidney transplantation in HIV-infected individuals (25,27,28,29). It was found that, despite recurrent acute rejection in 67% of recipients, outcomes with respect to the graft and patient survival at three years were reported to be 83% and 94%, respectively, similar to that of HIV–negative transplant patients (30). In addition, CD4 counts and viral loads showed no evidence of hastened HIV disease progression. Donor kidneys, at this stage, were only sourced from HIV-negative donors for fear of an emergent 'superinfection,' consequential drug resistance and hastened progression to AIDS, should positive donors be used (31).

In 2008 however, a South African (SA) surgeon pioneered the first ever kidney transplants involving four HIV-positive donors *and* recipients, with a view that South Africa's high HIV infection rate may offer a greater opportunity of finding donor kidneys, thus providing a chance to improve prognosis in patients, who would otherwise have demised within months (32). Qualifying recipient criteria include good adherence to ARVs and low viral loads of less than 50 copies per millilitre for longer than six months. Patients previously treated for Tuberculosis (TB) were not excluded from the transplant programme. In SA, virus resistance is fortunately still minimal and augmented dosages of protease inhibitors were used to reduce the transplanted viral strain (32). Since 2008, 43 HIV-positive patients have received transplants at Groote Schuur Hospital in Cape Town (33).

1.2 Significance of this study

While transplantation extends survival (34), malnutrition, obesity and co-morbidities in the pre- and post-transplant phase can present a threat to patient and graft survival as well as quality of life (35,36,37). Underlying HIV places patients at a greater risk since HIV itself is a health

burden with a myriad of on-going nutrition-related problems (38). To date however, nutritional aspects in this group have remained unexplored. Hence, the emphasis of related literature to date, has primarily focused on clinical and pharmaco-therapeutic strategies to extend survival (15), with nothing being documented about the nutrition related morbidity and quality of life the extended life expectancy affords.

Nutritional care is always preceded by an assessment of nutritional status as a baseline or reference point for decision making and the planning of intervention strategies (39,40). As no previous evaluation has been conducted, there is no guidance regarding patient nutritional status, or selection of the most appropriate nutritional assessment tools, for this patient group. As such, conducting an objective evaluation of nutritional health, with the inclusion of subjective health related quality of life (HRQOL) measures (40), it was anticipated that the data generated by this research will:

- Contribute significantly to the current body of knowledge by providing insight into the physical and metabolic changes that may occur in pre- and post-renal transplanted HIV positive patients.
- Identify patients at risk of developing clinical complications that could have an impact on their health and quality of life.
- Generate suggestions regarding appropriate nutritional indicators for monitoring and assessment of nutritional status.
- Identify dietary factors that will optimise post-transplant nutritional status and contribute to sustaining graft function and delay the development of co-morbidities.
- Provide a baseline assessment of HIV-positive kidney transplant patients that could be used for future evaluation of dietary intervention or related research.

1.3 Problem Statement

Both pre- and post-renal transplant patients present with nutritional challenges that pose serious morbidity and mortality risks. To date there is a paucity of data documenting the nutritional status or quality of life of HIV-positive pre- and post-renal transplant patients who have received a kidney from a HIV-positive donor, or who are on the waiting list to receive a kidney from a HIV- positive donor.

1.4 Research aims

The aims of this study were to conduct nutritional status and quality of life assessments in:

- HIV-positive kidney transplant recipients, who have received a kidney from a HIV-positive donor;
- HIV-positive kidney transplant candidates, who are on the waiting list for a kidney transplant from a HIV- positive donor.

1.5 Specific objectives

To evaluate participant nutritional status, the following objectives were formulated:

- To determine body composition by measurement of selected anthropometric indicators at baseline and six months follow-up.
- To determine dietary intake using a 24-hour recall at baseline and at six months follow-up.
- To determine gastrointestinal symptoms using a validated questionnaire at baseline and six months follow-up.
- To obtain bone mineral density and body composition using dual energy X-ray absorptiometry at baseline.
- To obtain biochemical indicators of nutritional health, namely lipid profile, protein status, blood glucose and vitamin D status at baseline and at six months follow-up.

To evaluate participant HRQOL using mixed methods, the following objective was formulated:

- To quantify and describe HRQOL using a validated questionnaire and semi-structured interviews respectively at baseline and six months.

Based on the study objectives, a diagrammatic representation of the study plan is shown in Figure 1.1

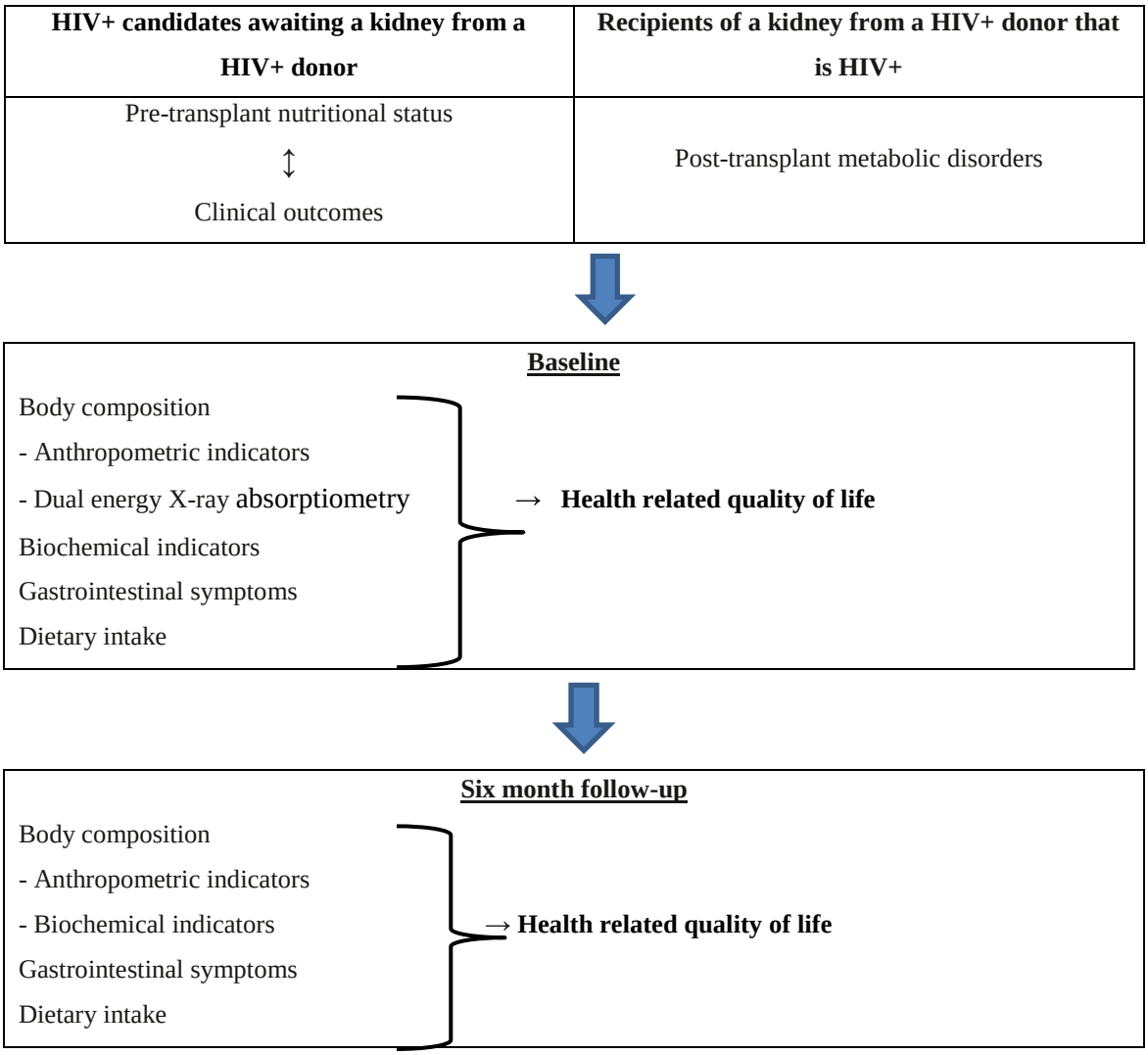

Figure 1.1: Outline of the study plan

1.6 Background to study sample data collection

The HIV "positive-to-positive" kidney transplant programme is a national programme with candidates and recipients resident across South Africa, however it is run from a single centre - Groote Schuur Hospital (GSH) in Cape Town. Potential candidates are referred by their attending nephrologist to determine whether they meet the waiting list inclusion criteria. Whilst awaiting a donor, candidates continue to receive dialysis at a private or state run dialysis centre in their home province. When a donor becomes available, patients travel to GSH to undergo the

transplant and return to their home province where they are again followed up by their nephrologist. At the time of the study, the programme was still in its infancy and was in the process of establishing a formal database. For the purposes of this study, the most recent list of transplant recipients and potential candidates was obtained from GSH. The number of candidates and recipients in this programme are still small, but represent 100% of the global population of this unique group. There were 92 prospective participants listed (68 transplant candidates, 24 transplant recipients) that were contactable either telephonically or at outpatient clinics, and were resident in six provinces. Of these, two transplant candidates and two transplant recipients declined participation, and 12 candidates were excluded due to missed appointments (typically two or more without reason), became ill or lost interest.

Written informed consent was obtained from the seventy six participants and they were assigned to two categories namely (i) HIV-positive transplant recipients who received a kidney from a HIV-positive donor; and (ii) HIV-positive transplant candidates who were on the waiting list to receive a kidney from a HIV-positive donor.

The map below (Figure 1.2) indicates the geographical distribution of study participants. Table 1.1 provides an overview of the resources and stakeholders that were required to facilitate data collection.

Figure 1.2: National distribution of study participants

Table 1.1 provides an overview of the stakeholders involved, and the resources required to facilitate data collection for this multi-centre study.

Table 1.1: Resources and logistics required for data collection

Stakeholders	Number
Patients in six provinces residing in 13 cities/towns	76
Private laboratories groups	3
Radiology practices	10
Nursing staff	5
Administrative/medical records personnel	2
Drivers/ patient transport	3
Dietitians	22
Dialysis centres	22

Ethics approval was obtained from the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BREC) (Approval number BE 327/13). Where necessary, site permission was obtained from state hospitals (Groote Schuur Hospital and Livingstone Hospital) as well as the Eastern Cape Department of Health. Permission was also sought from the Clinical Governance departments of major South African private healthcare care providers that manage private dialysis centres throughout the country. The doctors of all participants were contacted to inform them about the purpose and scope of the study, as many patients wanted to discuss their participation in the study with their doctors before providing consent. Approval was also required from clinical trial facilitators at private laboratories, and radiologists (for DEXA) for establishing accounts, payment of fees, and to ensure specimen collection from laboratories service points countrywide. Results were also sent to all the participants' doctors to be used for patient management.

Due to cost constraints, the follow-up period was six months. There were no crossovers during this period. Each participant received R150.00 after completion of assessments done at the baseline and again at six months (an amount suggested by the ethics committee), to minimise drop-out from the small patient population. In addition, where necessary, a transport stipend was provided or transport and a snack was arranged for participants to comply with their appointments.

Private practicing dietitians with practices close to the area where patients resided were recruited and trained to assist with data collection. To ensure that the information and training

provided was of a high standard, the training was accredited by the Health Professions Council of South Africa (HPCSA) as a continuing professional development (CPD) activity. Dietitians and all other individuals that assisted with data collection were remunerated in accordance with the University's hourly rate. The necessary equipment for data collection was couriered to fieldworkers.

1.7 Definition of terms

Anthropometry: Refers to measures of total body mass (including fat and fat-free mass), body dimensions and adiposity (41).

Antiretroviral therapy: Refers to a combination of three of more drugs that are used to suppress HIV viral replication (42).

Biochemical assessment: Within the context of nutritional assessment, biochemical assessment refers to objective laboratory assessment of nutritional status of serum/plasma values (43)**.**

Chronic kidney disease (CKD): Refers to damage to the kidney (regardless of the cause) or when the eGFR is < 60mL/min/1.73m^2 for a period of ≥ three months (44).

Chronic rejection: Occurs when the immune system of the transplant recipient, slowly and continuously attacks the transplanted kidney, causing a progressive loss of kidney function (45).

Clinical assessment: Includes a medical history and physical examination. It includes (but is not limited to) information on comorbidities, infectious diseases, pharmacotherapy and its side-effects, gastrointestinal and other symptoms that impact on nutritional status (41).

Delayed graft function: This term is used when the kidney does not start functioning immediately following the transplant. It may take between three to four weeks to resume adequate function. Dialysis will be required until then (45).

Dietary intake: Refers to the description of food and liquid intake (39).

Donor: The person from whom a kidney has been recovered to use for transplantation (46).

Graft: Refers to a transplanted organ such as the kidney (45)

Graft survival: Refers to the period of time that the transplanted organ continues to function optimally from the time of transplantation (45).

Health-related quality of life: Refers to multiple dimensions of health which incorporates physical, mental, emotional, and social functioning (47).

HIV- positive: Refers to a person who has the presence of antibodies against HIV (42).

Immunosuppression: Medications taken by the transplant recipient to prevent their immune system from rejecting the transplanted organ (45) .

Induction therapy: Medications given during the perioperative period to prevent acute rejection, and may be continued for a brief period following transplant (45).

Kidney transplant: Refers to the transfer of a human kidney from a donor to a recipient for the purpose of restoring kidney function (46).

Nutritional status: Takes into consideration multiple parameters of nutritional health including anthropometric, biochemical and clinical parameters as well as dietary intake (39).

Registry: A repository of data with information on individuals who are waiting for a transplant and who have received a transplant. It includes personal information, clinical notes and information on cells and tissue typing (46)**.**

Socio-demographic status: Socio-demographic data identifies characteristics of the sample population (41).

Transplant candidate: An individual registered on the organ transplant waiting list (45).

Transplant recipient: An individual into whom the donated kidney is transplanted (45).

Waiting list: The list of candidates registered to receive a human cell, tissue or organ transplant (46). The list contains a range of candidate information especially information pertaining to genetic compatibility (45).

1.8 Abbreviations

AIDS: Acquired immune deficiency syndrome

ALMI: Appendicular lean mass index

AMA: Arm muscle area

ART: Anti-retroviral therapy

BCM: Body cell mass

BMD: Bone mineral disease

BMI: Body mass index

BP: Bodily pain

CKD: Chronic kidney disease

CKD-MBD: Chronic kidney disease-mineral and bone disease

CVD: Cardiovascular disease

DEXA: Dual energy X-ray absorptiometry

eGRF: Estimated glomerular filtration rate

ESRD: End stage renal disease

FN: Femoral neck

GH: General health

GIS: Gastrointestinal system

GORD: Gastro-oesophageal reflux disease

GSRS: Gastrointestinal symptom rating scale

HAART: Highly active antiretroviral therapy

HD: Haemodialysis

HIV: Human immunodeficiency virus

HIVAN: HIV-associated nephropathy

HRQOL: Health related quality of life

Ht: Height

LDL: Low density lipoprotein cholesterol

LM: Lean mass

LS: Lumbar spine

MetS: Metabolic syndrome

MAMC: Mid arm muscle circumference

MH: Mental health

MUAC: Mid upper arm circumference

NHANES: National health and nutrition examination survey

NKF KDOQI: The National Kidney Foundation Kidney Disease Outcomes Quality Initiative

NCD: Non-communicable disease

NODAT: New-onset diabetes after transplantation

PD: Peritoneal dialysis

PF: Physical functioning

PEM: Protein energy malnutrition

PEW: Protein energy wasting

PI: Protease Inhibitor

PTH: Parathyroid hormone

QOL: Quality of life

RE: Role emotional

RP: Role physical

SAT: Subcutaneous adipose tissue

SF: Social functioning

SF-36: Short form - 36

TAT: Total abdominal adipose tissue

TH: Total hip

TF: Truncal fat

TSF: Triceps skinfold

UGIS: Upper gastrointestinal symptoms

VAT: Visceral adipose tissue

VL: Viral load

VT: Vitality

WC: Waist circumference

WHR: Waist to hip ratio

WHtR: Waist to height ratio

WT: Weight

25(OH)D: 25-hydroxyvitamin D

1.9 Thesis Structure

This thesis consists of eight chapters. In preparation for publication, each chapter was written as a stand-alone publication, including methodology, study design, validity and reliability specific to each chapter.

Chapter one, the introductory chapter, provided the background to the study and significance of the research. It includes the problem statement and research objectives that were investigated, relevant to the result chapters that followed.

Chapter two includes a review of the related literature on the topic under investigation. Five chapters (chapters three to seven) presenting the results, follow thereafter.

Chapter three describes the clinical assessment of gastrointestinal symptoms.

Chapter four is a cross-sectional study that evaluated the bone mineral density and prevalence of osteoporosis in transplant candidates and recipients.

Chapter five describes the findings of a correlational study that compares anthropometric measures of adiposity and musculature against a reference standard, namely dual-energy X-ray absorptiometry. Body composition is an important component of nutritional status. In order to accurately report on body composition requires verification of measurements that can be described as a form of quality assurance of the chosen method portrayed in this chapter.

Chapter six is a longitudinal assessment of overall and central obesity and dietary intake.

Chapter seven is a longitudinal study using a mixed methods approach to determine participants' health related quality of life and the association with musculature.
Chapter eight, the concluding chapter, puts forward the conclusions and recommendations based on the results presented in chapters three to seven.

1.10 References

1. UNAIDS. Global HIV & AIDS statistics — 2018 fact sheet. [Online]; 2018 [cited 20/03/2019]. Available from: http://www.unaids.org/en/resources/fact-sheet.

2. Kharsany ABM, Karim QA. HIV infection and AIDS in Sub-Saharan Africa: Current status, challenges and opportunities. Open AIDS J. 2016; 10: 34-48.

3. UNAIDS. Country fact sheets: South Africa 2017. [Online]; 2019 [cited 20/03/2019]. Available from: http://www.unaids.org/en/regionscountries/countries/southafrica.

4. StatsSA. Mid-year population estimates. Statistical Release P0302. 2018. [Online]; [cited 21/03/2019].Available from: https://www.statssa.gov.za/publications/P0302/P03022015.pdf

5. Deeks SG, Sharon R. Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet. 2013; 382(9903): 1525–1533.

6. Allavena C, Hanf M, Rey D, Duvivier C, BaniSadr F, Poizot-Martin I, Jacomet C, Pugliese P, Delobel P, Katlama C, Joly V, Chidiac C, Dournon N, Merrien D, May T, Reynes J, Gagneux-Brunon A, Chirouze C, Huleux T, Cabié A, Raffi F; Dat'AIDS study group. Antiretroviral exposure and comorbidities in an aging HIV-infected population: The challenge of geriatric patients. PLoS One. 2018; 13(9): e0203895. doi: 10.1371/journal.pone.0203895.

7. Hasse B1, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, Bertisch B, Bernasconi E, Weber R; Swiss HIV Cohort Study. Morbidity and aging in HIV-infected persons: The Swiss HIV cohort study. Clin Infect Dis. 2011; 53(11): 1130-1139.

8. Negin J, Martiniuk A, Cumming RG, Naidoo N, Phaswana-Mafuya N, Madurai L, Williams S, Kowal P. Prevalence of HIV and chronic comorbidities among older adults. AIDS. 2012; 26(Suppl 1): S55-63.

9. Post FA, Holt SG. Recent developments in HIV and the kidney. Curr Opin Infect Dis. 2009; 22(1): 43-48.

10. Oni T, Youngblood E, Boulle A, McGrath N, Wilkinson RJ, Levitt NS. Patterns of HIV, TB, and non-communicable disease multi-morbidity in peri-urban South Africa: A cross sectional study. BMC Infect Dis. 2015; 15: 20. doi: 10.1186/s12879-015-0750-1.

11. Lundgren JD, Battegay M, Behrens G, De Wit S, Guaraldi G, Katlama C, Martinez E, Nair D, Powderly WG, Reiss P, Sutinen J, Vigano A; EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. HIV Med. 2008; 9(2): 72-81.

12. Compston J. HIV infection and osteoporosis. Bonekey Rep. 2015; 4: 636. 2015; 4: 636. doi: 10.1038/bonekey.2015.3.

13. Röling J, Schmid H, Fischereder M, Draenert R, Goebel FD. HIV-associated renal diseases and highly active antiretroviral therapy—induced nephropathy. Clin Infect Dis. 2006; 42(10): 1488–1495.

14. de Silva TI, Post FA, Griffin MD, Dockrell DH. HIV-1 infection and the kidney: An evolving challenge in HIV medicine. Mayo Clin. Proc. 2007; 82(9): 1031-1148.

15. Gupta SK, Eustace JA, Winston JA, Boydstun II, Ahuja TS, Rodriguez RA, Tashima KT, Roland M, Franceschini N, Palella FJ, Lennox JL, Klotman PE, Nachman SA, Hall SD, Szczech LA. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2005; 40(11): 1559-1585.

16. Fabian J, Naicker S. HIV and kidney disease in sub-Saharan Africa. Nat Rev Nephrol.

2009; 5(10): 591-598.

17. Han TM, Naicker S, Ramdial PK, Assounga AG. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. Kidney Int. 2006; 69(12): 243–2250.

18. Gerntholtz TE, Goetsch SJW, Katz I. HIV-related nephropathy: A South African perspective. Kidney Int. 2006; 69(10): 1885–1891.

19. Campbell LJ, Ibrahim F, Fisher M, Holt SG, Hendry BM, Post FA. Spectrum of chronic kidney disease in HIV-infected patients. HIV Med. 2009; 10(6): 329-336.

20. Ross MJ, Klotman PE. Recent progress in HIV-associated nephropathy. JASN. 2002; 13(12): 2997-3004.

21. Assaram S, Magula NP2, Mewa Kinoo S3, Mashamba-Thompson TP. Renal manifestations of HIV during the antiretroviral era in South Africa: A systematic scoping review. Syst Rev. 2017 Oct 13;6(1):200. doi. 2017; 6(1): 200. doi: 10.1186/s13643-017-0605-5.

22. Naicker S, Han TM, Fabian J. HIV/AIDS—Dominant player in chronic kidney disease. Ethn Dis. 2006; 16(Suppl 2): S2-56-60.

23. Wyatt CM, Klotman PE, D'Agati VD. HIV-Associated Nephropathy: Clinical presentation, pathology, and epidemiology in the era of antiretroviral therapy. Semin Nephrol. 2008; 28(6): 513–522.

24. Muller E, Barday Z. HIV-positive kidney donor selection for HIV-positive transplant recipients. J Am Soc Nephrol. 2018; 29(4): 1090–1095.

25. Frassetto LA, Tan-Tam C, Stock PG. Renal transplantation in patients with HIV. Nat Rev Nephrol. 2009; 5(10): 582-589.

26. Zeier M, Ritz E. Preparation of the dialysis patient for transplantation. Nephrol Dial Transplant. 2002; 17(4): 552–556.

27. Locke JE, Mehta S, Reed RD, MacLennan P, Massie A, Nellore A, Durand C, Segev DL. A national study of outcomes among HIV-infected kidney transplant recipients. J Am Soc

Nephrol. 2015; 26(9): 2222-2229.

28. Mahesh E, John MM, Konana GC, Parampalli RM, Bande SR, Suryadevara S. Renal transplantation in HIV-positive patients - no more a scare. Saudi J Kidney Dis Transpl. 2017; 28(5): 1106-1111.

29. Gómez V, Fernández A, Galeano C, Oliva J, Diez V, Bueno C, Hevia V, Burgos FJ. Renal transplantation in HIV-infected patients: experience at a tertiary hospital in Spain and review of the literature. Transplant Proc. 2013; 45(3): 1255-1259.

30. Roland ME, Barin B, Carlson L, Frassetto LA, Terrault NA, Hirose R, Freise CE, Benet LZ, Ascher NL, Roberts JP, Murphy B, Keller MJ, Olthoff KM, Blumberg EA, Brayman KL, Bartlett ST, Davis CE, McCune JM, Bredt BM, Stablein DM, Stock PG. HIV-infected liver and kidney transplant recipients: 1- and 3-year outcomes. American Journal of Transplantation. 2008; 8(2): 355-365.

31. Trullas JC, Cofan F, Tuset M, Ricart MJ, Brunet M, Cervera C, Manzardo C,Lòpez-Dieguez M, Oppenheimer F, Moreno A, Campistol JM, Miro JM. Renal transplantation in HIV-infected patients: 2010 update. Kidney International. 2011; 79(8): 825-842.

32. Muller E, Kahn D, Mendelson M. Renal transplantation between HIV-positive donors and recipients. N Engl J Med. 2010; 362(24): 2336-2337.

33. Muller E, Barday Z. HIV-Positive kidney donor selection for HIV-positive transplant recipients. JASN. 2018; 29(4): 1090-1095.

34. Rabbat CG, Thorpe KE, Russell JD, Churchill DN. Comparison of mortality risk for dialysis patients and cadaveric first renal transplant recipients in Ontario, Canada. J Am Soc Nephrol. 2000; 11(5): 917-922.

35. Streja E, Molnar MZ, Kovesdy CP, Bunnapradist S, Jing J, Nissenson AR, Mucsi I, Danovitch GM, Kalantar-Zadeh K. Associations of pretransplant weight and muscle mass with mortality in renal transplant recipients. Clin J Am Soc Nephrol. 2011; 6(6): 1463-1473.

36. Phillips S, Heuberger R. Metabolic disorders following kidney transplantation. Journal of Renal Nutrition. 2012; 22(5): 451-460.

37. Raimundo P, Ravasco P, Proença V, Camilo M. Does nutrition play a role in the quality of life of patients under chronic hemodialysis. Nutrition Hosp. 2006; 21(2): 139-144.

38. Colecraft E. HIV/AIDS: Nutritional implications and impact on human development. Proc Nutr Soc. 2008; 67(1): 09-113.

39. Mahan KL, Escott-Stump S, Raymond JL. Krause's Food and the Nutrition Care Process. St Louis, Mo: Saunders/Elsevier; 2012. p. 1.

40. Blake C, Plant WD. Measures to improve quality of life in end stage stage renal disease patients. In Wilcox CS, editor. Therapy in Nephrology and Hypertension. Philadeliphia: Saunders Elsevier; 2008. p. 818-827.

41. Position of the American Dietetic Association and Dietitians of Canada. Nutrition intervention in the care of persons with Human Immunodeficiency Virus infection. J Am Diet Assoc. 2004; 104(9): 1425-1441.

42. UNAIDS. UNAIDS terminology guidelines. [Online]; 2011 [cited 21/02/2019]. Available from: http://www.unaids.org/sites/default/files/media_asset/JC2118_terminology-guidelines_en_1.pdf.

43. Litchford MD. Biochemical assessment. In Mahan KL, Escott-Stump S, editors. Krause's Food and the Nutrition Care Process. St Louis, Mo: Saunders/Elsevier; 2012. p. 191.

44. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005; 67(6): 2089-2100.

45. U.S. Department of Health and Human Services. Organ procurement and transplantation Network. [Online]. [cited 26/03/2019]. Available from: https://optn.transplant.hrsa.gov/resources/glossary/.

46. World Health Organization. Global glossary of terms and definitions on donation and transplantation. Geneva; 2009 [cited 26/04/2019]. Available from: https://www.who.int/transplantation/activities/GlobalGlossaryonDonationTransplantation.pdf.

47. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Healthy people 2020. [Online].; 2014 [cited 26/03/2019]. Available from: https://www.healthypeople.gov/2020/about/foundation-health-measures/Health-Related-Quality-of-Life-and-Well-Being.

CHAPTER 2

NUTRITIONAL STATUS IS RELATED TO CLINICAL OUTCOMES AND HEALTH-RELATED QUALITY OF LIFE: A REVIEW OF THE LITERATURE

ABSTRACT

Significant impairments to nutritional status accompany end stage renal disease (ESRD), and for patients on dialysis awaiting a transplant, one of the most serious complications being malnutrition. Malnutrition is associated with a higher mortality in the dialysis population, and continues to impact negatively on graft and patient outcomes after transplantation. Nutritional status improves after a transplant, but obesity and metabolic disorders threaten graft function, increase the risk of cardiovascular disease and impair health related quality of life (HRQOL). Hence, it is widely recognised that improving post-transplant prognosis begins in the pre-transplant period, by optimising nutritional health through regular nutritional assessment.

Studies show that clinical health, nutritional status and HRQOL in ESRD are made worse in the presence of various comorbidities. However, no such data has been published on HIV-positive ESRD patients, in particular transplant candidates and recipients from HIV-positive donors.

This review explores the topic of nutritional status and quality of life impairments in kidney transplant candidates and recipients with consideration to the probable impact of comorbid HIV. The literature also provides a framework for appropriate pre- and post- transplant nutritional status assessment, and the selection of the most appropriate nutritional and HRQOL indicators within the context of this patient group.

Keywords: Kidney transplant candidates, Kidney transplant recipients, Human immunodeficiency virus (HIV), Nutritional status, Nutritional assessment, Health related quality of life

2.1 Transplant candidates – pre-transplant protein energy wasting (PEW)

Poor nutrition-related health in the pre- and post-transplant period can predispose transplant candidates and recipients to malnutrition and metabolic complications respectively, which in turn has an impact on graft failure and patient survival. Improving post-transplant prognosis therefore begins in the pre-transplant period, through early identification and management of nutritional problems (1).

2.1.1 Pathophysiology of PEW

Although pre-transplant candidates on haemodialysis (HD) or peritoneal dialysis (PD) face a variety of challenges making it difficult to maintain an optimal nutritional status, one of the most overriding nutritional concerns is protein energy wasting (PEW). PEW, also referred to as malnutrition and uremic malnutrition (2,3), is the proposed nomenclature as it conveys with greater accuracy, the changes in nutritional status observed in chronic kidney disease (CKD) (4). It is argued that malnutrition in general, occurs due to a lack of food and nutrients. In addition, it is an adaptive process resulting in protective physiological responses that includes the sensation of hunger, a decline in energy expenditure and the selective use of fat over muscle reserves. Conversely, the PEW of CKD produces maladaptive responses, with persistently high energy expenditure and anorexia rather than hunger. Muscle and lean body mass is lost, and the body is said to be in a state of reduced protein and energy stores. Unlike malnutrition resulting from starvation, it cannot be treated by dietary intervention alone (4,5).

Identified as the ‘strongest risk factor for adverse outcomes and death’, PEW takes precedence over other nutritional issues in CKD, on account of the *time discrepancy hypothesis*. This premise applies to patients on dialysis who are thought to have higher short-term mortality risk from the consequences of under-nutrition, as they are unlikely to survive long enough to die as a result of health risks related to over-nutrition. Therefore strategies aimed at improving nutritional status by addressing wasting, have greater life-saving benefit when compared to usual long-term strategies that focus on hypercholesterolemia, obesity and other cardiac risk factors for individuals on dialysis (6,7). Despite the advancements in dialysis over the last 50 years (8), PEW unfortunately remains a persistent problem among dialysis populations globally. Differences in nutritional indicators and terminology notwithstanding, it has been identified in 15% to 66.7% of individuals in HD populations (9,10,11), and in between 58% and 85% of individuals in PD population (12,13).

Interrelated nutritional and non-nutritional pathways underlie the pathophysiology of PEW (14) that relate to the kidney's role in a host of homeostatic mechanisms (2). As PEW is independently associated with estimated glomerular filtration rate (eGFR), prevalence increases relative to the progression of CKD (15). Over time, the metabolic imbalances have an impact on several body systems and nutritional health (14). Early in the disease process, uraemia activates inflammation, producing inflammatory cytokines and increasing resting energy expenditure. Persistent inflammation, uremic toxins, metabolic acidosis and changes in hormonal activity produce a state of hyper metabolism that hastens protein catabolism, yet simultaneously reduces normal rates of synthesis (14). Dialysis improves uraemia but the procedure itself is associated with nutrient losses and an increase in resting energy expenditure, which if unmet, is fuelled by protein catabolism as a source of energy (16). Unfortunately, the requirements for protein and energy within this milieu are difficult to meet, due to additional factors such as dietary inadequacy and comorbidity (2,14), both of which are relevant to the current research.

2.1.2 Inadequate nutrient intake, utilisation and increased losses

The decrease in food intake, especially protein and energy, accompanies declining eGFR through the stages of CKD (17). Mehrotra et al reported an improvement in protein intake as well as nutritional status parameters six months after the initiation of haemodialysis (18). However, appetite remained reduced in up to a third of patients (19), ironically, being worse on dialysis versus non-dialysis days (20). An observation in PD patients suggests that at some point, an appetite threshold may be reached due to volume overload, satiety peptides, and inadequate dialysis which inhibits optimal intake (21). Added to this, there is interference with nutrient utilisation and absorption due to digestive disturbances or disease of varying severities (4,22,23,24) and loss of nutrients, especially amino acids, through the dialysates (25,26).

Studies conducted on patients in ESRD also show that an inadequate dietary intake can be attributed to the patient and their situational factors. These include complicated dietary restrictions (27), alterations in taste sensitivities (28,29), as well as dental and oral inflammation which could affect chewing and swallowing (30). Furthermore, financial difficulties are a barrier to obtaining a diet of a good quality (31,32), while psychological and social factors affect the availability, preparation and consumption of food (33).

2.1.3 The impact of comorbid HIV

Nutritional status is independently influenced by the presence of comorbidities (15), and is an additional factor in the development of PEW and malnutrition (14,34). Although little is known about comorbid HIV in the ESRD patient, it is likely to be significant, as the physiological impact of HIV, antiretrovirals (ARVs) and opportunistic infections on nutritional status is well documented (35,36).

One of the most significant and widely recognised effects of HIV is wasting (36). Weight loss, wasting and loss of lean body tissue commence in the early stages of HIV infection and can occur throughout the disease process, even in the era of highly active antiretroviral therapy (HAART) (37). The extensive use of HAART has reduced the prevalence of wasting to 17.2% (38). However, unintentional weight loss continues despite adequate viral suppression and higher CD4 cell counts (39). Determinants of weight loss in HIV are multifactorial, and according to Mangili and colleagues, can be categorised into two groups namely alterations in metabolism and insufficient nutrition (37). With regards to the former, HIV predisposes the individual to weight loss due to the physiological and metabolic effect of the virus, hormonal irregularities and cytokine dysregulation, which are intensified by the metabolic demands of ART (37). Metabolic changes in comorbidity alter nutritional status by increasing energy needs. In a small group of HD patients (n = 12), those with diabetes exhibited enhanced muscle breakdown as well as a trend towards higher resting energy expenditure when compared to matched non-diabetic HD controls (40). Oral and gastrointestinal manifestations are prevalent in approximately 50% of all patients, occurring at various stages during the course of the disease, thereby affecting nutrient assimilation. Symptoms include anorexia, abdominal pain, diarrhoea, vomiting, odynophagia or dysphagia (41) which reduces nutrient assimilation, absorption and utilisation (42). Inability to meet nutritional requirements could diminish immunity and increase susceptibility to opportunistic infections such as pulmonary tuberculosis, which can lead to a preferential loss of weight (80% - 90%) from protein stores (35).

Wasting and gradual depletion of body cell mass (BCM) may not be initially evident, as it is masked by fluid shifts or changes in adipose tissue (36,43), yet preservation of BCM is crucial for several reasons. Firstly, BCM influences patient survival regardless of CD4 or viral load (36). Secondly, being metabolically active, deterioration in BCM can affect the efficient metabolism of medication and essential nutrients (35). Thirdly, it is positively associated with quality of life parameters of improved physical ability, feelings of health and fewer sick days.

Hence the majority of dietary and lifestyle changes recommended for the management of HIV aim to preserve BCM (43).

2.1.4 The consequences of PEW as it relates to clinical outcomes

The resultant muscle and fat loss and a negative nitrogen balance indicated by various markers of nutritional status increase morbidity, mortality and predict outcome (23, 44). Malnutrition, using a composite PEM-score, was associated with increased infections (45). Anorexia, based on an appetite questionnaire was associated with a greater number of hospitalisations, reduced quality of life and a four to five fold higher mortality risk than HD patients with a normal appetite (19). Dialysis patients with a diet characterised by a low protein intake (< 1.0 g/kg/d) and low energy intake (< 25 kcal/kg/d), were significantly associated with poorer survival outcomes, as was a lower muscle mass estimated by mid arm muscle circumference (MAMC) (46). Similarly, in a five year cohort of 149 HD patients, an elevated mortality risk was observed relative to low subjective global assessment (SGA) scores, normalised protein equivalent of nitrogen appearance (nPNA) of < 1.15 g/kg per day, and lower phase angle values of body composition values determined by bioelectrical impedance (47). However, of all nutritional indicators, the preponderance of literature on outcomes associated with BMI. As a single index of nutritional status, BMI was historically recorded for eligible transplant candidates (48). Resultantly over time, decades of accumulated pre-transplant BMI data made retrospective analysis possible, linking pre-transplant BMIs to outcomes in the pre- and post-transplant phase (1,49).

2.1.5 Pre-transplant BMI on clinical outcomes

<u>The effect of pre-transplant BMI on clinical outcomes while on dialysis:</u>

A review by Park and co-authors listed a collection of studies demonstrating an inverse association between BMI and mortality in maintenance dialysis populations, and even a "reverse J-shaped" relationship. Lower BMIs were associated with a higher risk of mortality, a phenomenon confirmed by several larger cohorts of maintenance dialysis patients (50) as well as in candidates waitlisted for a transplant (51). With reference to the latter, research by Molnar <u>et al</u> reported on 14 632 waitlisted candidates, who as a group are typically in better health that HD patients who are not candidates for a transplant. They again confirmed a poorer survival in low BMI candidates and/or in those who experienced unintentional weight loss (51). Since this is contradictory to the relationship between BMI and survival in the general population (52),

this reverse epidemiological phenomenon was termed the *obesity paradox* (53) and has been documented among dialysis patients in Asian (54) and European populations (55) across gender (55), comorbidities (56), and across a number of ethnicities, with a greater strength of association amongst those of black ethnicity (57,58).

Attempts to identify the component of weight that offered the survival advantage was limited by the inability of BMI to differentiate between fat and muscle. Studies then used creatinine as a proxy for muscle mass, and this showed that the protective effect offered by the obesity paradox was due to the presence of a larger muscle mass. It was observed that a lower BMI or muscle mass (using creatinine) and/or unintentional weight loss or loss of muscle mass was significantly associated with higher mortality, while higher BMIs were related to enhanced survival. In the Dialysis Outcome and Practice Patterns Study (DOPPS), a lower relative risk in mortality was seen in patients above the BMI range of 23.0-24.9kg/m^2, even in those with moderate obesity (35.0-39.9 Kg/m^2). The best outcome was seen in patients with low body weight and a high muscle mass leading to recognize the important role of muscle mass in the obesity paradox (51,59). Despite the survival benefit of a high BMI while on dialysis, its effect on post-transplant outcomes are less consistent.

The effect of pre-transplant BMI on post-transplant outcomes:

Although some studies like the one by Marcén et al, showed that pre-transplant BMI was not associated with overall graft failure or patient survival over two years (60). A recent meta-analysis combining the data from 56 studies (n = 209 000) investigated the surgical, metabolic and mortality outcomes associated with BMI. It was determined that transplant recipients with a higher pre-transplant BMI do incur some post-transplant risk with respect to a greater probability of delayed graft failure and acute rejection, diabetes and hypertension (61).

2.2 Kidney transplant recipients – post transplant obesity and metabolic disorders

Transplantation improves quality of life and many of the nutritional anomalies associated with ESRD and dialysis. Thereafter, attention is turned to physical and metabolic changes that are caused or aggravated by immunosuppressive therapy (62,63). Equally important, in the current context, would be the physical and metabolic changes applicable to the context of HIV (64). In addition to immunosuppressive therapy, lifestyle factors such as diet and exercise are also thought to play a role and, according to Fong and Moore, attention to lifestyle factors has the potential to avert adverse post-transplant consequences of cardiovascular disease (CVD),

dyslipidaemia, diabetes and bone loss (65). Therefore, with consideration to metabolic abnormalities relevant to both transplantation and HIV, and which fall within the scope of long-term nutritional monitoring, the most pertinent ones are those indicated in Figure 2.1 (64,66). Of these, one of the earliest and most apparent is weight gain.

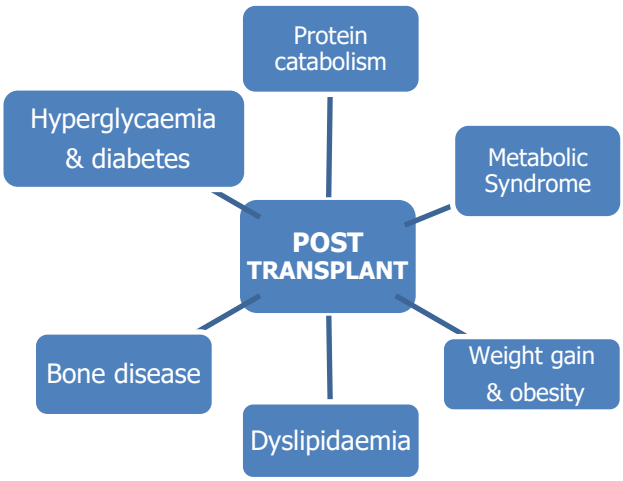

Figure 2.1: Theoretical framework of long term nutrition complications following a kidney transplant

2.2.1 Weight and body composition changes

Weight gain following a transplant is common. Increases in weight of between 5 kg to 13.6 kg during the first year have been documented (67,68,69), with the greatest extent of weight gain occurring in the first few months following transplantation. Cashion et al reported a 9.18 ± 6.59 kg weight gain over one year, although the greatest incremental gains were observed within the first three months (67). Similarly, Elster et al reported a rapid 5.0 kg weight gain in the first six months which gradually increased to 9.9 kg over 3 years (70).

The extent of post-transplant weight gain is notably higher among African Americans (69), and seems to occur irrespective of whether patients receive steroid inclusive or avoidance regimens (70). Determinants and predictors of weight gain are multifactorial. Factors that are responsible for weight gain in the general population, including reduced physical activity and inappropriate dietary intake, contribute to weight gain especially as appetite improves from pre-transplant uraemia (71,72).

Obesity is associated with known CVD risk factors such as hypertension, dyslipidaemia, and diabetes (73). CVD is the leading cause of death among transplant recipients (74). In fact, a high risk of premature CVD exists for all patients with ESRD, regardless of treatment modality. Compared to the general population, there is a 10 to 20 times and three to five time's greater risk of early CVD in transplant candidates and transplant recipients respectively (73). HIV-positive ESRD patients may, in all likelihood, have an even greater risk of CVD, given the fact that compared to uninfected individuals, they have a 1.5 to 2 fold higher relative risk of a myocardial infarction or coronary artery disease (75). But this would require investigation. Therefore, an important treatment goal among recipients is to address obesity and any factors that may increase the risk of CVD, as early as possible.

2.2.2 Dyslipidaemia following renal transplantation

The frequency of dyslipidaemia in kidney transplant recipients is generally high (73), especially hyperlipidaemia (76). In Iranian patients with dyslipidaemia, hypertriglyceridemia was the most prevalent form of dyslipidaemia, documented in 86.6% of recipients (77). Hypertriglyceridaemia and hypercholesterolaemia peaks between four to twelve months post-transplant, while high density lipo-protein cholesterol (HDL) and low density lipo-protein cholesterol (LDL) progressively worsened by one year post transplant (77). Dyslipidaemia is fuelled by immunosuppressants (73), age, genetics and donor source (hypercholesterolemia and hypertriglyceridemia is higher among recipients with kidneys from cadaveric donors than from living donors) (77) and are hence some of the non-modifiable determinants of dyslipidaemia, while obesity and a diet high in saturated fats, cholesterol and carbohydrates are modifiable risk factors (76).

How the presence of HIV in the renal transplant recipient is likely to alter or exaggerate the pattern of dyslipidemia, is uncertain, since both the virus and ART exert independent effects on lipid metabolism (78). HIV lowers HDL and LDL levels but causes an increase in triglyceride levels, while disease-related weight and protein loss lowers total cholesterol and LDL-cholesterol (78). The introduction of ART alters the lipid profile somewhat by increasing LDL, while HDL remains low (78). LDL abnormalities were observed among 33.1% of a sample of 308 HIV patients on ART, although hypertriglyceridemia was the most prevalent, affecting 59.1% of the sample, followed by hypercholesterolemia (41.9%) (79). ART also causes post-prandial lipaemia, a strong contributor to atherosclerosis, while hyperlipidemia is more

prevalent in individuals with lipodystrophy than those without (80). Of all ART drug categories, protease inhibitors have a significant lipid altering effect and are associated with hypercholesterolaemia. In the case of HIV-positive kidney transplant recipients receiving a kidney from a HIV-positive donor, dosages of protease inhibitors are augmented to subdue viral resistance (81), hence necessitating the regular monitoring of lipid levels.

2.2.3 Hyperglycaemia and post-transplant diabetes

There is a high prevalence of hyperglycaemia (46%) within the first year post-transplant. New Onset Diabetes Mellitus after Transplantation (NODAT) occurs in 4% to 20% of the transplant population in the first year (73). There is a known diabetogenic effect of post-transplant medication (82). However, influences during the pre- and post-transplant period that are also applicable to the general population, include ethnicity, age, gender, obesity and family history. Obesity, along with hepatitis C infection, and the type of anti-rejection therapy were identified as potentially modifiable risk factors, and compared to the other risk factors, obesity (defined as a BMI $\geq 30 kg/m^2$) conferred one of the highest risks (83).

The prevalence of type 2 diabetes in the HIV population increased from 6.8% in 2005 to 15.1% in 2015 (84). Although several factors were associated with the development of diabetes, weight gain after commencing antiretroviral therapy was a major factor (84). This was observed in a study of 1844 HIV-positive individuals where the probability of multi-morbidity was significantly greater in individuals that were classified as obese (85). HAART is associated with body fat re-distribution (lipodystrophy), especially as a result of the combined use of protease inhibitors and non-nucleoside reverse transcriptase inhibitors, with associated insulin resistance and dyslipidaemia (78).

Protease inhibitors are associated with the development of lipid abnormalities and insulin resistance (64). Hypertension is very prevalent among South Africans (86), and in combination with abdominal obesity, can be used to determine the presence of metabolic syndrome. The prevalence of metabolic syndrome in HIV-positive patients ranges from 17% to 42%, with a higher prevalence being documented among those with viraemia and an elevated BMI (78). Abdominal obesity can be prevalent prior to transplantation, as HD patients have presented with excess visceral fat (VAT), and possibly linked to alterations in lipid levels (87). The presence of the metabolic syndrome predisposes to diabetes, contributes to early graft loss and substantially increases the risk of a cardiovascular event (88).

2.2.4 Bone disease

Bone disease, such as osteoporosis, is an additional long term comorbidity that falls within the scope of the nutritional management of the kidney transplant recipient (88). Prior to undergoing a transplant, CKD-mineral and bone disorder (CKD-MBD) increases bone frailty and fracture susceptibility (89). Compared to the healthy population, both dialysis and transplant patients have a 17.2 times higher frequency of fractures, especially of the hip which affects quality of life and survival (89). Following a renal transplant, fracture risk increases. Retrospective information from the US Renal Data System which analysed 68 814 recipients over a ten year period found that 22.5% of the study sampled had a fracture within five years of transplantation (90).

Post-transplant prednisone, worsens the negative impact on bone mineralisation through reduction of calcium absorption, hyperparathyroidism and abnormal vitamin D metabolism (66). Kidney transplant recipients with HIV would be at an additional risk of developing bone complications related to alterations in bone metabolism and reduced bone mineral density (BMD) due to HIV (64). A meta-analysis by Brown and Qaqish (2006) found reduced BMD in 67% of patients infected with HIV and a greater than three-fold prevalence of osteoporosis in HIV-positive subjects compared to negative controls (91), possibly due to the viral effects of HIV, infections, and a low CD4 cell count (92). With the initiation of anti-retrovirals, decreases of up to 2.5% of total BMD over a two years period were observed (93), although there was a slight increase in mean BMD after 72 weeks related to virological suppression and an improved CD4 cell count (94).

Together with nutritional deficiencies, Efavirenz and protease inhibitors may interfere with vitamin D metabolism. The prevalence of vitamin D deficiency may be as high as 70% and the resultant osteomalacia causes bone pain, muscle weakness and stiffness (92). Therefore, a nutritional recommendation for the maintenance of optimal bone health focuses on an adequate intake of calcium, vitamin D and lifestyle changes (66). The important role of vitamin D in HIV continues to emerge as it is found to have a complex relationship involving ARVs and immunity as well as affecting disease progression and mortality (95). In view of these important associations between nutritional status and clinical outcomes, an accurate assessment of nutritional status is vital.

2.3 Nutritional assessment

Since no single indicator is an all-encompassing indicator of nutritional health, multiple parameters provide a more comprehensive picture. The commonly recommended "ABCD" method, is a composite evaluation of anthropometric, biochemical, clinical and dietary indicators (35). Within each category, selecting the most suitable from a range of simple or sophisticated indicators requires consideration of the assessment goals and context of the patients under evaluation, as well as available resources.

2.3.1 Anthropometric evaluation of body composition

Body composition is used to determine protein-energy status, diagnose and classify the severity of over-nutrition (overweight/obesity) and under-nutrition (PEW) (49). The ISRNM recommends the evaluation of low body weight, weight loss and reduced adiposity and musculature to identify PEW (5). Most suitably, this involves the anthropometric indicators BMI, triceps skin-fold (TSF) thickness, and mid arm muscle circumference (MAMC) (96).

Total and regional body fat: BMI estimates overall adiposity, moderately correlating with adiposity measured by underwater weighing and dual energy X-ray absorptiometry (DEXA) (97). In the context of CKD, weight and BMI are easy indicators to determine, as all dialysis units would be equipped with digital scales to record pre- and post-dialysis weights. Although the World Health Organisation (WHO) cut-off for underweight is 18.5kg/m^2, a higher cut-off of 23kg/m^2 is suggested by the ISRNM, with caution regarding its applicability to all population groups (5). BMI is useful as prognostic tool of survival (1) but has limitations as single indicator of health risk (49).

The differentiation between fat and fat-free or muscle mass as well as regionally distributed fat, exceed the limitations associated with BMI. Highly sophisticated methods are costly and impractical in resource-limited settings (98,99). In South Africa, as is the case with countries of a similar economic standing, the unequal distribution of medical resources, technology and infrastructure are important considerations (100). Sophisticated methods are options for single-site studies in well- resourced areas or could be used as reference methods. Hence skinfold and circumference measurements are an alternative for multiple sites that are unequally resourced.

An estimation of total body fat determined from subcutaneous fat as measured by skinfold thickness correlates strongly with DEXA in HD patients [r = 0.868 (P < .001)] (101). Although

multiple body sites can be included for estimating overall body adiposity, triceps skinfold thickness has comprehensive reference standards, is quick and practical, and can be used in the calculation of muscle circumference and muscle area (98). It should however be borne in mind that the equations and reference standards used are based on data from the general population, and varies with age and gender (101-103). As a possible criterion for PEW, body fat should not be less than 10% (5).

Like BMI, triceps skinfolds are not indicative of regional fat distribution. However, abdominal fat, especially visceral adipose tissue (VAT) is associated with an increased risk of type 2 diabetes mellitus and CVD (104). In pre-dialysis patients, there was a strong association between waist circumference and visceral fat and harmful serum lipids (105). Of the various indicators of abdominal obesity, waist circumference is most often used (98) as a simple, inexpensive means of identifying truncal obesity, even in those with a low BMI (106).

Lean body mass: Mid arm muscle circumference (MAMC) and arm muscle area (AMA) are calculated using measurements of upper arm circumference and triceps skinfolds to measure an estimate of muscle stores (98,102). The European Society for Clinical Nutrition (ESPEN) guidelines for HIV-positive patients recommend that nutritional status is ideally represented by muscle mass representing the body's protein stores, because muscle loss and BCM may not be detected by weight (36).

Muscle is affected by hydration status (107), and therefore an important concern in dialysis, or in HIV during acute illness, or increases in tissue fluids (108). Nevertheless, lean body mass changes using anthropometry shows good agreement with dual energy X-ray absorptiometry (DEXA) in HIV positive patients and has superior agreement with DEXA compared to bioelectrical impedance (108).

2.3.2 Biochemical parameters of selected nutritional status outcomes

Serum albumin is usually available via routine blood testing. More than 50% of all patients on maintenance HD have serum albumin <38g/L (109). It is more often used as a marker of illness and inflammation than an indicator of nutritional status and protein stores, as it is unrelated to dietary intake in CKD, and poorly correlates with other nutritional markers in patients undergoing dialysis (110,111). A possible reason for this is due to the opposing effects that inflammation and nutrition have on albumin catabolism and synthesis respectively (112). Nonetheless, it still has prognostic value in CKD, as it is associated with the risk of

hospitalisation (113) and is a strong predictor of mortality. In the 5058 patients from the renal data base study, each 10g/L decrease in serum albumin increased cardiovascular mortality risk by 39% (114). As a parameter of illness, clinical measures to improve albumin in CKD will also improve nutritional status (109). In addition, lower serum albumin during the pre-transplant period predicts greater post-transplant mortality, graft failure and delayed graft function (115). Prealbumin is the recommended alternative to evaluate visceral protein stores (5, 116). With a shorter half-life of two to three days, it is more sensitive to alterations in nutritional status, and low serum levels are an independent risk factor for mortality in PD patients (116). However, prealbumin is also subject to misinterpretation, as inflammation decreases prealbumin, while it increases in CKD (116). Prealbumin correlates with other markers of nutritional status and demonstrates good sensitivity and specificity (116,117). Serum-cholesterol is not affected by acute illness, and as amalnutrition screening tool is more reflective of energy rather than protein intake (5). Nonetheless, as a risk factor for CVD, total cholesterol is routinely assessed, while a fasting lipid profile is required when screening for dyslipidaemia (76).

Biochemical indicators are objective, but are not reliable as stand-alone nutritional status indicators as they are also sensitive to changes that accompany disease states (118). Hence it is recommended that clinical assessment is viewed as superior, especially in the evaluation of malnutrition (118,119).

2.3.3 Clinical evaluation of gastrointestinal symptoms (GIS)

The clinical component of the evaluation of nutritional status is frequently assessed by the subjective global assessment (SGA), which combines medical history and a physical assessment (120). However, as Gupta et al pointed out, its dependence on subjectivity and judgement makes it susceptible to the partiality of the observer (121), and is potentially limiting in multi-centre studies with numerous fieldworkers. An additional limitation is that it is restricted to recognising degrees of malnutrition rather than nutritional risk (122). So, although the SGA in its entirety is inappropriate for this study, the section related to GI disturbances is relevant, especially in the context of HIV (41). Therefore, it would be more prudent to use a GIS specific tool than the SGA. Amongst the dialysis populations, GIS have been gauged by questionnaires, interviews, prospective diaries and stool analysis (123). The appeal of questionnaires is that they are easy to administrator, non-invasive and inexpensive. Ideally, the instrument should be as inclusive as possible, have good psychometric properties and be suitable for the goals of the population. For example, the disease specific GERD Symptom Frequency Questionnaire

(GSFQ) used to screen for gastro-oesophageal reflux disease (124), is useful in CKD, however symptoms of the lower gut may be missed if they are relevant to the condition under investigation. The Gastrointestinal Quality of Life Index (GIQLI) specifically assesses the burden of GIS on five quality of life domains (125). The gastrointestinal symptom rating scale (GSRS) is inclusive of both upper and lower gastrointestinal symptoms. It is one of the most widely validated instruments used in the dialysis population (123), and along with the GIQLI, shows very good discriminant ability in kidney transplant recipients (125).

2.3.4 Evaluation of nutrient intake

The detailed description of macro- and micronutrient intake is feasible for small research samples and are valuable in clinical practice (102), as nutrients are associated with nutritional status and can be targeted for intervention. For example, in a study of HIV-positive men, BCM determined by bioelectrical impendence, correlated with dietary protein obtained via 24-hour recall (43). Similarly, a three day dietary recall helped to identify inadequate dietary protein as the key factor associated with malnutrition in 67.8% of study participants undergoing HD (34). The 24-hour recall has the advantage of being quick and simple to administer and does not rely on respondent literacy levels. Recall is immediate and does not alter dietary behaviour (126). Daily dietary differences in the general population imply that more than a single 24-hour recall is preferable to obtain an accurate representation of usual intake. Irrespective of the dietary assessment tool, accuracy is improved when attention is given to the estimation of portion size, and the use of professionals with experience in obtaining dietary information (102).

2.3.5 Evaluation of bone mineral density

Screening for osteoporosis and fracture risk is typically done by measuring bone mineral density using DEXA. DEXA is a quicker, more cost effective method with less radiation exposure than imaging techniques such as computed tomography or magnetic resonance imaging (127). The two sites most commonly measured are the lumbar spine and hip area. BMD scores are converted to T-scores which are used in the classification of osteoporosis (91).

2.4 Health-related quality of life

The purpose of a transplant is not only to prolong survival, but also to improve quality of life (128). Resultantly, health-related quality of life (HRQOL) has become an increasingly

important health outcome measure among recipients of a kidney transplant (129). Going beyond traditional indicators of morbidity and mortality, HRQOL evaluates multiple dimensions of health and well-being in daily life (130). In doing so, it is a more accurate reflection of one's condition as it incorporates a subjective view of health and the consequence of disease on daily living (129).

2.4.1 The concept health related quality of life

Quality of life (QOL) and HRQOL are separate concepts, although they have been used interchangeably, possibly because a clear definition of either remains elusive (131). HRQOL is more applicable to health and disease and is a multi-dimensional concept that captures the effects of a disease and its treatment on the physical, mental and social functions of an individual (132). It also draws on perceptions shaped by individual beliefs and culture and is inclusive of their aims and expectations, as well as aspects of life that they find concerning (132).

2.4.2 HRQOL of transplant candidates and recipients

HRQOL is reduced in ESRD patients on renal replacement therapy (133,134), affecting both mental and physical health. A study of 90 patients receiving dialysis, found that 40.8% were depressed, 39.6% were anxious, while 24.1% were afflicted with both conditions (135). In other studies, a higher prevalence of up to 72.5% of moderate to severe depression among HD patients have been reported (136). In addition, patients suffer from a deterioration in physical functioning (137) and chronic pain (138). HRQOL scores show an improvement after a transplant, closer to that of healthy subjects (139). One of the largest systematic reviews comparing clinical outcomes between dialysis and transplant recipients pooled the findings of 110 studies, thus including 1 922 300 participants. The results showed that transplantation is associated with a superior quality of life, regardless of research instrument used or context (140). However, psychological distress (141), and chronic pain (138) still persist.

Efforts to improve HRQOL gained considerable momentum as it became apparent that HRQOL is also predictive of clinical outcomes. Better quality of life scores were associated with improved treatment compliance (142), and depression was predictive of mortality risk in HD patients (143). A two year longitudinal study with a sample size of 14 815 patients on HD showed that both poor mental health and physical functioning scores were associated with

increased mortality (144). A later smaller cohort of the CONTRAST study including 714 HD patients from three countries, identified physical and social functioning as well as emotional health as the HRQOL domains associated with mortality risk. The strongest association documented between physical functioning and mortality (HR = 1.72, 95% CI = 1.02–2.73), showed that compared to participants with an adequate baseline physical functioning score, those with lower scores had a 3.6 times greater mortality risk (145). Similarly, in a 12 year study of transplant recipients, physical limitations increased the risk of both graft failure and death after adjusting for clinical, social and demographic factors (146). In another long term follow-up study on ten year post kidney transplant recipients, higher graft and host survival rates were observed in recipients with both higher physical and mental component scores of HRQOL (147). Given that one's personal view of health influences treatment and survival (130), assessment of HRQOL and related factors will help identify patients at risk of adverse outcomes and will be valuable in planning strategies for improving HRQOL (145).

2.4.3 Factors affecting HRQOL

There are numerous socio-demographic and clinical determinant of HRQOL in patients on renal replacement therapy (148). A national survey of kidney transplant recipients in France identified multiple socio-demographic and clinical factors that were associated with a significant reductions in HRQOL. These included being female, unemployed, less educated and residing alone. Clinical factors included, but were not limited to, infections, illness, longer duration of dialysis and hospitalisation, and high BMI (149). Two additional variables known to affect HRQOL, and relevant to the scope of the current study are comorbidity (150) and nutrition (151).

Lower HRQOL scores were found in ESRD patients with a higher number of comorbidities (150). Transplant recipients with more comorbidities according to the Charlson comorbidity index, had a lower HRQOL, particularly in the dimension of physical function (134). Despite the lack of corroborative research, it is highly likely that HIV, which in itself is a burdensome disease, will contribute to an unfavourable dynamic to the HRQOL of kidney transplant candidates and. HIV- positive individuals in the United Kingdom, who had considerably lower HRQOL than the general population, despite the fact that the majority of participants had stable viral suppression and immune-competence (152). Given the longevity that ART now affords, understanding the determinants of HRQOL in HIV is important in order to focus interventions that aim to improve HRQL. Research on populations consisting of HIV-positive individuals,

documented a number of factors (indicated in Table 2.2), that impact on HRQOL (42,153-156) Although several factors that are prevalent among ESRD populations are not modifiable, there are potentially modifiable factors in ESRD (130), including nutritional status.

Table 2.1 Factors contributing to a worse HRQOL and improved HRQOL in HIV-positive samples

Worse HRQOL		Better/improved HRQOL	
Infections	Comorbidities	Male	Fewer symptoms
Poor social/ relationships	Stigma	Higher socioeconomic status	Elevated haemoglobin
ART side-effects	CD4 count < 300cells/mm^3	Younger age	ART with fewer pills
Medical visits	Lack of support	Being employment	ART adherence
Malnutrition	Decline in work function	Low viral load, high CD4	
	Medication therapy		

2.4.4 The effect of nutritional status on HRQOL in HIV and kidney transplantation

In ESRD, a compromised nutritional status is associated with lower HRQOL scores, specifically in the physical domain (130). In HD patients, Noori et al demonstrated that a high MAMC, indicative of whole body muscle, is linked to improved QOL and survival (151). On the other hand, worse SF-36 mental and physical health scores were associated with lower serum albumin and creatinine levels and a higher total body fat percentage (157). In a study of HD patients by Raimundo et al (2006), weight loss negatively impacted on overall health, mobility, anxiety or depression, as well as usual activities in patients receiving haemodialysis (158). Psychological well-being has also been shown to be inversely related to gastrointestinal disturbances in CKD, regardless of treatment dialysis modality (159).

Less is documented about the influence of indicators of nutritional status on the HRQOL of transplant recipients. The few studies that were identified are summarised in Table 2.3. A decline in mental health was associated with increasing BMI (160), and increasing severity of GIS, accompanied by greater impairments to HRQOL (161,162).

Table 2.2: The association of nutritional status indicators with HRQOL of transplant recipients

Author, year	Sample	Study type	Instrument	Health related quality of life outcomes
Czyżewski et al 2014 [160]	N = 120 47 transplant, (30-PD,40-HD) Poland	Observational, prospective (3 months, 12 months)	SF-36 KDQOL-S.	Mental component score correlated negatively with BMI (r= –0.47; p < 0.05) at 1 year post- transplant.
Gentile et al 2013 [149]	N=1061 France	Cross-sectional multicentre	SF-36 ReTransQol	BMI > 30 kg/m^2 was negatively associated with physical functioning domain of the SF-36; (r = -5.8, p < 0.0065) BMI > 30 kg/m^2 was negatively associated with the physical health domain (r = -4.6, p <0.0021), and the treatment domain of the ReTransQoL; (r = -3.2, p = 0.0030)
Eckberg et al 2007 [161]	N= 4232 Denmark, Finland, Norway, Sweden	Observational cross-sectional.	SF-36 GSRS	GSRS score correlated with SF-36 scores for all dimensions. Greater severity of gastrointestinal symptoms related to worse HRQOL
Ponticelli et al 2010 [162]	N=1130 Italy	Observational, prospective. (baseline, 3 months, 6 months, 12 months)	GSRS GIQLI	Significantly lower HRQOL in the presence of GIS (patient & doctor reported) Presence of GIS was associated with reductions in All five GIQLI domains (P<0.0001), especially emotional and physical function domains with moderate-to-severe GIS

SF-36: Medical Outcomes Study 36 - the Short Form, KDQOL-SF: Kidney Disease Quality of Life Short Form, ReTransQol: French version of the SF-36,
GSRS: Gastrointestinal Symptom Rating Scale, GIQLI: Gastrointestinal Quality of Life Index.
BMI: Body Mass Index, GIS: Gastrointestinal symptoms

2.4.5 Measurement of HRQOL

Numerous quantitative and qualitative methodologies exist to interpret patients' subjective experience of their health (130). Whether it be for practice or research, the most appropriate method should be selected based on its suitability to the objectives of the investigation (153), the population under study and the context of the study. Interviews and focus groups are examples of qualitative techniques that aim to understand an individual's thoughts and feelings and how it shapes their perceptions and behaviour (163). Quantitative instruments which are used more often, are either used in economic analysis or the quantification of HROL and identification of the factors that can be modified to improve HRQOL (164). Quantitative instruments are classified into one of two types namely disease- specific and generic (130).

Disease specific tools include aspects of the condition and treatment peculiar to that disease. For example, the Kidney Disease-Quality of Life (KDQOL) for use in CKD (129) and the Medical Outcomes Study (MOS)-HIV tool for use in the HIV population (153). Disease-specific tools have the advantage of being sensitive to health changes during the course of the disease. On the other hand, highly specific instruments may be limiting following major changes in the course of treatment. For example, a recipient may be evaluated using a kidney transplant questionnaire that considers the effect of immunosuppressants (129). If kidney function deteriorates and the recipient needs to revert to dialysis, a dialysis specific instrument would then be more appropriate (129,164). However, in this way, continuity in follow-up is broken. A disease specific instrument also limits comparisons of HRQOL across healthy populations and among those with other disease conditions (164). Moreover, they may not capture the impact of a significant comorbid condition such as HIV. The alternative is a generic instrument.

Several generic instruments are available but two common tools are the Short-form (SF-36) and the WHOQOL-BREF (129,165). The former is one of the most widely used, featured in more than 2000 publications (129). As a very versatile tool, the SF-36 is used in comparative studies between healthy populations, different diseases and across renal replacement modalities (164).

The validity of the SF-36 has repeatedly been demonstrated. In transplant recipients, it has been found to be reliable; i.e. internal consistency, valid (high correlation with general HRQOL assessments), and discriminant (can distinguish changes in clinical status and is perceptive to longitudinal differences between waiting list patients and transplant recipients) (129,139,166). Similarly, in the HIV-positive population, the SF-36 is a recommended generic measure, that is

well substantiated by psychometric evidence. It has demonstrated adequate responsiveness to HIV symptoms and ART initiation, as well as alterations in CD4 count and viral load levels (153).

2.5 Conclusion

The literature drives home the point that unfavourable changes in nutrition status are highly prevalent, and predictive of adverse clinical and quality of life outcomes surrounding transplantation. However, there is a need for understanding the possible implications of underlying HIV with ESRD on nutritional health. Therefore the nutritional complications in HIV are also reviewed. Finally, the most suitable indicators, to optimally assess the nutritional status and HRQOL of both diseases during the pre- and post-transplant phase are discussed. Fortunately, nutrition is modifiable and improvements in nutritional status could potentially contribute to meaningful changes in health, and thereby maximise the quality and quantity of life that a transplant affords.

2.6 References

1. Lentine KL, Axelrod D, Abbott KC. Interpreting body composition in idney transplantation: Weighing candidate selection, prognostication, and interventional strategies to optimize health. Clin J Am Soc Nephrol. 2011; 6(6): 1238-1240.
2. Chung S, Koh ES, Shin SJ, Park CW. Malnutrition in patients with chronic kidney disease. OJIM. 2012; 2(2). doi: 10.4236/ojim.2012.22018
3. Ikizler TA. Protein and energy: Recommended intake and nutrient supplementation in chronic dialysis patients. Semin Dial. 2004; 17(6): 471-478.
4. Mak RH, Ikizler AT, Kovesdy CP, Raj DS, Stenvinkel P, Kalantar-Zadeh K. Wasting in chronic kidney disease. J Cachexia Sarcopenia Muscle. 2011; 2(1): 9–25.
5. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevinho-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney. Kidney Int. 2008; 73(4): 391-398.
6. Kopple JD. McCollum Award Lecture. 1996: Protein-energy malnutrition in maintenance dialysis patients. Am J Clin Nutr. 1997; 65(5): 1544-1557.
7. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J

Kidney Dis. 2003; 42(5): 864-881.

8. Karkar A. Advances in hemodialysis techniques. In H S, editor. Hemodialysis.: Intech Open; 2013.doi: 10.5772/52444
9. Yasui S, Shirai Y, Tanimura M, Matsuura S, Saito Y, Miyata K, Ishikawa E, Miki C, Hamada Y. Prevalence of protein-energy wasting (PEW) and evaluation of diagnostic criteria in Japanese maintenance hemodialysis patients. Asia Pac J Clin Nutr. 2016; 25(2): 292-299.
10. Ruperto M, Sánchez-Muniz FJ, Barril G. Predictors of protein-energy wasting in haemodialysis patients: A cross-sectional study. J Hum Nutr Diet. 2016; 29(1): 38-47.
11. Sedhain A, Hada R, Agrawal RK, Bhattarai GR, Baral A. Assessment of nutritional status of Nepalese hemodialysis patients by anthropometric examinations and Modified Quantitative Subjective Global Assessment. Nutr Metab Insights. 2015; 12(8): 21-27.
12. Abdu A, Ladeira N, Naidoo S, Naicker S. The nutritional status of continuous ambulatory peritoneal dialysis patients at a Johannesburg hospital. SAJCN. 2011; 24(3): 150-153.
13. Krishnamoorthy V, Sunder S, Mahapatra HS, Verma H, Sharma N, Jayaraman R, Sathi S, Khanna S, Mohamed A. Evaluation of protein-energy wasting and inflammation on patients undergoing continuous ambulatory peritoneal dialysis and its correlations. Nephrourol Mon. 2015; 7(6): e33143.doi: 10.5812/numonthly.33143
14. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, Mitch WE, Price SR, Wanner C, Wang AY, ter Wee P, Franch HA. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr. 2013; 23(2): 77-90.
15. Hyun YY, Lee KB, Han SH, Kim YH, Kim YS, Lee SW, Oh YK, Chae DW, Ahn C. Nutritional status in adults with predialysis chronic kidney disease: KNOW-CKD Study. J Korean Med Sci. 2017; 32(2): 257-263.
16. Zha Y, Qian Q. Protein nutrition and malnutrition in CKD and ESRD. Nutrients. 2017; 9(3). pii: E208. doi: 10.3390/nu9030208.
17. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, Scherch LK, Schulman G, Wang SR, Zimmer GS. Relationship between nutritional status and the glomerular filtration rate: Results from the MDRD study. Kidney Int. 2000; 57(4): 1688-1703.
18. Mehrotra R, Berman N, Alistwani A, Kopple JD. Improvement of nutritional status after initiation of maintenance hemodialysis. Am J Kidney Dis. 2002; 40(1): 133-142.

19. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr. 2004; 80(2): 299-307.

20. Burrowes JD, Larive B, Cockram DB, Dwyer J, Kusek JW, McLeroy S, Poole D, Rocco MV; Hemodialysis (HEMO) Study Group. Effects of dietary intake, appetite, and eating habits on dialysis and non-dialysis treatment days in hemodialysis patients: cross-sectional results from the HEMO study. J Ren Nutr. 2003; 13(3): 191-198.

21. Sutton D, Higgins B, Stevens JM. Continuous ambulatory peritoneal dialysis patients are unable to increase dietary intake to recommended levels. J Ren Nutr. 2007; 17(5): 329-335.

22. Dong R, Guo ZY, Ding JR, Zhou YY, Wu H. Gastrointestinal symptoms: A comparison between patients undergoing peritoneal dialysis and hemodialysis. World J Gastroenterol. 2014; 20(32): 11370-11375.

23. Heng A, Cano NJM. Nutritional problems in adult patients with stage 5 chronic kidney disease on dialysis (both haemodialysis and peritoneal dialysis). N D T Plus. 2009; 3(2): 109-117.

24. Lee YC, Hung SY, Wang HH, Wang HK, Lin CW, Chang MY, Ho LC, Chen YT, Wu CF, Chen HC, Wang WM, Sung JM, Chiou YY, Lin SH. Different risk of common gastrointestinal disease between groups undergoing hemodialysis or peritoneal dialysis or with non-end stage renal disease: A nationwide population-based cohort study. Medicine (Baltimore). 2015; 94(36): e1482.doi: 10.1097/MD.0000000000001482.

25. Stegmayr B. Dialysis procedures alter metabolic conditions. Nutrients. 2017; 9(6): 548. doi: 10.3390/NU9060548

26. Ikizler TA, Flakoll PJ, Parker RA, Hakim RM. Amino acid and albumin losses during hemodialysis. Kidney Int. 1994; 46(3): 830-837.

27. Kalantar-Zadeh K, Brown A, Chen JLT, Kamgar M, Lau W Moradi H, Rhee CM, Streja E, Kovesdy CP. Dietary restrictions in dialysis patients: is there anything left to eat? Semin Dial. 2015; 28(2): 159-168.

28. Middleton RA1, Allman-Farinelli MA. Taste sensitivity is altered in patients with chronic renal failure receiving continuous ambulatory peritoneal dialysis. J Nutr. 1999; 129(1): 122-125.

29. López-Pintor RM, López-Pintor L, Casañas E, de Arriba L, Hernández G. Risk factors

associated with xerostomia in haemodialysis patients. Med Oral Patol Oral Cir Bucal. 2017; 22(2): e185–e192. doi: 10.4317/medoral.21612

30. Akar H, Akar GC, Carrero JJ, Stenvinkel P, Lindholm B. Systemic consequences of poor oral health in chronic kidney disease patients. Clin J Am Soc Nephrol. 2011; 6(1): 218-226.
31. Gutiérrez OM. Contextual poverty, nutrition and chronic kidney disease. Adv Chronic Kidney Dis. 2015; 22(1): 31-38.
32. Dukkipati R, Kopple JD. Causes and prevention of protein-energy wasting in chronic kidney failure. Semin Nephrol. 2009; 29(1): 39-49.
33. Hung KC, Wu CC, Chen HS, Ma WY, Tseng CF, Yang LK, Hsieh HL, Lu KC. Serum IL-6, albumin and co-morbidities are closely correlated with symptoms of depression in patients on maintenance haemodialysis. Nephrol Dial Transplant. 2011; 26(2): 658-664.
34. Jahromi SR, Hosseini S, Razeghi E, Meysamie Ap, Sadrzadeh H. Malnutrition predicting factors in hemodialysis patients. Saudi J Kidney Dis Transpl. 2010; 21(5): 846-851.
35. The American Dietetic Association. Position of the American Dietetic Association: Nutrition intervention and human immunodeficiency virus infection. J Am Diet Assoc. 2010; 110(7): 1105-1119.
36. Ockenga J, Grimble R, Jonkers-Schuitema C, Macallan D, Melchior JC, Sauerewin HP, Schwenk A, DGEM (German Society for Nutritional Medicine), Süttmann U, ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on enteral nutrition: Wasting in HIV and other chronic infectious diseases. Clin Nutr. 2006; 25(2): 319-329.
37. Mangili A, Murman DH, Zampini AM, Wanke CA. Nutrition and HIV infection: Review of weight loss and wasting in the era of highly active antiretroviral therapy from the nutrition for healthy living cohort. Clin Infect Dis. 2006; 42(6): 836-842.
38. Wanke CA, Silva M, Knox TA, Forrester J, Speigelman D, Gorbach SL. Weight loss and wasting remain common complications in individuals infected with human immunodeficiency virus in the era of highly active antiretroviral therapy. Clin Infect Dis. 2000; 31(3): 803-805.
39. Tang AM, Jacobson DL, Spiegelman D, Knox TA, Wanke C. Increasing risk of 5% or greater unintentional weight loss in a cohort of HIV-infected patients, 1995 to 2003. JAIDS. 2005; 40(1): 70-76.
40. Pupim LB, Flakoll PJ, Majchrzak KM, Aftab Guy DL, Stenvinkel P, Ikizler TA. Increased

muscle protein breakdown in chronic hemodialysis patients with type 2 diabetes mellitus. Kidney Int. 2005; 68(4): 1857-1865.

41. Thompson T, Lee MG, Clarke T, Mills M, Wharfe G, Walters C. The prevalence of gastrointestinal symptoms among ambulatory HIV patients and a control population. Annals of Gastroenterology. 2012; 25(3): 243-248.
42. Thapa R, Amatya A, Pahari DP, Bam K, Newman MS. Nutritional status and its association with quality of life among people living with HIV attending public anti-retroviral therapy sites of Kathmandu Valley, Nepal. AIDS Res Ther. 2015; 12: 14. doi: 10.1186/S12981-015-0056-9
43. Williams SB, Bartsch G, Muurahainen N, Collins G, Raghavan SS, Wheeler D. Protein intake is positively associated with body cell mass in weight-stable HIV-infected men. J Nutr. 2003; 133(4): 1143-1146.
44. Bailey JL, Franch HA. Nutritional considerations in kidney disease: Core curriculum 2010. Am J Kidney Dis. 2010; 55(6): 1146-1161.
45. Herselman M, Moosa MR, Kotze TJ, Kritzinger M, Wuister S, Mostert D. Protein-energy malnutrition as a risk factor for increased morbidity in long-term hemodialysis patients. J Ren Nutr. 2000; 10(1): 7-15.
46. Araújo IC, Kamimura MA, Draibe SA, Canziani ME, Manfredi SR, Avesani CM, Sesso R, Cuppari L. Nutritional parameters and mortality in incident hemodialysis patients. J Ren Nutr. 2006; 16(1): 27-35.
47. Segall L, Moscalu M, Hogaş S, Mititiuc I, Nistor I, Veisa G, Covic A. Protein-energy wasting, as well as overweight and obesity, is a long-term risk factor for mortality in chronic hemodialysis patients. Int Urol Nephrol. 2014; 46(3): 615-621.
48. Pondrom S. News and issues that affect organ and tissue transplantation. Am J Transplant. 2009; 9(1): 1-2.
49. Johansen KL, Lee C. Body composition in chronic kidney disease. Curr Opin Nephrol Hypertens. 2015; 24(3): 268–275.
50. Park J, Ahmadi SF, Streja E, Molnar MZ, Flegal KM, Gillen D, Kovesdy CP, Kalantar-Zadeh K. Obesity paradox in end-stage kidney disease patients. Prog Cardiovasc Dis. 2014; 56(4): 415-425.
51. Molnar MZ, Streja E, Kovesdy CP, Bunnapradist S, Sampaio MS, Jing J, Krishnan M, Nissenson AR, Danovitch GM, Kalantar-Zadeh K. Associations of body mass index and weight loss with mortality in transplant-waitlisted maintenance hemodialysis patients. Am

J Transplant. 2011; 11(4): 725-736.

52. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999; 341(15): 1097-1105.
53. Kalantar-Zadeh K, Rhee CM, Chou J, Ahmadi SF, Park J, Chen JLT, Amin AN. The obesity paradox in kidney disease: How to reconcile it with obesity management. Kidney Int Rep. 2017; 2(2): 271-281.
54. Yen TH, Lin JL, Lin-Tan DT, Hsu CW. Association between body mass and mortality in maintenance hemodialysis patients. Ther Apher Dial. 2010; 14(4): 400-408.
55. Kopple JD, Zhu X, Lew NL, Lowrie EG. Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. Kidney Int. 1999; 56(3): 1136-1148.
56. Chazot C, Gassia JP, Di Benedetto A, Cesare S, Ponce P, Marcelli D. Is there any survival advantage of obesity in Southern European haemodialysis patients. Nephrol Dial Transplant. 2009; 24(9): 2871-2876.
57. Hall YN, Xu P, Chertow GM. Relationship of body size and mortality among US Asians and Pacific Islanders on dialysis. Ethn Dis. 2011; 21(1): 40-46.
58. Ricks J, Molnar MZ, Kovesdy CP, Kopple JD, Norris KC, Mehrotra R, Nissenson AR, Arah OA, Greenland S, Kalantar-Zadeh K. Racial and ethnic differences in the association of body mass index and survival in maintenance hemodialysis patients. Am J Kidney Dis. 2011; 58(4): 574-582.
59. Kalantar-Zadeh, K, Streja E, Molnar MZ, Lukowsky LR, Krishnan M, Kovesdy CP, Greenland S. Mortality prediction by surrogates of body composition: an examination of the obesity paradox in hemodialysis patients using composite ranking score analysis. Am J Epidemiol. 2012; 175(8): 793-803.
60. Marcén R, Fernández A, Pascual J, Teruel JL, Villafruela JJ, Rodriguez N, Martins J, Burgos FJ, Ortuño J. High body mass index and posttransplant weight gain are not risk factors for kidney graft and patient outcome. Transplant Proc. 2007; 39(7): 2205-2207.
61. Lafranca JA, IJermans JN, Betjes MG, Dor FJ. Body mass index and outcome in renal transplant recipients: A systematic review and meta-analysis. BMC Med. 2015; 13: 111. doi: 10.1186/S12916-015-0340-5.
62. Phillips S, Heuberger R. Metabolic disorders following kidney transplantation. Journal of Renal Nutrition. 2012; 22(5): 451-460.
63. Saxena A, Sharma RK. Nutritional surviellance after renal transplant: Review. Indian J Transplant. 2009; 3: 5-12.

64. Frassetto LA, Tan-Tam C, Stock PG. Renal transplantation in patients with HIV. Nat Rev Nephrol. 2009 Oct;5(10): 582-9. 2009; 5(10): 582-589.

65. Nolte Fong JV, Moore LW. Nutrition trends in kidney transplant recipients: The importance of dietary monitoring and need for evidence-based recommendations. Front Med (Lausanne). 2018; 5: 302. doi: 10.3389/fmed.2018.00302

66. Greater Metropolitan Clinical Taskforce (Renal Services Network). Evidence-based practice guidelines for the management of adult kidney transplant recipients. Sydney: GMCT; 2009 [cited 14/08/2014]. Available from: www.daa.asn.au.

67. Cashion AK, Hathaway DK, Stanfill A, Thomas F, Ziebarth JD, Cui Y, Cowan PA, Eason J. Pre-transplant predictors of one year weight gain after kidney transplantation. Clin Transplant. 2014; 28(11): 1271–1278.

68. de Oliveira CM, Moura ÁE, Gonçalves L, Pinheiro LS, Pinheiro FM Jr, Esmeraldo RM. Post-transplantation weight gain: prevalence and the impact of steroid-free therapy. Transplant Proc. 2014; 46(6): 1735-1740.

69. Baum CL, Thielke K, Westin E, Kogan E, Cicalese L, Benedetti E. Predictors of weight gain and cardiovascular risk in a cohort of racially diverse kidney transplant recipients. Nutrition. 2002; 18(2): 139-146.

70. Elster EA, Leeser DB, Morrissette C, Pepek JM, Quiko A, Hale DA, Chamberlain C, Salaita C, Kirk AD, Mannon RB. Obesity following kidney transplantation and steroid avoidance immunosuppression. Clin Transplant. 2008; 22(3): 354-359.

71. Cupples CK, Cashion AK, Cowan PA, Tutor RS, Wicks MN, Williams R, Eason JD. Characterizing dietary intake and physical activity affecting weight gain in kidney transplant recipients. Prog Transplant. 2012; 22(1): 62-70.

72. Aksoy N. Weight gain after kidney transplant. Exp Clin Transplant. 2016; 14(Suppl 3): 138-140.

73. Jardine AG, Gaston RS, Fellstrom BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet. 2011; 378(9800): 1419-1427.

74. Briggs JD. Causes of death after renal transplantation. Nephrol Dial Transplant. 2001; 16(8): 1545-1549.

75. Triant VA. Cardiovascular disease and HIV infection. Curr HIV/AIDS Rep. 2013; 10(3): 199–206.

76. Agarwal A, Prasad GV. Post-transplant dyslipidemia: Mechanisms, diagnosis and management. World J Transplant. 2016; 6(1): 125-134.

77. Hosseini MS, Rostami Z, Einollahi B. Dyslipidemia after kidney transplantation and correlation with cyclosporinel level. Nephrourol Mon. 2013; 5(1): 831-834.

78. van Wijk JP, Cabezas MC. Hypertriglyceridemia, metabolic syndrome, and cardiovascular disease in HIV-infected patients: Effects of antiretroviral therapy and adipose tissue distribution. Int J Vasc Med. 2012; 201027. doi: 10.1155/2012/201027.

79. Limas TG, Pinto Gde A, Marcato LM, Coelho DR. Analysis of the prevalence of dyslipidemia in individuals with HIV and its association with antiretroviral therapy. Rev Soc Bras Med Trop. 2014; 47(5): 547-551.

80. Feeney ER, Mallon PWG. HIV and HAART-associated dyslipidemia. Open Cardiovasc Med J. 2011; 5: 49-63.

81. Muller E, Kahn D, Mendelson M. Renal transplantation between HIV-Positive donors and recipients. N Engl J Med. 2010; 362(24): 2336-2337.

82. van Hooff JP, Christiaans MH, van Duijnhoven EM. Evaluating mechanisms of post-transplant diabetes mellitus. Nephrol Dial Transplant. 2004; 19(Suppl 6): vi8-vi12.

83. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant. 2003; 3(2): 178-185.

84. Duncan AD, Goff LM, Peters BS. Type 2 diabetes prevalence and its risk factors in HIV: A cross-sectional study. PLoS One. 2018; 13(3): p. e0194199. doi: 10.1371/journal.pone.0194199.

85. Kim DJ, Westfall AO, Chamot E, Willig AL, Mugavero MJ, Ritchie C, Burkholder GA, Crane HM, Raper JL, Saag MS, Willig JH. Multimorbidity patterns in HIV-infected patients: The role of obesity in chronic disease clustering. J Acquir Immune Defic Syndr. 2012; 61(5): 600-605.

86. Monakali S, Ter Goon D, Seekoe E, Owolab EO. Prevalence, awareness, control and determinants of hypertension among primary health care professional nurses in Eastern Cape, South Africa. Afr. J. Prm. Health. Care. Fam. Med. 2018; 10(1). doi: 10.4102/phcfm.v10i1.1758

87. Odamaki M, Furuya R, Ohkawa S, Yoneyama T, Nishikino M, Hishida A, Kumagai H. Altered abdominal fat distribution and its association with the serum lipid profile in non-diabetic haemodialysis patients. Nephrol Dial Transplant. 1999; 14(10): 2427-2432.

88. Guida B, Trio R, Laccetti R, Nastasi A, Salvi E, Perrino NR, Caputo C, Rotaia E, Federico S, Sabbatini M. Role of dietary intervention on metabolic abnormalities and nutritional status after renal transplantation. Nephrol Dial Transplant. 2007; 22(11): 3304-3310.

89. Sidibé A, Auguste D, Desbiens LC, Fortier C, Wang YP, Jean S, Mac-Way F. Fracture risk in dialysis and kidney transplanted patients: A systematic review. JBMR Plus. 2019; 3(1): 45-55.

90. Nikkel LE, Hollenbeak CS, Fox EJ, Uemura T, Ghahramani N. Risk of fractures after renal transplantation in the United States. Transplantation. 2009; 87(12): 1846-1851.

91. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS. 2006; 20(17): 2165-2174.

92. McComsey GA, Tebas P, Shane E, Yin MT, Overton ET, Huang JS, Aldrovandi GM, Cardoso SW, Jorge Santana JL, Brown TT. Bone disease in HIV infection: A practical review and recommendations for HIV care providers. Clin Infect Dis. 2010; 51(8): 937-946.

93. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. J Acquir Immune Defic Syndr. 2009; 51(5): 554-561.

94. Mondy K, Yarasheski K, Powderly WG, Whyte M, Claxton S, DeMarco D, Hoffmann M, Tebas P. Longitudinal evolution of bone mineral density and bone markers in human immunodeficiency virus-infected individuals. Clin Infect Dis. 2003; 36(4): 482-490.

95. Yin M, Stein E. The effect of antiretrovirals on vitamin D. Clin Infect Dis. 2011; 52(3): 406-408.

96. Bakshi N, Singh K. Nutrition assessment and its effect on various clinical variables Nutrition assessment and its effect on various clinical variables. HepatoBiliary Surg Nutr 2016;5(4):358-371. 2016; 5(4): 358-371.

97. Centers for Diease Control and Prevention. Defining adult overweight and obesity. [Online]; 2017 [cited 23/04/2018]. Available from: https://www.cdc.gov/obesity/adult/defining.html.

98. Hammond KA, Litchford MD. Inflammation, physical, and functional assessments. In: Mahan KL, Escott-Stump S, Raymond JL editors. Krause's Food Nutrition & Diet therapy. St Loius, Mo: Saunders/Elsevier; 2004. p. 163-177.

99. Finkelstein JL, Gala P, Rochford R, Glesby MJ, Mehta S. HIV/AIDS and lipodystrophy: Implications for clinical management in resource-limited settings. J Int Aids Soc.2015; 18(1). doi: 10.7448/IAS.18.1.19033

100. Carvalho IR, Pinto JA, Cardoso CA, Candiani TM, Kakehasi FM. Evaluation of hematological, virologic and anthropometric parameters as progression markers in HIV-1

infected children. J Pediatr (Rio J). 2009; 85(2): 149-156.

101. Rymarz A, Szamotulska K, Niemczyk S. Comparison of skinfold thicknesses and bioimpedance spectroscopy to dual-energy X-ray absorptiometry for the body fat measurement in patients with chronic kidney disease. Nutr Clin Pract. 2017; 32(4): 533–538.
102. Foster BJ, Leonard MB. Measuring nutritional status in children with chronic kidney disease. Am J Clin Nutr. 2004; 80(4): 801-814.
103. Duren DL, Sherwood RJ, Czerwinski SA, Lee M, Choh AC, Siervogel RM, Cameron Chumlea W. Body composition methods: Comparisons and interpretation. J Diabetes Sci Technol. 2008; 2(6): 1139–1146.
104. Dekkers JC, van Wier MF, Hendriksen IJ, Twisk JW, van Mechelen W. Accuracy of self-reported body weight, height and waist circumference in a Dutch overweight working population. BMC Med Res Methodol. 2008; 8: 69. doi: 10.1186/1471-2288-8-69
105. Sanches FM, Avesani CM, Kamimura MA, Lemos MM, Axelsson J, Vasselai P, Draibe SA, Cuppari L. Waist circumference and visceral fat in CKD: A cross-sectional study. Am J Kidney Dis. 2008; 52(1): 66-73.
106. Chan NPT, Tarrant M, Ngan E, So HK, Lok KYW, Nelson EAS. Agreement between self-/home-measured and assessor-measured waist circumference at three sites in adolescents/children. PLoS One. 2018; 13(3): p. e0193355. doi: 10.1371/journal.pone.0193355
107. Razak K, Gupta S, Razak UH, Meena GL. Impact of hydration on body status pre and post dialysis: A radiological appraisal by DEXA scan. J of Biosens Biomark Diagn. 2017; 2(2): 1-3.
108. Knox TA, Zafonte-Sanders M, Fields-Gardner C, Moen K, Johansen D, Paton N. Assessment of nutritional status, body composition, and human immunodeficiency virus-associated morphologic changes. Clin Infect Dis. 2003 Apr 1;36(Suppl 2):S63-8. 2003; 36(Suppl 2): S63-S68.
109. Kalantar-Zadeh K (e), Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn H Jr, Kopple JD, Greenland S. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. Nephrol Dial Transplant. 2005; 20(9): 1880-1888.
110. Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. JASN. 2010; 21(2): 223-230.

111. Gama-Axelsson T, Heimbürger O, Stenvinkel P, Bárány P, Lindholm B, Qureshi AR. Serum albumin as predictor of nutritional status in patients with ESRD. Clin J Am Soc Nephrol. 2012; 7(9): 1446-1453.

112. Kaysen GA, Dubin JA, Müller HG, Mitch WE, Rosales LM, Levin NW. Relationships among inflammation nutrition and physiologic mechanisms establishing albumin levels in hemodialysis patients. Kidney Int. 2002; 61(6): 2240-2249.

113. Wazlawik E. Serum albumin can predict risk of hospitalization in women with chronic kidney disease submitted to hemodialysis. Revista de Nutrição. 2016; 29(3). Revista de Nutrição. 29: 1-1.

114. Fung F, Sherrard DJ, Gillen DL, Wong C, Kestenbaum B, Seliger S, Ball A, Stehman-Breen C. Increased risk for cardiovascular mortality among malnourished end-stage renal disease patients. Am J Kidney Dis. 2002; 40(2): 307-314.

115. Molnar MZ (b), Kovesdy CP, Bunnapradist S, Streja E, Mehrotra R, Krishnan M, Nissenson AR, Kalantar-Zadeh K. Associations of pretransplant serum albumin with post-transplant outcomes in kidney transplant recipients. Am J Transplant. 2011; 11(5): 1006-1015.

116. Lee KH, Cho JH, Kwon O, Kim SU, Kim RH, Cho YW, Jung HY, Choi JY, Kim CD, Kim YL, Park SH. Low prealbumin levels are independently associated with higher mortality in patients on peritoneal dialysis. Kidney Res Clin Pract. 2016; 35(3): 169-175.

117. Devoto G, Gallo F, Marchello C, Racchi O, Garbarini R, Bonassi S, Albalustri G, Haupt E. Prealbumin serum concentrations as a useful tool in the assessment of malnutrition in hospitalized patients. Clin Chem. 2006; 52(12): 2281-2285.

118. Bharadwaj S, Ginoya S, Tandon P, Gohel TD, Guirguis J, Vallabh H, Jevenn A, Hanouneh I. Malnutrition: laboratory markers vs nutritional assessment. Gastroenterol Rep (Oxf). 2016; 4(4): 272-280.

119. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: A systematic review and meta-analysis. Nutrients. 2017; 9(829). pii: E829. doi: 0.3390/nu9080829.

120. Detsky AS, Mclaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN. What is subjective global assessment of nutritional status? Journal of Parenteral and Enteral Nutrition. 1987; 11(1): 8-13.

121. Gupta D, Lammersfeld CA, Vashi PG, Dahlk SL, Lis CG. Can subjective global assessment of nutritional status predict survival in ovarian cancer? J Ovarian Res. 2008; 1:

p. 5. doi: 10.1186/1757-2215-1-5.

122. Barbosa-Silva MC, Barros AJ. Indications and limitations of the use of subjective global assessment in clinical practice: an update. Curr Opin Clin Nutr Metab Care. 2006; 9(3): 263-269.

123. Zuvela J, Trimingham C, Le Leu R, Faull R, Clayton P, Jesudason S, Meade A. Gastrointestinal symptoms in patients receiving dialysis: A systematic review. Nephrology (Carlton). 2018; 23(8): 718-727.

124. Paré P, Meyer F, Armstrong D, Pyzyk M, Pericak D, Goeree R. Validation of the GSFQ, a self-administered symptom frequency questionnaire for patients with gastroesophageal reflux disease. Can J Gastroenterol. 2003 May;17(5):307-12. 2003; 17(5): 307-312.

125. Kleinman L, Faull R, Walker R, Ramesh Prasad GV, Ambuehl P, Bahner U. Gastrointestinal-specific patient-reported outcome instruments differentiate between renal transplant patients with or without GI complications. Transplant Proc. 2005; 37(2): 846-849.

126. Steyn NP, Labadarios DL. www.sahealthinfo.org/nutrition/food5dietaryintake.pdf. In: The National Food Consumption Survey (NFCS), Stellenbosch South Africa. [Online]; 2000 [cited 08/03/2014]. Available from: http://sun025.sun.ac.za/portal/page/portal/Health_Sciences/English/Departments/Interdisciplinary_Health_Sciences/Human_nutrition/Research/National%20Survey/nfcs.

127. Krugh M, Langaker MD. Dual energy xray absorptiometry (DEXA) [Online]; [cited 24/01/2019]. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519042/.

128. Shah VS, Ananth A, Sohal GK, Bertges-Yost W, Eshelman A, Parasuraman RK, Venkat KK. Quality of life and psychosocial factors in renal transplant recipients. Transplant Proc. 2006; 38(5): 1283-1285.

129. Fiebiger W, Mitterbauer C, Oberbauer R. Health-related quality of life outcomes after kidney transplantation. Health Qual Life Outcomes. 2004; 2(2). doi 10.1186/1477-7525-2-2

130. Blake C, Plant WD. Measures to improve quality of life in end stage renal disease patients. In CS W, editor. Therapy in Nephrology and Hypertension. 3rd ed. Philadelphia: Saunders Elsevier; 2008. 818-827.

131. Karimi M, Brazier J. Health, health-related quality of life, and quality of life: What is the difference? Pharmacoeconomics. 2016; 34(7): 645-649.

132. The WHOQOL Group. The World Health Organization Quality of life assessment (WHOQOL): Development and general psychometric properties. Soc Sci Med. 1998; 46(12): 1569-1585.

133. Wasserfallen JB, Halabi G, Saudan P, Perneger T, Feldman HI, Martin PY, Wauters JP. Quality of life on chronic dialysis: comparison between haemodialysis and peritoneal dialysis. Nephrol Dial Transplant. 2004; 19(6): 1594-1599.

134. von der Lippe N, Waldum B, Brekke FB, Amro AA, Reisæter AV, Os I. From dialysis to transplantation: A 5-year longitudinal study on self-reported quality of life. BMC Nephrol. 2014; 15: 191. doi: 10.1186/1471-2369-15-191.

135. Semaan V, Noureddine S, Farhood L. Prevalence of depression and anxiety in end-stage renal disease: A survey of patients undergoing hemodialysis. Appl Nurs Res. 2018; 43: 80-85.

136. Danial K, Khurram A, Ahmed K, Ali Z. Prevalence of depression among the patients with end stage renal disease and their care givers, and its associated factors at a tertiary care hospital in Karachi. APMC. 2016; 10(4): 217-221.

137. van Loon I, Hamaker ME, Boereboom FTJ, Grooteman MPC, Blankestijn PJ, van den Dorpel RMA, Nubé MJ, Ter Wee PM, Verhaar MC, Bots ML. A closer look at the trajectory of physical functioning in chronic hemodialysis. Age Ageing. 2017; 46(4): 594-599.

138. Nourbala MH, Hollisaaz MT, Nasiri M, Bahaeloo-Horeh S, Najafi M, Araghizadeh H, Rezaie Y, Lak M. Pain affects health-related quality of life in kidney transplant recipients. Transplant Proc. 2007; 39(4): 1126-1129.

139. Maglakelidze N, Pantsulaia T, Tchokhonelidze I, Managadze L, Chkhotua A. Assessment of health-related quality of life in renal transplant recipients and dialysis patients. Transplant Proc. 2011; 43(1): 376-379.

140. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, Klarenbach S, Gill J. Systematic review: Kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant. 2011; 11(10): 2093-2109.

141. Schulz T, Niesang J, Stewart RE, Westerhuis R, Hagedoorn M, Ploeg RJ, Homan van der Heide JJ, Ranchor AV. The role of personal characteristics in the relationship between health and psychological distress among kidney transplant recipients. Soc Sci Med. 2012; 75(8): 1547-1554.

142. Nagasawa H, Tachi T, Sugita I, Esaki H, Yoshida A, Kanematsu Y, Noguchi Y, Kobayashi

Y, Ichikawa E, Tsuchiya T, Teramachi H. The effect of quality of life on medication compliance among dialysis patients. Front Pharmacol 2018; 9: 488. doi: 10.3389/fphar.2018.00488

143. Kimmel PL, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Cruz I, Veis JH. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. Kidney Int. 2000; 57(5): 2093-2098.

144. Knight EL, Ofsthun N, Teng M, Lazarus JM, Curhan GC. The association between mental health, physical function, and hemodialysis mortality. Kidney Int. 2003; 63(5): 1843-1851.

145. van Loon IN, Bots ML, Boereboom FTJ, Grooteman MPC, Blankestijn PJ, van den Dorpel MA, Nubé M, Ter Wee PM, Verhaar MC, Hamaker ME. Quality of life as indicator of poor outcome in hemodialysis: relation with mortality in different age groups. BMC Nephrol. 2017; 18: 217. doi: 10.1186/s12882-017-0621-7

146. Griva K, Davenport A, Newman SP. Health-related quality of life and long-term survival and graft failure in kidney transplantation: a 12-year follow-up study. Transplantation. 2013; 95(5): 740-749.

147. Prihodova L, Nagyova V, Rosenberger J, Roland R, Groothoff JW, Majernikova M, van Dijk JP. Health-related quality of life 3 months after kidney transplantation as a predictor of survival over 10 years: A longitudinal study. Transplantation. 2014; 97(11): 1139-1145.

148. Rebollo P, Ortega F, Baltar JM, Badía X, Alvarez-Ude F, Díaz-Corte C, Naves M, Navascúes RA, Ureña A, Alvarez-Grande J. Health related quality of life (HRQOL) of kidney transplanted patients: Variables that influence it. Clin Transplant. 2000; 14(3): 199-207.

149. Gentile S, Beauger D, Speyer E, Jouve E, Dussol B, Jacquelinet C, Briançon S. Factors associated with health-related quality of life in renal transplant recipients: results of a national survey in France. Health Qual Life Outcomes 10.1186/1477-7525-11-88. 2013; 11: 88. doi: 10.1186/1477-7525-11-88

150. Jofre R, López-Gómez JM, Valderrábano F. Quality of life for patient groups. Kidney Inyernational. 2000; 57(S74): S121-S130.

151. Noori N, Kopple JD, Kovesdy CP, Feroze U, Sim, JJ, Murali SB, Luna A, Gomez M, Luna C, Bross R, Nissenson AR, Kalantar-Zadeh K. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. Clin J Am Soc Nephrol. 2010; 5(12): 2258–2268.

152. Miners A, Phillips A, Kreif N, Rodger A, Speakman A, Fisher M, Anderson J, Collins S,

Hart G, Sherr L, Lampe FC; ASTRA (Antiretrovirals, Sexual Transmission and Attitudes) Study. Health-related quality-of-life of people with HIV in the era of combination antiretroviral treatment: a cross-sectional comparison with the general population. Lancet HIV. 2014; 1(1): p. e32-40. doi: 10.1016/S2352-3018(14)70018-9.

153. Cooper V, Clatworthy J, Harding R, Whetham J, Emerge Consortium. Measuring quality of life among people living with HIV: A systematic review of reviews. Health Qual Life Outcomes. 2017; 15: 220. doi: 10.1186/s12955-017-0778-6.
154. Yen CF, Tsai JJ, Lu PL, Chen YH, Chen TC, Chen PP, Chen TP. Quality of life and its correlates in HIV/AIDS male outpatients receiving highly active antiretroviral therapy in Taiwan. Psychiatry Clin Neurosci. 2004; 58(5): 501-506.
155. Basavaraj KH, Navya MA, Rashmi R. Quality of life in HIV/AIDS. Indian J Sex Transm Dis AIDS. 2010; 31(2): 75-80.
156. Jadhav PS, Payal S, Laad PS , Chaturvedi RM. Quality of life factors affecting quality of life in people living with HIV/AIDS in an urban area. Med Public Health. 2017; 4(8): 3031-3036.
157. Feroze U, Noori N, Kovesdy CP, Molnar MZ, Martin DJ, Reina-Patton A, Benner D, Bross R, Norris KC, Kopple JD, Kalantar-Zadeh K. Quality-of-life and mortality in hemodialysis patients: roles of race and nutritional status. Clin J Am Soc Nephrol. 2011; 6(5): 1100-1111.
158. Raimundo P, Ravasco P, Proença V, Camilo M. Does nutrition play a role in the quality of life of patients under chronic haemodialysis? Nutr Hosp. 2006; 21(2): 139-144.
159. Strid H, Simrén M, Johansson AC, Svedlund J, Samuelsson O, Björnsson ES. The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological general well-being. Nephrol Dial Transplant. 2002; 17(8): 1434-1439.
160. Czyżewski L, Sańko-Resmer J, Wyzgał J, Kurowski A. Assessment of health-related quality of life of patients after kidney transplantation in comparison with hemodialysis and peritoneal dialysis. Ann Transplant. 2014; 19: 576-585.
161. Ekberg H, Kyllönen L, Madsen S, Grave G, Solbu D, Holdaas H. Increased prevalence of gastrointestinal symptoms associated with impaired quality of life in renal transplant recipients. Transplantation. 2007; 83(3): 282-289.
162. Ponticelli C, Colombo D, Novara M, Basilisco G; CETRA Study Group. Gastrointestinal symptoms impair quality of life in Italian renal transplant recipients but are under-

recognized by physicians. Transpl Int. 2010; 23(11): 1126-1134.

163. Sutton J. Qualitative research: data collection, analysis, and management. Can J Hosp Pharm. 2015; 68(3): 226-231.

164. Ortega F, Valdés C, Ortega T. Quality of life after solid organ transplantation. Transplant Rev. 2007; 21(3): 155-170.

165. World Health Organisation. WHOQOL: Measuring quality of life. [Online]; 2019 [cited 12/02/2019]. Available from: https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/.

166. Chiu SF, Wong HS, Morad Z, Loo LH. Quality of life in cadaver and living-related renal transplant recipients in Kuala Lumpur hospital. Transplant Proc. 2004; 36(7): 2030-2031.

CHAPTER 3

GASTROINTESTINAL SYMPTOMS IN HIV-POSITIVE KIDNEY TRANSPLANT CANDIDATES AND RECIPIENTS FROM A HIV-POSITIVE DONOR

ABSTRACT

Background: Gastrointestinal symptoms (GIS) often occur among those with chronic kidney disease (CKD). Pre- and post-kidney transplant recipients infected with HIV may be at an even greater risk of developing GIS. However, this has not been investigated.

Objective: To determine the frequency and severity of GIS in HIV-positive kidney transplant patients from HIV-positive donors, and those awaiting a transplant.

Methods: 76 participants completed the gastrointestinal symptom rating scale (GSRS) at baseline and six month follow-up. GIS frequency was defined as having at least one symptom (GSRS > 1). Severity was indicated by GSRS score.

Results: Transplant candidates: GIS frequency was 88.9% and 86.3% at baseline and six months respectively. Indigestion was the most frequent (79.6% and 66.7% at baseline and six months), and severe GIS (GSRS 2.3). Females had a significantly higher GSRS scores compared to males for abdominal pain, indigestion, diarrhoea and the overall global mean ($p = 0.030$) at either or both assessments. Negative correlations were found between global and reflux scores and age. Indigestion, constipation and reflux scores were related to increased duration on dialysis.

Transplant recipients: GIS frequency was 95.2% and 76.2% at baseline and 6 months respectively. At both assessment points, indigestion occurred most frequently (85.7% and 61.9% respectively). Highest GSRS was reported for indigestion at baseline (2.33) and at six months (1.33). Waist circumference (WC) was positively associated with the severity of constipation GSRS.

Conclusion: The presence of GIS was high among HIV-positive transplant recipients and those awaiting a transplant from a HIV-positive donor. For candidates on a waiting list managed on dialysis, GIS severity decreased with age, but increased with a longer period on dialysis. The level of symptom severity experienced by transplant recipients was associated with increasing WC.

Keywords: Kidney transplant candidates, Kidney transplant recipients, Human immunodeficiency virus (HIV), gastrointestinal symptoms

3.1 Introduction

Patients with impaired kidney function very often experience gastrointestinal symptoms (GIS) at all stages of chronic kidney disease (CKD) (1). Symptoms begin early, appearing well before end-stage renal disease (ESRD), at stage 3 (eGFR 45 ml/min/1.73 m^2), and become increasingly burdensome as kidney function declines (2). Uraemia and dialysis predispose patients to gastrointestinal (GI) mucosal lesions and functional disorders (3) that may or may not cause GIS (4). In two recent studies, ESRD dialysed and non-dialysed patients reported a prevalence of GIS of 61.6% to 81.0% (5,6). Following a transplant, renal function is restored, however, the occurrence of GIS remain frequent and is often an under-estimated problem (7). At this point however, GIS is largely attributable to opportunistic infections and immunosuppressant therapy (8,9).

CKD often coexists with other illnesses that affect the GIT through the disease process and its treatment. In HIV-positive individuals, replication of the virus in gut-associated lymphoid tissues (10), pharmacological side-effects and opportunistic as well as non-opportunistic infections (11), are known determinants of GIS. Resultantly, GIS may present at any time, in any area of the GIT (12). Despite a paucity of data, in all probability the prevalence of GIS among HIV-positive patients with ESRD will be higher than among uninfected patients with HIV.

Regardless of aetiology, the severity of GIS range from mild to severe, thereby compromising nutritional status, (13) psychological health, (14) and quality of life (7). More importantly, GIS could be indicative of high risk complications such as upper gastrointestinal intestinal (UGI) bleeding in dialysed patients (15) or graft failure in transplant recipients (16).

Individually, both CKD and HIV have a significant impact on the GIT. However, the nature of GIS in ESRD together with HIV is unknown. For this reason, the primary aim of this study was to describe GIS in terms of frequency and severity as experienced by HIV- infected pre- and post-transplant recipients at baseline and six month follow-up. In addition, the study investigated the relationship between GIS and selected nutritional and clinical parameters.

3.2 Methods

3.2.1 Participants

Participants were recruited through the kidney transplant programme for HIV-positive patients at Groote Schuur Hospital, Cape Town, to take part in this longitudinal observational study. Participants were recruited based on whether they were transplant recipients or were awaiting a transplant and hence managed with dialysis. From the outset they were therefore categorised as: (i) HIV-positive kidney transplant recipients who have received a kidney from a HIV-positive donor and (ii) HIV-positive transplant candidates on the waiting list to receive a HIV-positive donor kidney. Prospective participants were contacted telephonically or at their respective outpatient clinics and invited to participate. Patients did not qualify for participation if they were severely ill, were not contactable, were uncooperative or missed several interview appointments (typically more than two without reason). In total, 76 patients agreed to participate after the purpose of the study and practical implications were explained to them. This was followed by obtaining written informed consent. The study was approved by The University of KwaZulu-Natal's Biomedical Research Ethics Committee (Approval number BE 327/13). Data was collected over a one year period, commencing in June 2015, with patients being followed up across six provinces. Assessments were conducted at two time points namely baseline and at six month follow-up.

3.2.2 Socio-demographic and clinical characteristics

Socio-demographic information was collected using an interviewer-administered structured questionnaire, developed for the purpose of the study. Clinical information was obtained from medical records or during patient interviews.

3.2.3 Anthropometry

Weight (WT), height (Ht) and waist circumference (WC) measurements were taken according to the National Health and Nutrition Examination Survey (NHANES) guidelines (17) by a qualified dietitian. The mean of three readings were used for data analysis. Weight was determined post dialysis. BMI was classified according to the World Health Organization (WHO) categories as kg/m^2: Underweight (< 18.5), Normal (18.5 - 24.9), Overweight (25.0 – 29.9), Obese Class I (30.0 – 34.9), and Obese Class II (35.0 – 39.9) (18).

3.2.4 Measurement of gastrointestinal symptoms

The Gastrointestinal Symptom Rating Scale (GSRS) was used to determine the frequency and severity of GIS (19). Although originally designed for GIS assessment of gastrointestinal diseases, it has been used in all stages of CKD including dialysis (14) and transplant recipients (20). It consists of 15 items that are collapsed into 5 symptom subscales viz; abdominal pain (abdominal pain, hunger pain and nausea), reflux syndrome (heartburn and acid regurgitation), diarrhoea syndrome (diarrhoea, loose stools and urgent need for defecation), indigestion syndrome (borborygmus, abdominal distension, eructation and increased flatus) and constipation syndrome (constipation, hard stools and a feeling of incomplete evacuation) (19,21).

GIS Frequency: The frequency of GIS was defined as having at least one symptom or a GSRS score > 1 (14,21,22).

GIS Severity: To determine the severity of a symptom, each question is rated using a seven-point Likert Scale ranging from one (no discomfort at all) to seven (severe discomfort) to obtain a total score ranging from 15 (minimum) to 105 (maximum) or mean values between one and seven. The combined severity scores of the five subscales, are presented as a global mean score and a mean score per subscale. Higher GSRS scores are indicative of a higher symptom burden. GSRS severity scores were correlated with patients' clinical, demographic and nutritional parameters.

3.2.5 Statistical analysis

Data was analysed using the Statistical Package for Social Sciences (SPSS®) version 25.0. Means and standard deviation were calculated for all continuous variables, and frequencies with percentages were determined for categorical variables. The means of groups were compared using the independent samples t-test. Cronbach's alpha was used to determine the internal reliability of the GSRS. Spearman's correlation was used to determine the relationship between GSRS subscales and clinical and nutritional variables. A p value of <0.05 was taken as statistically significant.

3.3 Results

3.3.1 Patient characteristics

As all 76 patients completed the GSRS at least once, at either time points, no participants were excluded. At baseline, one patient did not complete the GSRS and four did not complete it at six month follow-up for reasons that included hospitalisation, missed appointments and the demise of two participants. Of the 76 participants surveyed, 22 HIV-positive kidney transplant recipients received a kidney from a HIV-positive donor, while 54 HIV-positive patients were on the waiting list to receive a kidney from a HIV-positive donor. The latter group were managed with haemodialysis (HD) (n = 51) or peritoneal dialysis (PD) (n =3).

Characteristics of the study population are given in Table 3.1 and 3.2. The study sample, who were predominantly black (93.4 %) and male (60.5%), had a mean age of 43.6 ± 8.1 years. Transplant candidates were on dialysis for a mean duration of 3.9 ± 3.0 years (range: 0.3 - 11.5 years), while transplant recipients averaged 2.7 ± 22.3 years (range: 0.0 – 6.75 years) since transplantation. The majority of participants were hypertensive (92.1%), while only four had hypercholesterolemia. There were significantly more patients with diabetes in the dialysis group compared to the transplant group (29.6% versus 4.5%, p = 0.017). Transplant recipients had a higher mean CD4 count (447.3 ± 282.70 cells/µL versus 382.1 ± 178.02 cells/µL), and higher viral loads (94.7% versus 79.6% of participants with levels lower than detectable limits) when compared to transplant candidates. This difference was non-significant. Serum albumin levels were higher in the transplant group, 43.1 ± 4.1 and 41.3 ± 4.1 versus 35.9 ± 4.5 and 37.2 ± 4.8 in the dialysis group. The majority of participants in the transplant group had a normal weight at each assessment time point (71.4% and 59.1%), although two additional participants were classified as obese class I. In the dialysis group, 38.5% and 40.8% of participants were classified as overweight and 36.5% and 38.85 with normal weight at baseline and six month follow-up respectively.

3.3.2 Gastrointestinal symptoms

The frequency of at least one GIS (GSRS score of > 1) in the study sample is shown in Figure 3.1, being 90.7% and 83.3% at baseline and six month follow-up respectively.

The final Cronbach's Alpha for the global mean at baseline and six month follow-up, was 0.813 and 0.862 respectively. GSRS for all GIS in the whole group (Figure 3.2) was higher at baseline

than at six month follow-up. At baseline, the global mean GSRS was 1.80 ± 0.76 and lower at six months at 1.55 ± 0.74. The individual GIS show a similar order of severity at each assessment time point. Indigestion and diarrhoea had the highest and lowest GSRS respectively.

Frequency and severity of GIS in transplant candidates

Overall, 88.9% of dialysed participants reported at least one GIS at baseline and 81.5% at six month follow-up (Figure 3.1). At baseline, indigestion (79.6%), abdominal pain (64.8%) and reflux (48.1%) were the most commonly reported GIS, while diarrhoea and constipation were experienced to a lesser extent at 44.4% and 42.6%, respectively (Figure 3.3). At six month follow-up, indigestion was still the most frequent GIS, albeit to a lesser extent (66.7%). However, more participants complained of constipation, increasing in frequency to 51.0%.

The GSRS scores indicated the severity of symptoms (Table 3.3) for each treatment group. The most severe GIS for PD patients (n=3) was diarrhoea at six months (GSRS 4). For HD patients, indigestion was slightly more severe than the other GIS at both times (GSRS 1.67). Females had significantly higher median GSRS for several GSRS subscales as well as the global mean at baseline ($p = 0.030$).

In the transplant candidate group, Spearman's correlations with GSRS (Table 3.4) were positive for the global mean score with the length of time on dialysis at baseline and six months (baseline rho = 0.287, $p = 0.036$ and rho=0.440, $p = 0.001$). Age correlated negatively with GIS global mean (rho= -0.338, $p = 0.015$).

Prevalence and severity of GIS in transplant recipients

Over nine out of ten (95.2%) of the transplant group experienced GIS at baseline. However, the prevalence of symptoms decreased by 19.0% to 76.2% at six month follow-up. The frequency of symptoms across the five subscales is depicted in Figure 3.4. Transplant recipients reported indigestion as the most prevalent symptom at baseline (85.7%), this was followed by abdominal pain (81.0%), reflux (42.9%), with diarrhoea and constipation both occurring at a prevalence of 38.1%. At six month follow-up, frequency of GIS symptoms deceased by 19%, from 95.24% to 76.19%. The frequency in each symptom category also decreased but maintained a similar frequency sequence. Indigestion was the most frequently experienced GIS in the transplant

group with 85.7% prevalence at baseline and 61.9% at six month follow-up. Only one participant reported diarrhoea (4.8%) at six month follow-up.

Indigestion was the most severe GIS with the highest median GSRS score of 2.33 at baseline and 1.33 at six months (Table 3.3). All GSRS were lower at six month follow-up with the global mean decreasing from 1.86 to 1.15. In the transplant group, WC was positively associated with constipation at baseline (rho=0.471, p=0.048).

Table 3.1: Socio-demographic and clinical characteristics of the study sample

Patient Characteristics	Whole group (N = 76)	Transplant (n = 22)	Dialysis (n = 54)
Age (years): mean ± SD	43.6 ± 8.1 range: 28.0 – 63.0		
Gender			
Male	46 (60.5)		
Female	30 (39.5)		
Ethnicity			
Black	71 (93.4)		
Coloured[a]	4 (5.3)		
White	1 (1.3)		
Type of treatment			
Transplant		22 (28.9)	
Haemodialysis			51 (67.1)
Peritoneal dialysis			3 (3.9)
Length of time on current treatment (years)		2.7 ± 2.3 range: 0.0 – 6.8	3.9 ± 3.0 range: 0.3 - 11.5
Chronic illness			
Diabetes		1 (4.5)*	16 (29.6)*
Hypertension		19 (86.4)	51 (94.4)
Hypercholesteraemia		1 (4.5)	3 (5.6)
CD4 (cells/µL)[b]		447.25 ± 282.70	382.12 ± 178.02
Viral load (copies /ml)[c]			
LDL		18 (94.7)	39 (79.6)
≤ 10 000		1 (5.3)	7 (14.3)
> 10 000		0 (0.0)	3 (6.1)

Data expressed as percentages or means with standard deviation

[a] Coloured is the term used in South Africa denoting mixed racial ancestry

[b] transplant patients: n = 20, dialysis recipients: n = 52

[c] transplant patients: n = 19, dialysis patients: n = 49

*Significant difference in the number of patients with diabetes between transplant recipients and transplant candidates patients (p = 0.017)

LDL: lower than detectable limit

Table 3.2: Nutritional characteristics of transplant candidates and recipients (N = 76).

Nutritional Characteristics	Transplant (n = 22)				Dialysis (n = 54)			
	n	Baseline	**n**	6 months	**n**	baseline	**n**	6 months
Albumin (g/L)	20	43.1 ± 4.1	22	41.3 ± 4.1	48	35.9 ± 4.5	52	37.2 ± 4.8
BMI (kg/m^2)	21	24.5 ± 4.6	22	25.6 ± 5.8	52	26.3 ± 4.8	49	25.7 ± 4.8
Underweight				1 (4.5)		1 (1.9)		1 (2.0)
Normal		15 (71.4)		13 (59.1)		19 (36.5)		19 (38.8)
Overweight		2 (9.5)		2 (9.1)		20 (38.5)		20 (40.8)
Obese Class I		4 (19.0)		6 (27.3)		11 (21.2)		8 (16.3)
Obese Class II						1 (1.9)		1 (2.0)
WC (cm)	18	89.6 ± 13.1[a]	18	95.8 ± 12.3[a]	36	92.2	46	90.7 ± 4.2

Data expressed as percentages or means with standard deviation or frequency with percentages

[a]WC is significantly larger at 6 months than at baseline, paired samples t-test: t(14) = -2.861, p 0.013

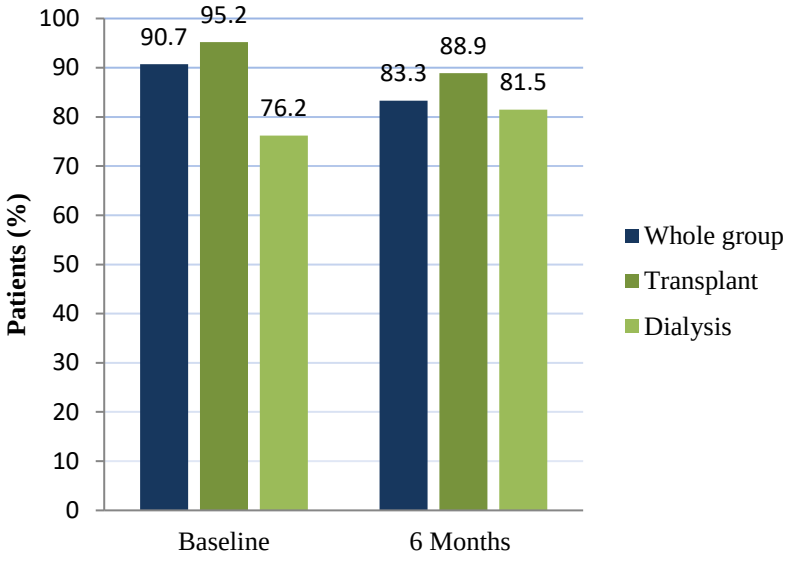

Figure 3.1: Frequency of gastrointestinal symptoms for the whole group and per treatment modality at baseline and six month follow-up (N= 76).

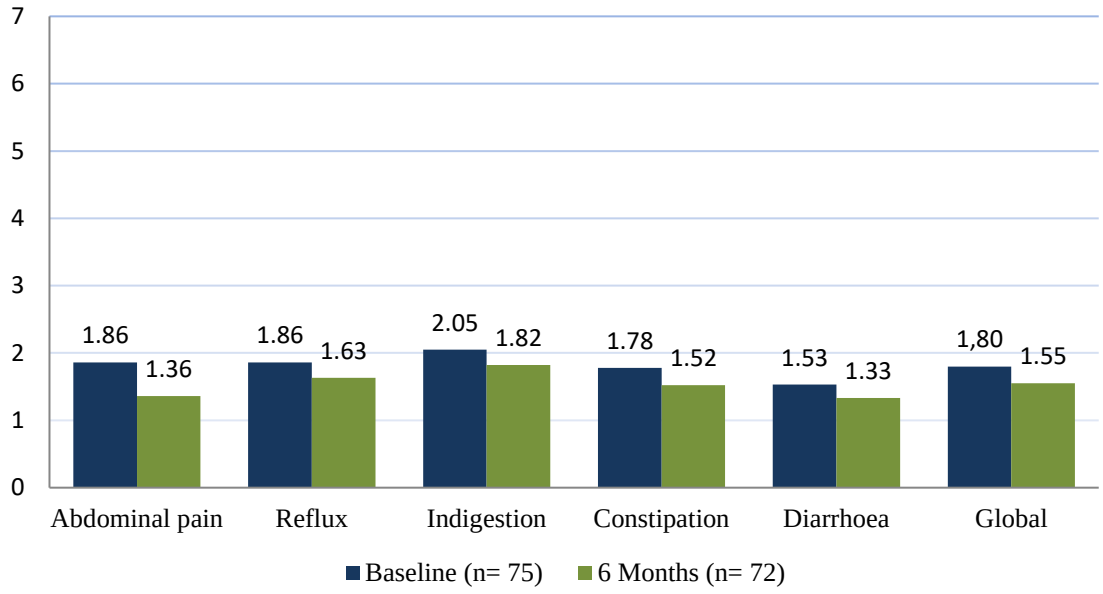

Figure 3.2: GSRS for the whole group across each subscale at baseline and six month follow-up.

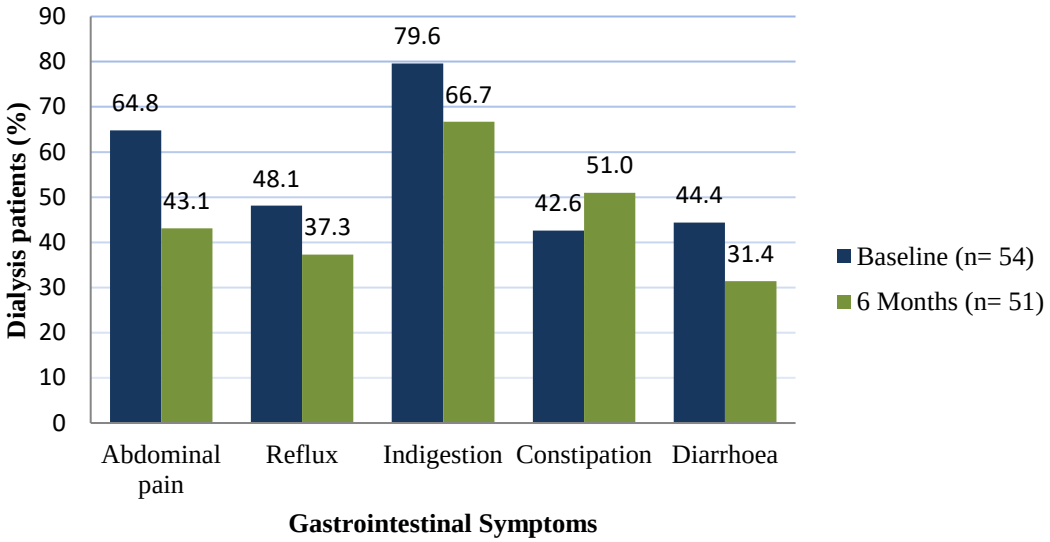

Figure 3.3: Frequency of gastrointestinal symptoms in transplant candidates at baseline and six month follow-up.

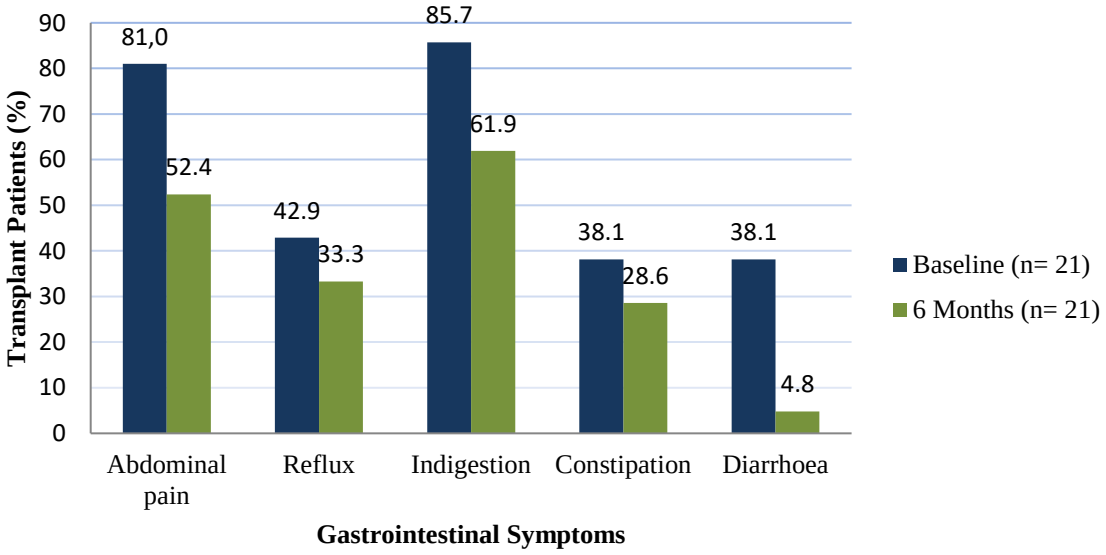

Figure 3.4: Frequency of gastrointestinal symptoms in transplant recipients at baseline and six month follow-up.

Table 3.3: GSRS scores per treatment group at baseline and six month follow-up

	Haemodialysis		Peritoneal Dialysis		Dialysis (HD + PD)		Transplant	
Subscale	**Baseline n = 51**	**6 months n = 48**	**Baseline n = 3**	**6 months n = 3**	**Baseline n = 54**	**6 months n = 51**	**Baseline n = 21**	**6 months n = 21**
Abdominal pain	1.67 (4) [g]	1 (2.5)	2 (2.67)	1 (6)	1.67 (1) [a]	4 (6) [e]	1.67 (4.67)	1 (1)
Reflux	1 (5)	1 (4)	1 (4)	1 (5.5)	1 (1)	5 (5.5)	1 (4)	1 (5)
Indigestion	1.67 (6) [h]	1.67 (5)	2 (1)	1 (3)	1.67 (1.67) [b]	6 (5) [f]	2.33 (3)	1.33 (2.33)
Constipation	1 (6)	1.33 (6)	2 (4.5)	1 (1.67)	1 (1.33)	6 (6)	1 (2)	1 (2)
Diarrhoea	1 (3)	1 (4.5)	1 (6)	4 (5)	1 (1) [c]	6 (5)	1 (2)	1 (0)
Global mean	1.57 (3.14)	1.38 (3.62)	1.5 (3.5)	1.77 (3.62)	1.57 (1.38)[d]	3.93 (3.62)	1.86 (1.79)	1.15 (1.46)

GSRS scores as median (range)

[a] Significantly higher for females (mean rank = 32.66) than males (mean rank=23.95), p = .040

[b] Significantly higher for females (mean rank = 34.00) than males (mean rank= 23.03), p = .011

[c] Significantly higher for females (mean rank = 32.27) than males (mean rank= 22.22), p = .022

[d] Significantly higher for females (mean rank = 33.09) than males (mean rank= 23.66), p = .030

[e] Significantly higher for females (mean rank = 30.85) than males (mean rank= 22.87), p = .025

[f] Significantly higher for females (mean rank = 31.83) than males (mean rank= 22.24), p = .020

[g] Significantly higher for females (mean rank = 30.83) than males (mean rank= 22.62), p = .045

[h] Significantly higher for females (mean rank = 31.93) than males (mean rank= 21.85), p = .016

Table 3.4: Correlations of GSRS scores with clinical and nutritional parameters in transplant candidates and recipients at baseline and at six month follow-up

Variable	n	Global mean		Reflux		Indigestion		Constipation		Diarrhoea		Abdominal pain	
		rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
Dialysis													
Duration of treatment													
Baseline	54	0.287*	0.036	0.279*	0.041								
6 months	51	0.44**	0.001			0.457**	0.001	0.3**	0.033				
Age													
Baseline	54												
6 months	51	-0.338*	0.015	-0.317*	0.023							-0.354*	0.011
Transplant													
WC (cm)													
Baseline	18							0.471*	0.048				

*Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed)

3.4 Discussion

The occurrence of at a least one GIS (GSRS > 1) in the total group, at baseline and at 6 months was high. At 90.7% and 83.3% respectively, this finding supports previous research that renal patients experience a greater frequency of GIS than non-renal patients (23) and the general population (14,24,25).

3.4.1 Transplant candidates

Frequency and severity of GIS

The frequency of GIS amongst dialysed participants was fairly consistent at both time points (88.9% and 81.5%). These values fell within the 76% - 90% GIS frequency range experienced by HD and PD populations elsewhere (26,27). Across the five subscales indigestion, abdominal pain and, to a lesser extent, reflux occurred at higher freqency than constipation and diarrhoea at baseline. At six month follow-up however, more participants suffered from constipation, and with greater severity . These findings are in agreement with a systematic review of GIS in 30 studies conducted among 5161 HD and PD participants. Despite differences in methodology, these studies also reflected constipation, indigestion, abdominal pain and reflux as the most frequently reported GIS (3). Constipation in particular, affects up to 71.7% of HD patients (28) and is attributed to restrictive diets, medication, inactivity and ignoring the urge to defaecate whilst on dialysis (29). Although constipation affected about half of the participants on dialysis, it was not the most bothersome GIS. Indigestion was a frequent and severe GIS at baseline and at six month follow-up.

Indigestion, or dyspepsia is a common occurrance in the HD and PD population, with a frequency ranging between 30.0% - 72.3% and 31.5% - 93.1% respectively and is responsible for the regular consumption of acid suppressants in 41.0% - 76.4% of patients (30,31). Endoscopy in dyspeptic patients shows upper gastrointestinal (UGI) pathology in 60.0% - 68.0% of patients, with erosive and ulcerative changes found in the stomach, oesophagus and duodenum. The causes of UGI morbidity are complex. In addition to risk factors in the general population (32), CKD determinants include hypergastrinaemia, inflammation and high levels of ammonia (33). Delayed gastric emptying or heparin use in dialysis (4,34,35) adds to GIS such that dialysed patients may have a greater symptom burden than non-dialysed ESRD patients (14). Within the dialysed group itself, PD participants (albeit only three), had more pronounced GIS than HD participants. This is a common (36,37) but inconsistent finding (5) related to the

effects of the dialysate present in the abdomen (37). Between the sexes, females reported significantly higher GSRS, similar to that observed in a Turkish HD group (38). However, this is not exclusive to CKD. In the general population, women experience more dyspeptic and irritable bowel syndrome symptoms (39,40,41) on account of gender specific psychosocial factors, hormonal activity, as well as anatomical and functional differences in pain transmission pathways affecting sensitivity (42,43).

Correlations between GSRS severity scores, clinical and nutritional variables

This study examined the relationships between severity (GSRS scores), rather than frequency of GIS, with selected clinical and nutritional parameters. Although expected, no significant associations were found between GSRS and serum albumin. Lower serum albumin is likely due to underlying illness or inflammation, such as infections rather than nutritional status (44), which could worsen the severity of GIS. Abdominal pain and reflux scores decreased with age, possibly due to the disinclination of older individuals to report symptoms. Furthermore, there appears to be an adaptation to intensity of chronic symptoms as well as symptoms becoming less specific, and more vague with advancing age (45,46).

GSRS scores were positively associated with the duration of dialysis. The increasing severity of indigestion, constipation and reflux with a longer period on dialysis, is not a universal finding (45), as typically the opposite occurs. More GIS is noted at the start of PD (37) and in HD, related to hypotensive episodes at HD initiation (47).

3.4.2 Transplant recipients

Frequency and severity of GIS

GI complications are a common occurrence following a solid organ transplant, potentially affecting any area of the GIT (9). Severe complications are rare (10.0%), occurring primarily in the first year post transplant (48). A transplant is expected to relieve GIS related to uraemia and dialysis, and explains the lower global GSRS scores in this study's transplant candidates versus transplant recipients. However, for many transplant recipients GIS still persist, albeit with a lower level of severity. The transplant recipients in the current study had a high frequency of GIS at baseline (95.2%), similar to findings in European (88.3% - 92.0%) (7,22) and African (96%) transplant recipients (49). In a study by Ponticelli et al, with a cohort of 1130 kidney transplant recipients, patients demonstrated stable GIS throughout the year-long study period

(7). In contrast, the frequency of GIS dropped by 19.0% to 76.2% in the present study, for reasons that are unclear.

As was the case in the dialysis group, indigestion was a frequent symptom. It was the most severe at baseline and at six month follow-up, possibly due to underlying gastropathology. Dyspeptic transplant recipients have shown a high prevalence of erosive changes on endoscopy, mainly gastritis (78.6%), that could be present pre-transplant (50) and/or is aggravated by immunosuppressants (8). Tacrolimus, which has been linked to duodenitis (50), forms part of the anti-rejection regimen in addition to mycophenolate mofetil (MMF), and prednisone (51), and could be a contributing factor. It is also interesting to note that indigestion, together with abdominal pain and reflux, were the three most frequent GIS at baseline and six month follow-up, similar to a survey of 4232 transplant recipients across four north European countries (22). Taken together, these three GIS are typical of gastro-oesophageal reflux disease (GORD) (52), for which CKD, transplantation and anti-rejection medication are risk factors (53).

Anti-rejection medication also increases the risk of infectious and non-infectious diarrhoea by increasing vulnerability to infectious agents and compromising gut mucosal integrity and function (9). In 13 out of 25 (52.0%) transplant recipients with chronic diarrhoea, infections and drug-related colitis associated with MMF were identified via colonoscopy (47), while diarrhoea was linked to the toxicity profile of Tacrolimus (54). Despite the combination of these two drugs in the current study's participants treatment regime, diarrhoea was not as bothersome as the other GIS. Diarrhoea affected eight transplant candidates (38.1%) and only one (4.8%) transplant recipient at baseline and six month follow-up respectively. Furthermore, the severity scores of diarrhoea were low (GSRS of 1.00). Earlier studies report the frequency of diarrhoea to be between 22.8% - 53.0% and GSRS scores of between 1.44 ± 0.88 and 1.80 ± 1.10 in transplant recipients (7,22). In the majority of cases, diarrhoea is transient and resolved with appropriate pharmaceutical and dietary management (55). This is probably the reason for the difference in frequency at baseline and then at 6 months.

Correlations between GSRS severity scores, clinical and nutritional variables

Significant associations between GSRS constipation scores with WC were identified at baseline in the transplant group. In the general population, obesity is a risk factor for GORD and erosive oesophagitis in the long term (25), while central obesity is related to non-erosive oesophageal disease (56). However, the association of obesity with constipation and functional dyspepsia is less clear (57).

It would therefore be sensible to ensure weight maintenance and a WC at optimum values. In 332 non-CKD participants who participated in a weight intervention programme that targeted behaviour, diet, and physical activity, participants reported an 81.0% and 55.0% decrease and resolution of GIS respectively (58). In other research, weight management was less likely to improve symptoms in 211 participants for which the BMI – reflux relationship was independent of diet and exercise (59). This highlights the contribution of clinical, pharmaceutical and demographic factors to GIS.

3.4.3 Gastrointestinal symptoms and HIV

The contribution of coexisting illness to GIS in ESRD was clearly applicable to this patient group. HIV has always been associated with GIS, and it was not uncommon for HIV-positive individuals to experience regular episodes of diarrhoea (60). However, defining research by Mönkemüller et al has shown a change in the pattern of GI manifestations since the HAART era. The occurrences of opportunistic infections have reduced (61), while UGI manifestations have increased (11). HIV-positive Japanese patients, report higher UGIS severity scores than non-HIV infected patients (62). Findings of mucosal changes such as gastritis (48%) and gastric erythema (45%) (63), and reflux, *H pylori* infection, and GORD have increased (11). In all probability, these would aggravate UGI pathology of ESRD, and could underlie the higher frequency and severity of indigestion compared to the other GIS in the current study sample.

This study has several strengths. It is the first to investigate the frequency and severity of GIS in pre- and post-kidney transplant recipients infected with HIV. Secondly, the GSRS which has been previously validated in South Africa and elsewhere (64) encompasses a range of symptoms applicable to the upper and lower GIT. Thirdly, despite the small study sample, the findings of this research are still generalizable as the majority of patients on the transplant lists were included in this study, and as such, are a fair representation of this group. A study limitation in this regard is that the number of PD patients (n=3) is extremely small. Thus, the power of the statistical analysis using this group is severely limited. Hence, correlations were done using PD and HD combined into a single group (n=54). The lack of information on medication used to relieve GIS, as well as detailed renal function parameters, which would have benefited the analysis of the study results, is also a drawback. The study design, which provides a snapshot of GIS at two assessment points is suitable for prevalence studies, but limits the exploration of causal relationships (65). Finally, this study did not have a control group to compare GIS with

and without the presence of HIV, but should be considered in future research, along with a longer follow-up period to provide better insight into whether the symptoms documented are pervasive or transient.

In conclusion, this research contributes to the body of evidence on GIS experienced by kidney transplant candidates and recipients but extends to an understanding of these symptoms among those infected with HIV. The data confirm a high prevalence of GIS in both treatment groups, although similar to that documented for non-HIV infected dialysis and transplant recipients. Indigestion was a prevalent and severe GIS in the whole group at both time points, while those on dialysis experienced a greater frequency of constipation at six month follow-up. A comparison of GSRS scores between groups showed the highest severity scores in transplant candidates, and Spearman's correlations with specific GIS were positive for duration of dialysis and negative for age. In the transplant group, specific GIS were positively associated with WC.

Both kidney transplants and dialysis are major medical interventions that are often accompanied by complications, and frequent hospitalisation. However, GIS (especially if they are chronic and low grade), may be discounted by patients and clinicians until they become severe and debilitating. Major gastrointestinal complications are rare, but do occur. The GSRS is a quick, simple, and cost effective monitoring tool that can be used for early identification of, or progression of GI manifestations.

3.5 References

1. Osorio MS, Giraldo GC. Gastrointestinal manifestations of chronic kidney disease. Rev. Colomb. Nefrol. 2017; 4(1): 3 - 12.
2. Zhang X,Bansal N,Go AS, Hsu C. Gastrointestinal symptoms, inflammation and hypoalbuminemia in chronic kidney disease patients: a cross-sectional study. BMC Nephrology. 2015; 16(211): 1-8.
3. Zuvela J, Trimingham C, Leu RL, Faull R, Clayton P, Jesudason S, Meade A. Gastrointestinal symptoms in patients receiving dialysis: a systematic review. Nephrology. 2018; 23(8): 718-727.
4. Sreelatha M, Kumar VS, Shekar GC, Shekar VC. Upper gastrointestinal manifestations in chronic renal failure through upper gastrointestinal endoscopy. IJSS. 2017; 5(2): 221-225.
5. Dong R, Guo Z, Ding J, Zhou Y, Wu H. Gastrointestinal symptoms: A comparison between

patients undergoing peritoneal dialysis and hemodialysis. World J Gastroenterol. 2014; 20(32): 11370-11375.

6. Ariffin NFM, Naing L, Pisharam J, Khalil MAM, Tamin N, Chong VH, Tan J. Appetite and gastrointestinal symptoms in end stage renal disease patients. J Clin Exp Nephrol. 2016; 1(6). doi: 10.21767/2472-5056.100006.
7. Ponticelli C, Colombo D, Novara M, Basilisco G, CETRA Study Group. Gastrointestinal symptoms impair quality of life in Italian renal transplant recipients but are under-recognized by physicians. Transpl Int. 2010; 23(11): 1126-1134.
8. Helderman JH, Goral S. Gastrointestinal complications of transplant immunosuppression. JASN. 2002; 13(1): 277 - 287.
9. Lucan VC, Berardinelli L. Gastrointestinal side effects of post-transplant therapy. J Gastrointestin Liver Dis. 2016; 25(3): 367 - 373.
10. Thompson CG, Gay CL, Kashuba ADM. HIV persistence in gut-associated lymphoid tissues: pharmacological challenges and opportunities. AIDS Res Hum Retroviruses. 2017: 33(6): 513–523.
11. Nkuize M, De Wit S, Muls V, Arvanitakis M, Buset M. Upper gastrointestinal endoscopic findings in the era of highly active antiretroviral therapy. HIV Med. 2010; 11(6): 412-417.
12. Thompson T, Lee MG, Clarke T, Mills M, Wharfe G, Walters C. Prevalence of gastrointestinal symptoms among ambulatory HIV patients and a control population. Ann Gastroenterol. 2012; 25(3): 243–248.
13. Hydarinia-Naieni Z, Nobahar M, Ghorbani R. Study of nutritional status and gastrointestinal health in patients undergoing hemodialysis and their association with laboratory parameters and dialysis adequacy in Semnan, Iran. Middle East J Rehabil Health Stud. 2017; 4(3): e12686. doi: 10.5812/mejrh.12686.
14. Strid H , Simrén M, Johansson C, Svedlund J, Samuelsson O, Björnsson ES. The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological general well being. Nephrol Dial Transplant. 2002; 17(8): 1434-1439.
15. Laeeq SM, Tasneem AA, Hanif FM, Luck NH, Mandhwani R, Wadhva R. Upper gastrointestinal bleeding in patients with end stage renal disease: causes, characteristics and factors associated with need for endoscopic therapeutic intervention. J Transl Int Med. 2017; 5(2): 106–111.
16. Bunnapradist S1, Neri L, Wong W, Lentine KL, Burroughs TE, Pinsky BW, Takemoto SK,

Schnitzler MA. Incidence and risk factors for diarrhea following kidney transplantation and association with graft loss and mortality. Am J Kidney Dis. 2008; 51(3): 478-86.

17. Centers of Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) Anthropometry Procedures Manual. [Online]; 2009 [cited 22/07/2015]. Available from: https://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf.
18. World Health Organization. Obesity. Preventing and managing the global epidemic. [Online]; 2000. [cited 12/03/2018]. Available from: https//Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation (WHO Technical Report Series 894). Geneva:; 2000.
19. Svedlund J SIDG. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;(33): 129-134.
20. Ponticelli C, Passerini P. Gastrointestinal complications in renal transplant recipients. Transpl Int. 2005; 18(6): 643-650.
21. Uehara R, Isomoto H, Minami H, Yamaguchi N, Ohnita K, Ichikawa T, Takeshima F, Shikuwa S, Nakao K. Characteristics of gastrointestinal symptoms and function following endoscopic submucosal dissection and treatment of the gastrointestinal symptoms using rikkunshito. Exp Ther Med. 2013; 6(5): 1083–1088.
22. Ekberg H, Kyllönen L, Madsen S, Grave G, Solbu D, Holdaas H. Increased prevalence of gastrointestinal symptoms associated with impaired quality of life in renal transplant recipients. Transplantation. 2007; 83(3): 282-289.
23. Cano AE, Neil AK, Kang JY, Barnabas A, Eastwood JB, Nelson SR, Hartley I, Maxwell D. Gastrointestinal symptoms in patients with end-stage renal disease undergoing treatment by hemodialysis or peritoneal dialysis. Am J Gastroenterol. 2007;102(9):1990-1997.
24. Aziz I, Palsson OS, Törnblom H, Sperber AD, Whitehead WE, Simrén M. Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: A cross-sectional population-based study. Lancet Gastroenterol Hepatol. 2018; 3(4): 252-262.
25. Chang P, Friedenberg F. Obesity & GERD. Gastroenterol Clin North Am. 2014; 43(1): 161–173.
26. Dong R, Guo Z. Gastrointestinal symptoms in patients undergoing peritoneal dialysis: Multivariate analysis of correlated factors. World J Gastroenterol. 2010; 14(16): 2812-2817.
27. Daniels G, Robinson JR, Walker C, Pennings JS, Anderson ST. Gastrointestinal symptoms among African Americans undergoing hemodialysis. Nephrol Nurs J. 2015; 42(6): 539- 548.

28. Zhang J, Huang C, Li Y, Chen J, Shen F, Yao Q, Qian J, Bao B, Yao X. Health-related quality of life in dialysis patients with constipation: a cross-sectional study. Patient Prefer Adherence. 2013; 7: 589–594.
29. Yasuda G1, Shibata K, Takizawa T, Ikeda Y, Tokita Y, Umemura S, Tochikubo O. Prevalence of constipation in continuous ambuatory peritoneal dialysis and comparison with hemodialysis patients. Am J Kidney Dis. 2002; 39(6): 1292 -1299.
30. Chong VH, Tan J. GI and psychosomatic symptoms in Asian ESRD. Nephrology (Carlton). 2013; 18(2): 97-103.
31. Strid H, Simrén M, Björnsson ES. Overuse of acid suppressant drugs in patients with chronic renal failure. Nephrol Dial Transplant. 2003; 18(3): 570 – 575.
32. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part I: Overall and upper gastrointestinal diseases. Gastroenterology. 2009; 136(2): 376 - 386.
33. Krishnan A, Sigamani R, Venkataraman J. Gastrointestinal evaluation in chronic kidney diseases. J Nephrol Therapeutic. 2011; 1(3): 1:110. doi:10.4172/2161-0959.1000110.
34. Junior LDS, Santos PR, Santos AA, Ponte de Souza MHL. Dyspepsia and gastric emptying in end-stage renal disease patients on hemodialysis. BMC Nephrology. 2013; 14: 275. doi.org/10.1186/1471-2369-14-275
35. Brown-Cartwright D, Smith HJ, Feldman M. Gastric emptying of an indigestible solid in patients with end-stage renal disease on continuous ambulatory peritoneal dialysis. Gastroenterology. 1988; 95(1): 49-51.
36. Salamon K, Woods J, Paul E, Huggins C. Peritoneal dialysis patients have higher prevalence of gastrointestinal symptoms than hemodialysis patients. J Ren Nutr. 2013; 23(2): 114-118.
37. Kosmadakis G. Albaret J. da Costa Correia E. Somda F, Aguilera D. Gastrointestinal disorders in peritoneal dialysis patients. Am J Nephrol. 2018; 48(5): 319–325.
38. Gök EG , İnci A, Çoban M , Kutsal DA , Kürşat S. Functional bowel disorders and associated risk factors in hemodialysis patients in Turkey. Turk J Gastroenterol. 2017; 28: 12-19.
39. Lee SY, Kim JH, Sung IK, Park HS, Jin CJ, Choe WH, Kwon SY, Lee CH, Choi KW. Irritable bowel syndrome is more common in women regardless of the menstrual phase: a Rome II-based survey. J Korean Med Sci. 2007; 22(5): 851–854.
40. Kawakubo H, Tanaka Y, Tsuruoka N, Hara M, Yamamoto K, Hidaka H, Sakata Y, Shimoda R, Iwakiri R, Kusano M, Fujimoto K. Upper gastrointestinal symptoms are more frequent in female than male young healthy Japanese volunteers as evaluated by questionnaire. J

Neurogastroenterol Motil. 2016; 22(2): 48-253.

41. Napthali K, Koloski N, Walker MM, Talley NJ. Women and functional dyspepsia. Womens Health (Lond). 2016; 12(2): 241–250.
42. Mayer EA, Naliboff B, Lee O, Munakata J, Chang L. Review article: Gender-related differences in functional gastrointestinal disorders. Aliment Pharmacol Ther. 1999; 13(Suppl. 2): 65-69.
43. Cain KC, Jarrett ME, Burr RL, Rosen S, Hertig VL, Heitkemper MM. Gender differences in gastrointestinal, psychological, and somatic symptoms in irritable bowel syndrome. Dig Dis Sci. 2008; 54(7): 542-1549.
44. Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. JASN. 2010; 21(2): 223-230.
45. Carrera-Jiménez D, Miranda-Alatriste P, Atilano-Carsi X, Correa-Rotter R, Espinosa-Cuevas Á. Relationship between nutritional status and gastrointestinal symptoms in geriatric patients with end-stage renal disease on dialysis. Nutrients. 2018; 10(4): 425 doi:10.3390/nu10040425.
46. Becher A, Dent J. Systematic review: ageing and gastro-oesophageal reflux disease symptoms, oesophageal function and reflux oesophagitis. Aliment Pharmacol Ther. 2011; 33: 442-454.
47. Thomas R, Panackal C, John M, Joshi H, Mathai S, Kattickaran J, Iqbal M. Gastrointestinal complications in patients with chronic kidney disease--a 5-year retrospective study from a tertiary referral center. Ren Fail. 2013; 35(1): 49-55.
48. Sarkio S, Halme L, Kyllönen L, Salmela K. Severe gastrointestinal complications after 1,515 adult kidney transplantations. Transpl Int. 2004; 17(9): 505-510.
49. Maru RM. Gastrointestinal symptoms and gastrointestinal quality of life in renal transplant patients: a descriptive cross sectional study. [Masters]. University of Nairobi; 2016.
50. Nazeer A, Rai AA, Luck NH. Factors leading to dyspepsia in renal transplant recipients. Pan Afr Med. 2017; 28: 120. doi: 10.11604/pamj.2017.28.120.12767
51. Muller E, Barday Z, Mendelson M, Kahn D. Renal transplantation between HIV-positive donors and recipients justified. S Afr Med J. 2012; 102(6): 497–498.
52. Van Rensburg CJ, Kulich KR, Carlsson J, Wiklund IK. What is the burden of illness in patients with reflux disease in South Africa? SAHARA J: Journal of Social Aspects of HIV/AIDS Research Alliance / SAHARA, Human Sciences Research Council. [Online]; 2006 [cited 22/09/2018]. Available from:

https://www.ajol.info/index.php/saharaj/article/view/50461.

53. Abdulrahman IS, Al-Quorain AA. Prevalence of gastroesophageal reflux disease and its association with helicobacter pylori infection in chronic renal failure patients and in renal transplant recipients. Saudi J Gastroenterol. 2008; 14(4): 183–186.
54. Ekberg H, Bernasconi C, Nöldeke J, Yussim A, Mjörnstedt L, Erken U, Ketteler M, Navrátil P. Cyclosporine, tacrolimus and sirolimus retain their distinct toxicity profiles despite low doses in the Symphony study. Nephrology Dialysis Transplantation. 2010; 25(6): 2004-2010.
55. Maes B, Hadaya K, de Moor B, Cambier P, Peeters P, de Meester J, Donck J, Sennesael J, Squifflet J-P. Severe diarrhea in renal transplant patients:results of the DIDACT study. Am J Transplant. 2006; 6: 1466-1472.
56. Kim KJ, Lee BS. Central obesity as a risk factor for non-erosive reflux disease. Yonsei Med J. 2017; 58(4): 743–748.
57. Ho W, Spiegel BMR. The relationship between obesity and functional gastrointestinal disorders. Causation, association, or neither? Gastroenterol Hepatol (N Y). 2008; 4(8): 572–578.
58. Singh M, Lee J, Gupta N, Gaddam S, Smith BK, Wani SB, Sullivan DK, Rastogi A, Bansal A, Donnelly JE, Prateek Sharma P. Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: A prospective intervention trial. Obesity (Silver Spring). 2013; 21(2): 284-290.
59. Nandurkar S, Locke GR, Fett S, Zinsmeister AR, Cameron AJ, Talley NJ. Relationship between body mass index, diet, exercise and gastro-oesophageal reflux symptoms in a community. Alimetary Pharmacology and Therapeutics. 2008; 20(5): 497-505.
60. Knox TA, Zafonte-Sanders M, Fields-Gardner C, Moen K, Johansen D, Paton N. Assessment of nutrional status, body composition and human immunodeficiency virus-associated morphological changes. Clin Infect Dis. 2003; 36(S2): S63-S68.
61. Mönkemüller KE, Call SA, Lazenby AJ, Wilcox CM. Declining prevalence of opportunistic gastrointestinal disease in the era of combination antiretroviral therapy. Am J Gastroenterol. 2000; 95(2): 457-62.
62. Takahashi Y, Nagata N, Shimbo T, Nishijima T, Watanabe K, Aoki T, Sekine K, Okubo H, Watanabe K, Sakurai T, Yokoi C, Mimori A, Oka S, Uemura N, Akiyama J. Upper gastrointestinal symptoms predictive of candida esophagitis and erosive esophagitis in HIV and non-HIV patients: An endoscopy-based cross-sectional study of 6011 patients. Medicine

(Baltimore). 2015; 94(47): e2138. doi: 10.1097/MD.0000000000002138.

63. Parvin R , Koll S, Shah J , Jhaveri M, Reddy M.. Upper and lower gastrointestinal endoscopic findings in HIV-infected patients in the era of highly active antiretroviral therapy. Gastroenterol Res. 2018; 11(2): 95-99.

64. Kulich KR, Madisch A, Pacini F, Piqué JM, Regula J, Van Rensburg CJ, Újszászy L, Carlsson J, Halling K, Wiklund IK. Reliability and validity of the gastrointestinal symptom rating scale (GSRS) and quality of life in reflux and dyspepsia (QOLRAD) questionnaire in dyspepsia: A six-country study. Health Qual Life Outcomes. 2008; 6(12). doi: 10.1186/1477-7525-6-12.

65. Mann CJ. Observational research methods. Research design II: Cohort, cross sectional, and case-control studies. Emerg Med J. 2003; 20: 54-60.

CHAPTER 4
PREVALENCE OF OSTEOPOROSIS AND FACTORS ASSOCIATED WITH BONE DENSITY IN HIV-POSITIVE TRANSPLANT CANDIDATES AND RECIPIENTS FROM A HIV-POSITIVE DONOR

ABSTRACT

Background: Previous studies have shown that kidney transplant candidates and recipients have a low bone mineral density (BMD). Consequently, they have a higher prevalence of osteoporosis and a greater risk of fracture. However, little is known about the prevalence of osteoporosis and associated factors among transplant recipients and those awaiting a transplant who are infected with human immunodeficiency virus (HIV).

Objective: To determine the prevalence of osteopenia and osteoporosis and investigate the socio-demographic, clinical and nutritional factors associated with BMD in HIV-positive transplant candidates and recipients from a HIV-positive donor.

Methods: Fifty six HIV-positive patients participated in this cross-sectional study. Twenty were recipients of a transplant from a HIV-positive donor, while 36 were on haemodialysis (HD) and awaiting a transplant. BMD and body composition were measured by dual-energy X-ray absorptiometry (DEXA). Vitamin D status was measured using serum 25-hydroxyvitamin D [25(OH)D]. Vitamin D and calcium dietary intake was obtained from a single 24 hour recall.

Results: There were 55.4% male participants, while the remainder (44.6%) were female. The majority of participants were black (92.9%). The mean age of all participants was 43.8 ± 8.3 years. Serum 25(OH)D levels were low for the group as a whole, with a mean of 22.04 ±12.74 ng/ml. BMD was normal in 64.3% of all participants. Osteoporosis was more prevalent amongst transplant recipients (20.0%) than transplant candidates (13.9%). Conversely, more osteopenia was present amongst transplant candidates (27.8%), whereas only 1/20 (5.0%) transplant recipients had osteopenia. T-scores strongly correlated positively, with lean mass and BMD of the spine ($r = 0.707$, $p = 0.007$), and moderately with each side of the total hip BMD ($r = 0.455$, $p = 0.007$ and $r = 0.420$, $p = 0.007$). Fat mass did not correlate with osteoporosis or BMD. There was a significant positive associations between dietary calcium and all BMD sites for transplant recipients.

Conclusion: The prevalence of osteoporosis was similar, and in some cases, lower than in transplant recipients elsewhere. Lean mass was positively associated with BMD, but serum 25(OH)D which was low in both groups, was not related to BMD. In transplant recipients only, dietary calcium intake was positively associated with BMD.

Keywords: Kidney transplant candidates, Kidney transplant recipients, Human immunodeficiency virus (HIV), Dual-energy X-ray absorptiometry, Bone mineral density, Osteopenia, Osteoporosis, Vitamin D, Calcium

4.1 Introduction

Following a kidney transplant, bone mineral density (BMD) decreases by 2.9% to 9.0%, with the most apparent changes occurring within the first 18 months (1), before levelling off or increasing slightly (2). It is largely, though not exclusively, attributable to high doses of glucocorticosteroids in the early transplant period (1), as prior to transplantation, deterioration in bone density and micro-structure from chronic kidney disease-mineral and bone disease (CKD-MBD) is already present (3), and exacerbated during dialysis (4). Consequently, both transplant candidates and recipients have a greater prevalence of osteoporosis and a higher frequency of fractures than the general population (2,5).

Human immunodeficiency virus (HIV) – positive individuals also have a lower bone density (6,7) and a three-fold higher prevalence of osteoporosis compared to HIV-negative controls (8). Viral effects on BMD have been implicated through inflammation and HIV proteins on bone modelling, exacerbated by factors such as infections, nutritional deficiencies and a low CD4 count (9). Furthermore, with the initiation of antiretrovirals, BMD decreases by 2.0% to 6.0% in the first two years, while steadying or showing a slight increase thereafter (10-12).

Considering the impact that both chronic kidney disease (CKD) and HIV have, independently on the skeletal system, it is highly likely that living with this double burden, increases the likelihood of significant changes in bone density. However, as this has not been investigated, the purpose of this study was to determine the BMD and prevalence of osteoporosis in this unique group, as well as their association with selected socio-demographic, clinical and nutritional parameters.

4.2 Methods

4.2.1 Participants

For the purpose of this cross-sectional study, prospective participants were recruited through the kidney transplant programme for HIV-positive patients at Groote Schuur Hospital, Cape Town. Recruitment was based on whether they were transplant recipients or were awaiting a transplant and hence managed on dialysis. From the outset they were therefore categorised as: (i) HIV-positive kidney transplant recipients who have received a kidney from a HIV-infected donor; and (ii) HIV-infected transplant awaiting candidates who were on the waiting list to receive a

kidney from a HIV-positive donor. Prospective participants were contacted telephonically or at their respective outpatient clinics and invited to undergo a dual- energy X-ray absorptiometry (DEXA) evaluation during the study period spanning a year. Patients were included if they were clinically stable at the time of recruitment. Patients did not qualify for participation if they declined participation, were severely ill, were not contactable, uncooperative or had missed several interview appointments (typically two or more without reason). Fifty six participants agreed to the DEXA assessment and written informed consent was obtained prior to them undergoing assessment. The study was approved by the University of KwaZulu-Natal's Biomedical Research Ethics Committee (Approval number BE 327/13).

4.2.2 Socio-demographic and clinical characteristics

Socio-demographic information was collected using an interviewer-administered structured questionnaire developed for the purpose of the study. Clinical information was obtained from medical records or during participant interviews.

4.2.3 Bone densitometry measurements

DEXA assessments were conducted by experienced radiographers at a radiology centre closest to where participants resided. The Hologic (Models: Discovery or Horizon) were used at eight of the centres, and the GE Lunar Prodigy (Advance) at two of them. Only three of the ten centres were able to provide body composition information as well as BMD measurements.

Assessments were done according to standard procedure, with height and weight being determined prior to DEXA assessment and body mass index (BMI) calculated as weight divided by height squared (kg/m^2). Subsequently BMI was classified according to the World Health Organization categories: Underweight (<18.50), normal (18.50 – 24.99), overweight (≥ 25.00-29.99), obese class I (30.00-34.99), obese class II (35-39.99) and obese class III (≥40) (13).

BMD was recorded at L1 – L4 of the lumbar spine (LS), and each side of the total hip (TH) and femoral neck (FN) and presented as absolute values (g/m2), Z-scores and T-scores, based on machine software reference data. Z-scores, presented as standard deviations (SD) are preferred in younger patients, as it compares the individual's BMD with the mean value in a population of similar age and gender (14). T-scores reflect comparisons as the SD above or below the mean values of a healthy population of young adults (15). T-scores were used to classify BMD according to the World Health Organization (WHO) criteria: Normal (T-score ≥ -1.0);

osteopenia (T-score between -1.0 and -2.5); osteoporosis (T-score ≤ - 2.5); or severe osteoporosis (T-score ≤ - 2.5 with one or more fractures) (16). All DEXA results and classifications were reviewed by a clinician. Osteoporosis classification by region was made based on the BMD measurement site with the lowest T-score.

4.2.4 Vitamin D measurement

Serum levels of 25-hydroxyvitamin D [25(OH)D] was measured using chemiluminescence (Immunlite 2000, Siemens, USA). Normal and deficiency states were defined as deficiency: < 20ng/ml; partial deficiency: 20 − 29 ng/ml; and optimal level: > 30 ng/ml (17).

4.2.5 Dietary intake

Information on dietary vitamin D and calcium intake was obtained from a single quantified 24-hour recall. Participants recalled all foods and beverages consumed in the previous 24 hours, while being recorded according to the name of the dish and description of the preparation method or recipe, the time it was consumed and the amount eaten (18). A number of measures were put in place to improve accurate recall of food and beverage consumption during the interview process. These include the following: All 24-hour recalls were administered by registered dietitians with experience in recording of dietary intake data; training was provided to ensure the use of standardised protocols during the dietary interview technique such as the use of similar probing questions to minimise interviewer bias. These measures were based on the Nordic Cooperation Group of Dietary Researchers' interview recommendations to reduce misclassification and misrepresentation of information (19). As a higher level of response accuracy is obtained from interviews conducted in the vernacular of participants (19), an interpreter was used when required. Portion size estimation was improved through the use of household measuring utensils (19) and a food-portion booklet that referenced food portions against common household objects, applicable to the South African context (20). All dietary data was analysed using Foodfinder 3 for Windows^{R} (The South African Medical Research Council).

4.2.6 Pilot Study

The socio-demographic questionnaire and 24-hour recall was assessed for understanding and ease of administration during a pilot study. The pilot study was conducted on eight and four HIV-negative transplant candidates and recipients respectively. They were both deemed acceptable for use in the main study as they proved understandable and easy to administer.

4.2.7 Statistics

Data was analysed using the Statistical package for Social Sciences (SPSS®) version 25.0. Means and standard deviations were calculated for all continuous variables and frequencies with percentages for the categorical variables. Independent samples t-test was used to determine differences between transplant candidates and recipients and between males and females for clinical and nutritional variables. Chi-square tests and ANOVA was used to determine associations between osteopenia/osteoporosis and categorical and numerical variables respectively. Pearson's correlation was used to determine the relationship between BMD and other scale scores. Results with a *P* value of <0.05 was taken as statistically significant.

4. 3 Results

4.3.1 Participant characteristics

The study sample consisted of 56 HIV-positive participants with end stage renal disease (ESRD). Of these, 20 had received a transplant from a HIV-positive donor and 36 were on haemodialysis (HD) while awaiting a transplant. Demographic and clinical characteristics are presented in Table 4.1. There were more males 31/56 (55.4%) than females 25/56 (44.6%) with the majority of participants being black Africans 52/56 (92.9%). The mean age of all participants was 43.8 ± 8.3 years. The mean duration of treatment for the entire study sample was 3.9 ± 2.8 years, although that of candidates on dialysis was slightly longer than recipients of a transplant (4.4 ± 3.0 versus 2.9 ± 2.3 years). The majority of participants were hypertensive 51/56 (91.1%), whereas diabetes was only present amongst those on dialysis. Three participants were receiving treatment for hypercholesterolaemia. HIV parameters showed 47/56 (92.2%) of participants had viral loads lower than detectable limits, and the mean CD4+ count was 412.57 ± 230.00 cells/µL. Vitamin D levels measured as serum 25(OH) D, was low across the entire study sample, with a mean value of 22.04 ± 12.74 ng/ml. Transplant recipients had a lower mean 25(OH) D compared to candidates. Optimal levels were observed among 9/36 (29.0%) of

transplant candidates, while 71.0% were either partially deficient or deficient. Even fewer transplant recipients had optimal levels 2/20 (11.1%), while more 18/20 (88.9%) were either partially deficient or deficient. There were no significant differences in laboratory values between the two treatment groups.

Table 4.1: Demographic and clinical characteristics of the study sample

Patient Characteristics	Total group N = 56	Transplant candidates n = 36	Transplant recipients n = 20
Gender			
Male	31 (55.4)	19 (52.8)	12 (60.0)
Female	25 (44.6)	17 (47.2)	8 (40.0)
Age (years)	43.8 ± 8.3	45.1 ± 8.3	41.4 ± 7.7
Male	44.5 ± 8.1	45.6 ± 8.4	44.5 ± 7.5
Female	42.9 ± 8.6	44.5 ± 8.5	39.4 ± 8.2
Ethnicity			
Black	52 (92.9)	33 (91.7)	19 (95.0)
Coloured[a]	3 (5.4)	2 (5.6)	1 (5.0)
White	1 (1.8)	1 (2.8)	0 (0.0)
Duration of current treatment (years)	3.9 ± 2.9	4.5 ± 3.0	2.9 ± 2.3
Chronic illness			
Diabetes	10 (17.9)	10 (27.8)	0 (0.0)
Hypertension	51 (91.1)	34 (94.4)	17 (85.0)
Hypercholesterolaemia	3 (5.4)	2 (5.6)	1 (5.0)
CD4 (cells/µL)[b]	412.57 ± 230.00	392.18 ± 194.40	447.25 ± 282.70
Viral load (copies /ml)[c]			
Lower than detectable limit (LDL)	47 (92.2)	29 (90.6)	18 (94.7)
≤ 10000 copies/ml	4 (7.8)	9.4	1 (5.3)
25(OH) D ng/ml[d]	22.04 ±12.74	23.74±14.03	19.19 ± 9.95
Optimal (> 30ng/ml)	11 (22.4)	9 (29.0)	2 (11.1)
Partial deficiency (20-29ng/ml)	9 (18.4)	6 (19.4)	3 (16.7)
Deficiency (< 20ng/ml)	29 (59.2)	16 (51.6)	13 (72.2)

Data give as means and standard deviation or frequency and percentages

[a] Coloured refers to a person of mixed ancestry in South Africa

[b] CD4: n = 54 (dialysis: n = 34 , transplant: n = 20), [c] Viral load: n = 51 (dialysis: n = 32, n = 19)

[d] 25(OH) D : n = 48 (dialysis: n = 30, transplant: n = 18)

4.3.2 Bone mineral density of participants

BMD values and corresponding T- and Z- scores of the LS, TH and FN are presented in Table 4.2. There were no significant differences in BMD values between the two treatment groups. According to the WHO classification, BMD was normal among 36/56 (64.3%) of participants. However, osteoporosis was more prevalent among transplant recipients (20.0%), especially in the spine, than transplant candidates (13.9%), while only 1/20 (5.0%) transplant recipient had osteopenia. Conversely, the prevalence of osteopenia among transplant candidates was 10/26 (27.8%), while 5/26 (13.9%) had osteoporosis, mainly in the LS and FN. When categorised by gender, more women were osteoporotic than osteopenic, while the reverse held true for men (Figure 4.2).

Table 4.2: BMD and related classification in transplant candidates and transplant recipients

	Transplant candidates n = 36		**Transplant recipients** n = 20	
Measurement site	**n**		***n***	
Lumbar Spine (L1—L4)				
BMD (g/cm^2)	35	1.001 ± 0.181	20	0.962 ± 0.198
T score	25	- 0.508 ± 1.622	8	-1.175 ± 2.245
Z score	35	- 0.309 ± 1.390	20	- 0.725 ± 1.716
Femoral Neck (Left)				
BMD (g/cm^2)	31	0.770 ± 0.146	19	0.781 ± 0.125
T score	22	- 0.723 ± 1.196	7	- 0.786 ± 1.358
Z score	32	- 0.500 ± 1.276	19	- 0.426 ± 1.016
Femoral Neck (Right)				
BMD (g/cm^2)	27	0.758 ± 0.137	19	0.794 ± 0.168
T score	19	- 1.006 ± 1.214	7	- 0.900 ± 2.246
Z score	28	- 0.625 ± 0.950	19	- 0.311 ± 1.429
Total Hip (Left)				
BMD (g/cm^2)	29	0.872 ± 0.148	20	0.873 ± 0.144
T score	21	- 0.514 ± 1.392	8	- 0.813 ± 1.626
Z score	30	- 0.563 ± 1.305	20	- 0.565 ± 1.115
Total Hip (Right)				
BMD (g/cm^2)	28	0.870 ± 0.139	20	0.866 ± 0.173
T score	20	- 0.660 ± 1.325	8	- 0.913 ± 2.122
Z score	29	- 0.583 ± 1.120	20	- 0.615 ± 1.347
BMD Classification	36		20	
BMD normal		21 (58.3)		15 (75)
Osteopenia		10 (27.8)		1 (5)
Osteoporosis[a]		5 (13.9)		4 (20)
Osteoporosis (LS)[b]		2 (5.6)		3 (15)
Osteoporosis (FN)[b]		2 (5.6)		
Osteoporosis (TH)[b]		1 (2.8)		1 (5)

Data expressed as means and standard deviations
LS - lumbar spine, TH – total hip, FN – femoral neck
[a] Overall prevalence of osteoporosis, [b] Prevalence of osteoporosis per region

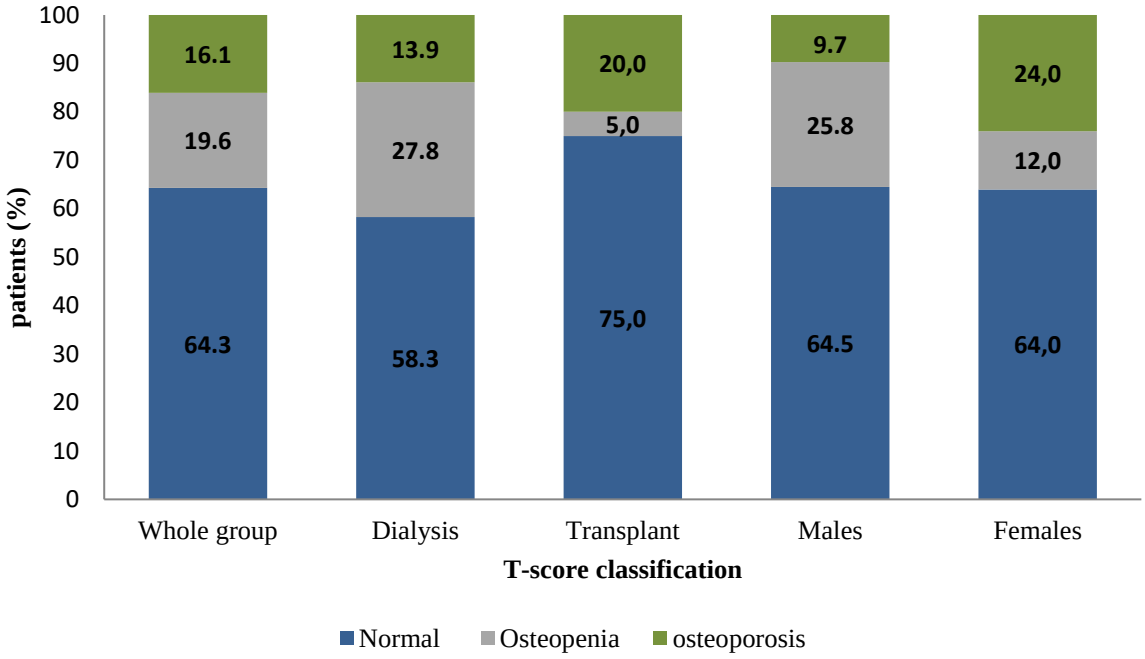

Figure 4.1: Classification of osteoporosis and osteopenia by gender and treatment group

4.3.3 Nutritional status parameters

Body composition and dietary intake data presented in Table 4.3 indicate that the mean BMI of transplant recipients was 24.1 ± 4.5kg/m^2 compared to the higher mean BMI (27.7± 4.5kg/m^2) of transplant candidates.

This was also evident in the higher lean and fat mass components in transplant candidates compared to transplant recipients, although this difference was non-significant. Significantly more transplant recipients had a normal BMI 13/20 (86.7%), compared to transplant candidates 3/36 (16.7%) (p = 0.031), and significantly more transplant candidates were overweight compared to the transplant recipients (50.0% versus 6.7%, p = 0.031).

In terms of micronutrients, mean daily calcium and vitamin D intake was 485.4 ± 227.0 mg and 4.61 ± 4.5mg respectively, with no significant differences between the two treatment groups.

Chi-square analysis showed no significant relationships between osteopenia/osteoporosis with categorical measures of BMI, co-morbidities, gender and vitamin D status. ANOVA applied to

osteopenia/osteoporosis group categories with continuous variables showed that length of time on current treatment modality was significantly longer for participants with osteoporosis than those with normal BMD (p = 0.025). In addition, lean mass was significantly lower for those with osteoporosis compared to normal and osteopenic participants (p = 0.016), while those with a normal BMI had significantly lower LS T-scores than overweight participants.

Correlation analysis showed that absolute BMD and T-scores correlated with BMI at all three skeletal measurement sites. T-scores strongly correlated with lean mass and BMD of the spine (r = 0.707, p = 0.007), and moderately with BMD at the left and right TH (r = 0.455, p = 0.007 and r = 0.420, p = 0.007) respectively. Fat mass did not correlate with osteoporosis or BMD. For the study sample as a whole, serum 25(OH) D did not correlate with BMD or T-scores or Z-scores. Calcium intake was associated with the T-score of the TH. However, when split by treatment group (Table 4.5), there was a significant positive association with dietary calcium intake at all BMD measurement sites for transplant recipients. No association was found between calcium intake and BMD amongst transplant candidates. However, Z-scores of the FN were negatively associated with vitamin D intake (r = -399, p = 0.036).

Table 4.3: Body composition and dietary intake parameters of the study sample

	Whole group N = 56	Transplant candidates n = 36	Transplant recipients n = 20
Anthropometry (n = 33)			
Weight (kg)	71.63 ± 12.99	75.58 ± 11.14	66.89 ± 13.83
Height (cm)	165.93 ± 8.80	165.53 ± 8.46	166.41 ± 9.47
Body mass index (kg/m^2)	26.1 ± 4.80	27.7 ± 4.54[a]	24.1 ± 4.50[a]
- Normal	16 (48.5)	3 (16.7)[b]	13 (86.7)[b]
- Overweight	9 (27.3)	9 (50.0)[c]	1 (6.7)[c]
- Obese class I	6 (18.2)	5 (27.8)	1 (6.7)
- Obese class II	2 (6.1)	1(5.6)	0 (0.0%)
DEXA body composition (n = 34)			
Total mass (kg)	65.36 ± 20.70	65.93 ± 25.56	64.73 ± 14.17
Lean mass (kg)	48.08 ± 8.39	49.5 ± 7.78	46.4 ± 9.00
Fat mass (kg)	19.48 ± 11.41	22.3 ± 10.82	16.3 ± 11.54
Dietary intake			
Vitamin D intake (mcg)	4.61 ± 4.51	5.44 ± 4.88	3.10 ± 3.37
Calcium intake (mg)	485.43 ± 277.00	480.94 ± 280.80	493.5 ± 277.03

Data given as means and frequency and means and standard deviation

[a] BMI of transplant candidates was significantly higher than transplant recipients (t = -2.264, p = 0.031)

[b] Significantly more transplant recipients had a normal BMI compared to transplant candidates (p = 0.031)

[c] Significantly more transplant candidates were overweight compared to the transplant recipients (p = 0.031).

Table 4.4: Correlations between selected variables and BMD, T-scores and Z- scores of the spine, total hip and femoral neck for the whole group

Variable		Bone mineral density variable		Pearson's correlation	
	n	**site**	**BMD/T-score/Z-score**	**r**	**P**
Age (years)	33	TH (left)	Z-score	0.319	0.24*
Current treatment duration (years)[a]	13	FN (left)	T-score	- 0.401	0.031*
25 (OH) Vitamin D		NS	NS	NS	NS
BMI (kg/m^2)	13	LS	T-score	0.575	0.040*
	13	FN (left)	T-score	0.638	0.019*
	13	FN (right)	T-score	0.688	0.009**
	13	TH (left)	T-score	0.578	0.038*
	13	TH (right)	T-score	0.594	0.032*
Fat mass (kg)		NS	NS	NS	NS
Lean mass (kg)[b]	13	LS	T-score	0.707	0.007**
	34	TH (left)	BMD	0.455	0.007**
	34	TH (right)	BMD	0.420	0.013*
Calcium intake (mg)	29	TH (left)	T-score	0.368	0.049*
Vitamin D intake (mcg)		NS	NS	NS	NS

BMD in g/m^2

[a] significantly greater for osteoporosis participants than those classified as normal ($p = 0.025$)

[b] significantly higher in normal and osteopenia than in osteoporosis ($p = 0.16$)

* correlation is significant at $p < 0.05$, ** correlation is significant at $p < 0.01$

Table 4.5: Correlations between dietary calcium and vitamin D intake and BMD, T-scores and Z-scores of the spine, total hip and femoral neck per treatment group

Measurement site	Transplant candidates n = 36				Transplant recipients n = 20			
	Calcium	Vitamin D			Calcium			Vitamin D
		n	r	p	*n*	r	p	
Lumbar Spine (L1—L4)	NS		NS					
BMD (g/cm^2)					20	0.509*	0.022	NS
T-score					8	0.826*	0.012	
Z-score					20	0.495*	0.027	
Femoral Neck (Left)	NS		NS					NS
BMD (g/cm^2)					19	0.686**	0.001	
T-score					7	0.833*	0.003	
Z-score					19	0.645**	0.003	
Femoral Neck (Right)	NS		NS					
BMD (g/cm^2)					19	0.643**	0.003	NS
T-score					7	0.816*	0.025	
Z-score		28	- 399*	0.036	19	0.608**	0.006	
Total Hip (Left)	NS		NS					
BMD (g/cm^2)					20	0.682**	0.001	NS
T-score					8	0.808*	0.015	
Z-score					20	0.623**	0.003	
Total Hip (Right)	NS		NS					
BMD (g/cm^2)					20	0.673**	0.001	NS
T-score					8	0.831*	0.011	
Z-score					20	0.629**	0.003	

* correlation is significant at $p < 0.05$, ** correlation is significant at $p < 0.01$

4.4 Discussion

This study investigated the prevalence of osteopenia and osteoporosis in HIV-positive transplant candidates on dialysis, i.e. awaiting a transplant, and transplant recipients from a HIV-positive donor.

Amongst transplant candidates, 13.9% were classified as osteoporotic or per skeletal region: 5.6% (LS); 5.6% (FN); and 2.8% (TH). This finding is comparable to the 12.7% reported among 63 Taiwanese HD participants (21), but slightly lower than the 14.3% (LS) and 21.4% (FN) observed in a smaller sample (n = 37) of HD patients in Greece (22). Some HD populations samples report even higher frequencies of osteoporosis at 33.0% and 34.0% (23,24). In the sample of Greek subjects, twice as many (27.8%) were osteopenic, while also bearing similarities to other HD samples that reported two and up to a five times higher frequency of osteopenia than osteoporosis among those on haemodialysis (22).

By comparison, the transplant recipient group had more participants with osteoporosis (20.0%) than the transplant candidates. This is likely, given the added effect of immunosuppressants on bone already compromised by CKD (25). Previous studies on kidney transplant recipients, reported the presence of osteoporosis among 22.0% to 26.0% of patients (26,27) or regional values of 12.4% to 21.3% in the LS and between 9.8% to 45.1% in the FN (28,29). In the present study, osteoporosis by skeletal region among transplant recipients was 15.0% (LS), and 5.0% (TH). Surprisingly, only one transplant recipient (5.0%) presented with osteopenia, in sharp contrast to the high prevalence of osteopenia (36.3% - 54.5%) reported among other transplant recipients (26-28). As the present study documented that 75.0% of transplant recipients had a normal BMD, this finding is unexpected given the presence of comorbid HIV, which in isolation is associated with lowered BMD (7). Typically, 67.0% of HIV-positive individuals have a reduced BMD (8). The findings of the current study can be explained in the context of the protective, as well as risk factors this patient group are exposed to.

The length of treatment time either as transplant awaiting candidates on dialysis, or number of years post transplant was of significance in the present study. The treatment duration for the whole group correlated positively with osteoporosis and BMD T-scores at the right FN. The length of time on the current treatment was significantly longer for osteopenia participants than for those unaffected by bone disease. The effect of treatment duration on bone health has been previously demonstrated (4), although not consistently so (5,21,27). This effect was aptly

described in a cohort of 101 039 transplant awaiting patients where significant differences in fracture risks were found between the two groups, in that kidney transplant recipients had a higher fracture risk compared to those on dialysis in the critical period immediately following a transplant (30). This finding corresponds to severe bone loss experienced due to high doses of immunosuppressants used in induction therapy in the early post-transplant period (31). This risk decreases over time following a transplant and the improvement of pre-transplant bone risk factors. Between one to three years post-transplant, the risk is lowered below those on dialysis (30), and normalized ten years post-transplant (32). In the pre-transplant population, waiting time is also an important consideration as patients who spent more than one year on dialysis had a greater fracture risk after a transplant than those who were on dialysis for less than three months (30).

In the general population, traditional risk factors for the development of osteoporosis include aging, female sex (particularly after menopause) and ethnicity (33). Regarding age, the current study found a weak association between BMD Z-score and age, probably due to the overall low mean age of the study sample. Although more women were diagnosed with osteoporosis, there was no significant association with BMD or osteoporosis and gender, or significant differences in these variables between males and females. This is possibly due to the fact that the females in the current study, with a mean age 42.9 ± 8.6 years, were younger than the average menopausal age of 49.2 years for black South African women, and still young enough before differences between the sexes become more pronounced (34,35). Some evidence of this phenomenon was documented in other studies. For example, no association was found between BMD and age or gender among young Iranian dialysis (mean age 38.0 ± 10.6 years) and transplant participants (39.0 ± 11.8 years) (5), while Huang et al found an inverse relationship between BMD and age among their older (55.7 ± 13.5 years) HD group (21). Similarly, Kadam et al did not find a significant deterioration in BMD with age in healthy pre-menopausal women even among those older than 50 years of age, but a significant decline following menopause (36). Lastly, 92.9 % of our study sample was black for whom higher BMDs have consistently been observed when compared to Caucasian and Asian populations (14, 37, 38). A possible reason for this disparity is related to differences in body weight as was documented in a study among black and white South African women (39).

It is recognized that there is a relationship between weight, BMI and BMD (40). Higher body weights accompany higher hip and vertebral BMDs. Hence, overweight and obese individuals are at a lower risk of osteoporosis compared to their normal weight counterparts (BMI < 25.0

kg/m^2) (41). This was also evident in the current study, where participants with a normal BMI had significantly lower T-scores at the LS than overweight participants. In addition, for all participants BMI correlated strongly to BMD at all measurement sites.

Body weight is a combination of muscle and fat mass, and a recent meta-analysis that weighed the influence of each component on BMD, reported that both fat mass and lean mass have a relationship with BMD. However the cumulative results of 44 studies including 20 226 participants, showed a stronger association between lean mass and BMD than fat mass (40). Likewise, in the current study, BMD positively correlated with lean mass, with a greater strength of association at the LS. However, the same did not hold true for fat mass. This is an important finding, as it supports the importance of the muscle-bone unit as a potentially modifiable risk factor in skeletal health. This relationship, viewed as a biomechanical model of load-bearing muscle mass on bone (38), highlights the importance of skeletal muscle preservation through exercise and diet to delay bone loss (42).

Preservation of muscle mass in CKD is challenging due to imbalances in synthesis and breakdown of muscle mass (43). Therefore muscle preservation strategies should optimise management of these abnormalities as well as support muscle synthesis. For example, correction of metabolic acidosis with alkali supplementation has demonstrated positive effects on muscle mass (44). Appropriate exercise can improve muscle mass, strength and balance to reduce falls (42,45,46) as exercise stimulates protein synthesis, which in turn will require adequate dietary support. This however, will necessitate an individualised approach to ensure that protein intake is of adequate quantity and quality, and appropriately timed to support muscle synthesis (42). Apart from protein, several other foods and nutrients have recently been linked to bone health (47). Two micronutrients synonymous with skeletal health are vitamin D and calcium.

Consistent with findings in dialysis (22), kidney transplant (48) and HIV-positive populations (49,50) elsewhere, the majority of the current study's study sample did not have sufficient 25 (OH)D levels. Vitamin D deficiency was the most prevalent among transplant recipients where only 11.1% had optimal levels. There is a longstanding relationship between vitamin D and BMD (17,51). Vitamin D deficiency has a negative impact on calcium balance with secondary hyperparathyroidism affecting bone matrix and mineralization, resulting in osteomalacia, osteoporosis and fractures (17). Studies investigating the link between 25(OH)D and BMD yield conflicting results, by showing either a significant association between 25(OH)D and BMD (30,52), or no association at all (53) in different patient groups. One of the discrepancies in the

association between 25(OH)D and BMD is based on race and ethnicity, as noted in a study conducted among adult males, where a significant association between serum 25(OH)D and BMD in white males, but no correlation in black males was found (54). Similarly, the present study found no association between serum 25(OH) D and BMD or osteoporosis in this predominantly black study sample. The preservation of skeletal integrity despite suboptimal 25(OH)D in the black population, is possibly due to the fact that black ethnicity may offer more resistance to the bone-resorption process (55). Another contributor to vitamin D deficiency is inadequate UV exposure, although this is an unlikely factor due to the geographic location of the current study sample in the Southern hemisphere. However, this phenomenon does not appear to be specific to patients with a chronic disease. In a study conducted among healthy adults in Hawaii, found that participants had low vitamin D levels despite exposure to the tropical climate (56).

The vitamin D intake of transplant candidates was close to recommended levels, although their daily intake requirements should ideally be determined based on serum calcium, phosphate and PTH levels (57), and will therefore require an individual approach. With the exception of a weak association at the FN amongst transplant candidates, there was no association between dietary vitamin D intake and BMD at any other site for either treatment group. Optimising 25(OH)D still deserves due consideration in bone health, as a vitamin D deficiency increases the likelihood of falls through its negative affect on physical ability (58) and strength (49,58,59). More importantly, vitamin D deficiency is independently associated with disease progression in HIV (60), and reduced glomerular filtration rate (GFR), one year post transplant (61). It is therefore kidney function in the first year post-transplant that influences long term transplant outcome (62).

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, recommend 500mg of calcium from dietary sources, although a daily intake of 2000mg/day for peritoneal and haemodialysis patients should not be exceeded to prevent hypercalcaemia and vascular calcification (57,63,64). The dietary calcium intake in this study's dialysis group (480.94 ± 280.80mg/day) closely matched this amount, but not more recent recommendations of 800mg to 1000mg/day (65). Dietary calcium was not associated with BMD at any site for transplant candidates. Similar results were described among haemodialysis patients in the UK where no association was found between dietary calcium and BMD, yet a positive correlation existed between calcium in the form of supplements and BMD at the FN. The lack of association was presumed to be due to low dietary calcium intake of less than 500mg (66). This reason is less

probable in the current study, as transplant recipients who had a similar dietary calcium intake of 493.5 ± 277.03mg/day was positively associated with BMD at all sites. Transplant recipients consumed a mean daily calcium intake of 493.5 ± 277.0 mg/day, which was lower than the daily calcium intake of 623.2 ± 208.2mg (67) and 868.0 ± 387.0mg (68) in transplant recipients one month and three years post- transplant respectively. This daily intake was much lower than the recommended daily intake of 1200-1500mg/day (57), and is a concern as calcium malabsorption, together with 25(OH) D deficiency, can cause further bone deterioration (63). Given the association with BMD, it could potentially be one of many contributors to the higher prevalence of osteoporosis in the transplant group. However, this finding requires further investigation. Dietary adequacy can be improved through nutrition education, although monitored supplementation may be necessary (63). Vitamin D and calcium supplements have been used with some success in decreasing the extent of bone loss immediately post-transplant (69).

This study is limited by its overall small sample size and partial availability of data due to differences in bone images, depth of information and reporting styles from the different assessment centres. The cross-sectional design is also limiting in terms of investigating causal relationships. Future studies should consider a prospective design that includes pre-transplant BMD with regular follow-up post- transplant to monitor change in BMD over time as well as the effects of intervention. A single 24-hour recall is less likely to be a valid reflection of habitual intake, lowering the likelihood of significant correlations with the micronutrients. On the other hand however, the intake information on calcium and vitamin D still provides some constructive dietary insight. The interpretation of results were also limited by the lack of certain biochemical parameters including PTH, bone markers and serum calcium, which were not assessed as they were beyond the resources of the current study. Moreover history of supplement use, a physical activity questionnaire and menopausal status would also add value to data interpretation, but would have contributed to respondent fatigue. Nevertheless, this study makes a significant contribution to the limited data on bone health in HIV especially in Sub-Saharan Africa (70), and provides the first insight into the prevalence of osteoporosis in HIV-positive transplant candidates and recipients from a HIV-positive donor.

In summary, the prevalence of osteoporosis is similar to, if not slightly lower than that of transplant recipients and dialysed patients reported elsewhere. The higher prevalence of osteopenia among transplant candidates highlight the importance of introducing preventative strategies prior to transplant, given the rapid deterioration of BMD post-transplant and the

difficulty associated with treating osteoporosis after onset. The link between calcium intake and lean mass with BMD are important and optimistic findings, in that diet and exercise are potentially safe, cost effective interventions that can curb bone loss. Hence, a lack of attention to diet and exercise will contribute to premature bone loss and a higher fracture risk.

4.5 References

1. Weisinger JR, Carlini RG, Rojas E, Bellorin-Font E. Bone disease after renal transplantation. Clin J Am Soc Nephrol. 2006; 1(6): 300–1313.

2. Mitterbauer C, Oberbauer R. Bone disease after kidney transplantation. Transpl Int. 2008; 21(7): 615-624.

3. Lima GA, Paranhos-Neto Fde P, Pereira GR, Gomes CP, Farias ML. Osteoporosis management in patient with renal function impairment. Arq Bras Endocrinol Metabol. 2014; 58(5): 530-539.

4. Avramovski P, Sikole A. The progression of bone mineral density loss in dialysis patients compared with the general population. Korean J Intern Med. 2012; 27(4): 436-442.

5. Nouri-Majalan N, Sanadgol H, Rahimian M, Soleimani H. Bone mineral density in kidney transplant recipients and patients on hemodialysis. A comparison with healthy individuals. IJKD. 2008; 2(3): 154-159.

6. Cazanave C, Dupon M, Lavignolle-Aurillac V, Barthe N, Lawson-Ayayi S, Mehsen N, Mercié P, Morlat P, Thiébaut R, Dabis F for the Groupe d' Epidémiologie Clinique du SIDA en Aquitaine. Reduced bone mineral density in HIV-infected patients: prevalence and associated factors. AIDS. 2008; 22(3): 395-402.

7. Dolan SE, Huang JS, Killilea KM, Sullivan MP, Aliabadi N, Grinspoon S. Reduced bone density in HIV-infected women. AIDS. 2004; 18(3): 475-483.

8. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS. 2006; 20(17): 2165–2174.

9. McComsey GA, Tebas P, Shane E, Yin MT, Overton ET, Huang JS, Aldrovandi GM, Cardoso SW, Santana JL, Brown TT. Bone Disease in HIV Infection: A practical review and recommendations for HIV care providers. Clin Infect Dis. 2010; 51(8): 937-946.

10. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JMAH, Miller MD, Coakley DF, Lu B, Toole JJ, Cheng AK for the 903 Study Group. Efficacy and safety of Tenofovir DF vs Stavudine in combination therapy in antiretroviral-naive patients. JAMA. 2004; 292(2): 191-201.

11. Mondy K, Yarasheski K, Powderly WG, Whyte M, Claxton S, DeMarco D, Hoffmann M, Tebas P. Longitudinal evolution of bone mineral density and bone markers in human immunodeficiency virus—infected individuals. Clin Infect Dis. 2003; 36(4): 482-490.

12. Premaor MO, Compston JE. The hidden burden of fractures in people living with HIV. JBMR Plus. 2018; 2(5): 247–256.

13. World Health Organization. Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation (WHO Technical Report Series 894). [Online]; 2000. [cited 12/03/2018]. Available from: https//Obesity: preventing and managing the global epidemic. Report of a WHO Consultation (WHO Technical Report Series 894). Geneva; 2000.

14. Wilkin LD, Jackson MC, Sims TD, Haddock BL. Racial/ethnic differences in bone mineral density of young adults. Int J Exerc Sci. 2010; 3(4): 197-205.

15. Bradford R. DXA scanning to diagnose osteoporosis: Do you know what the results mean? Cleve Clin J Med. 2003; 70(4): 353-360.

16. Sözen T, Lale Özışık L, Başaran NC. An overview and management of osteoporosis. Eur J Rheumatol. 2017; 4(1): 46–56.

17. Holick MF. The vitamin D epidemic and its health consequences. J Nutr. 2005; 135(11): 2739S–2748S.

18. Abdu A, Naidoo S, Naicker S. The nutritional status of continuous ambulaory peritoneal dialysis patients at a Johannesburg hospital. SAJCN. 2011; 24(3): 150-153.

19. Nelson M, Bingham SA. Assessment of food consumption and nutrient intake. In: Margetts BM, Nelson M, editor. Design concepts in nutritional epidemiology. Oxford: Oxford University Press; 1997. p. 123-169.

20. Senekal M, Steyn NP. Food Photo Manal. Parow: Medical Research Council. 2004

21. Huang GS, Chu TS, Lou MF, Hwang SL, Yang RS. Factors associated with low bone mass in the hemodialysis patients. BMC Musculoskelet Disord. 2009; 10(60).doi: 10.1186/1471-2474-10-60.

22. Polymeris A, Doumouchtsis K, Grapsa E. Bone mineral density and bone metabolism in hemodialysis patients. Correlation with PTH, 25OHD3 and leptin. Nefrologia. 2012; 32(1): 73 -7 8.

23. Brunerová L, Ronová P, Verešová J, Beranová P, Potoèková J, Kasalický P, Rychlík I. Osteoporosis and Impaired Trabecular Bone Score in Hemodialysis Patients. Kidney Blood Press Res. 2016; 41: 345 - 354.

24. Malluche HH, Davenport DL, Cantor T, Monier-Faugere MC. Bone mineral density and

serum biochemical predictors of bone loss in patients with CKD on dialysis. Clin J Am Soc Nephrol. 2014; 9(7): 1254 - 1262.

25. Song L, Xie X, Peng L, Yu S, Peng Y. Mechanism and treatment strategy of osteoporosis after transplantation. Int J Endocrinol. 2015: 280164. doi: 10.1155/2015/280164

26. Alis G, Alis M, Erturk T, Karayagiz AH, Berber I, Cakir U. Evaluation of bone disease in kidney transplant recipients. Transplant Proc. 2017; 49(3): 509-511.

27. Ahmadpoor P, Reisi S, Makhdoomi K, Ghafari A, Sepehrvand N, Rahimi E. Osteoporosis and related risk factors in renal transplant recipients. Transplant Proc. 2009; 41(7): 2820-2822.

28. Savaj S, Ghods FJ. Vitamin D, parathyroid hormone, and bone mineral density. IJKD. 2012; 6(4): 295-299.

29. Najar M S, Mir MM, Muzamil M. Prevalence of osteoporosis in patients with chronic kidney disease (stages 3–5) in comparison with age- and sex-matched controls: A study from Kashmir Valley Tertiary Care Center. Saudi J Kidney Dis Transpl. 2017; 28: 538-544.

30. Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL, Kestenbaum BR, Stehman-Breen C. Risk of hip fracture among dialysis and renal transplant recipients. JAMA. 2002; 288(23): 3014-3018.

31. Julian BA, Laskow DA, Dubovsky J, Dubovsky EV, Curtis JJ, Quarles LD. Rapid loss of vertebral mineral density after renal transplantation. N Engl J Med. 1991; 325(8): 544-550.

32. Carlini RG, Rojas E, Weisinger JR, Lopez M, Martinis R, Arminio A, Bellorin-Font E. Bone disease in patients with long-term renal transplantation. Am J Kidney Dis. 2000; 36(1): 160-166.

33. Lin X, Xiong D, Peng Y, Sheng Z, Wu X-Y, Wu X-P, Wu F, Yuan L, Liao E. Epidemiology and managemet of osteoporosis in the People's Republic of China: Current perspectives. Clin Interv Aging. 2015; 10: 1017-1033.

34. Hunter DJ, Sambrook PN. Bone loss: Epidemiology of bone loss. Arthritis Res. 2000; 2(6): 441–445.

35. Thomas F, Renaud F, Benefice E, De Meeüs T , Guegan JF. International variability of ages at menarche and menopause: patterns and main determinants. Hum Biol. 2001; 73(2): 271-290.

36. Kadam NS, Chiplonka SA, Khadilka AV, Khadilkar VV. Prevalence of osteoporosis in apparently healthy adults above 40 years of age in Pune City, India. Indian J Endocrinol Metab. 2018; 22(1): 67-73.

37. Zengin A, Pye SR, Cook MJ, Adams JE, Wu FC, O'Neill TW, Ward KA. Ethnic differences in bone geometry between White, Black and South Asian men in the UK. Bone. 2016; 91: 180-185.

38. Barondess DA, Nelson DA, Schlaen SE. Whole body bone, fat, and lean mass in Black and White Men. J Bone Miner Res. 1997; 12: 967-971.

39. Conradie M, Conradie MM, Kidd M, Hough S. Bone density in black and white South African women: contribution of ethnicity, body weight and lifestyle. Arch Osteoporos. 2014; 9: 193. doi: 10.1007/s11657-014-0193-0

40. Ho-Pham LT, Nguyen UDT, Nguyen TV. Association between lean mass, fat mass, and bone mineral density: A meta-analysis. J Clin Endocrinol Metab. 2014; 99(1): 30-38.

41. Salamat MR, Salamat AH, Abedi I, Janghorbani M. Relationship between weight, body mass index, and bone mineral density in men referred for dual-energy X-ray absorptiometry scan in Isfahan, Iran. J Osteoporos. 2013; doi: 10.1155/2013/205963

42. Agostini D, Zeppa SD, Lucertini F, Annibalini G, Gervasi M, Marini CF, Piccoli G, Stocchi V, Barbieri E, Sestili P. Muscle and bone health in postmenopausal women: Role of protein and vitamin D supplementation combined with exercise training nutrients. 2018; 10(1103): doi:10.3390/nu10081103.

43. Wang XH, Mitch WE. Mechanisms of muscle wasting in chronic kidney disease. Nat Rev Nephrol. 2014; 10(9): 504–516.

44. Stein A, Moorhouse J, Iles-Smith H, Baker F, Johnstone J, James G, Troughton J, Bircher G, Walls J. Role of an improvement in acid-base status and nutrition in CAPD patients. Kidney Int. 1997; 52(4): 1089-1095.

45. Chen W, Abramowitz MK. Treatment of metabolic acidosis in patients with CKD. Am J Kidney Dis. 2014; 63(2): 311-317.

46. Workeneh BT, Mitch WE. Review of muscle wasting associated with chronic kidney disease. Am J Clin Nutr. 2010; 91(4): 1128S–1132S.

47. Higgs J, Derbyshire E, Styles K. Nutrition and osteoporosis prevention for the orthopaedic surgeon: a wholefoods approach. EFORT Open Rev. 2017; 2: 300-308.

48. Ewers B, Gasbjerg A, Moelgaard C, Frederiksen AM, Marckmann P. Vitamin D status in kidney transplant patients: need for intensified routine supplementation. Am J Clin Nutr. 2008; 87(2): 431-437.

49. Allavena C, Delpierre C, Cuzin L, Rey D, Viget N, Bernard J, Guillot P, Duvivier C, Billaud E, Raffi F. High frequency of vitamin D deficiency in HIV-infected patients: effects of HIV-related factors and antiretroviral drugs. J Antimicrob Chemother. 2012; 67(9):

2222-2230.

50. Dao CN, Patel P, Overton ET, Rhame F, Pals SL, Johnson C, Bush T, Brooks JT, Study to understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN) investigators. Low vitamin D among HIV-infected adults: Prevalence of and risk factors for low vitamin D Levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the US general population. Clin Infect Dis. 2011; 52(3): 396-405.

51. Gennari C. Calcium and vitamin D nutrition and bone disease of the elderly. Public Health Nutr: 4(2B), 547±559. 2001; 4(2B): 547-559.

52. Lips P, Tu Duong T, Oleksik A, Black D, Cummings S, Cox D, Nickelsen T. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of Raloxifene evaluation clinical trial. J Clin Endocrinol Metab. 2001; 86(3): 1212–1221.

53. Labronici PJ, Blunck SS, Lana FR, Esteves BB, Franco JS, Fukuyama JM, Pires RES. Vitamin D and its relation to bone mineral density in postmenopause women. Revista Brasileira de Ortopedia (English Edition). 2013; 48(3): 228-235.

54. Hannan MT, Litman HJ, Araujo AB, McLennan CE, McLean RR, McKinlay JB. Chen TC, Holick MF. Serum 25-hydroxyvitamin D and bone mineral density in a racially and ethnically diverse group of men. J Clin Endocrinol Metab. 2008; 93(1): 40–46.

55. Cosman F, Morgan DC, Nieves JW, Shen V, Luckey MM, Dempster DW, Lindsay R, Parisien M. Resistance to bone resorbing effects of PTH in black women. J Bone Miner Res. 1997; 12(6): 958–966.

56. Binkley N, Novotny R Krueger D, Kawahara T, Daida YG, G. Lensmeyer G, Hollis BW, Drezner MK. Low vitamin D status despite abundant sun exposure. J Clin Endocrinol Metab. 2007; 92(6): 2130–2135.

57. National Department of Health, Directorate: Nutrition. National Renal Nutrition Practice Guidelines for Adults.[Online];2018 [cited 24/01/2019]. Available from: http://www.saspen.com/Websites/saspen/images/Renal%20Nutrition%20web.pdf

58. Houston DK, Cesari M, Ferrucci L, Cherubini A, Maggio D, Bartali B, Johnson MA, Schwartz GG, Kritchevsky SB. Association between vitamin D status and physical performance: the InCHIANTI Study. J Gerontol A Biol Sci Med Sci. 2007; 62(4): 440–446.

59. Foo LH, Zhang Q, Zhu K, Ma G, Hu X, Greenfield H, Fraser DR. Low vitamin D status has an adverse influence on bone mass, bone turnover, and muscle strength in Chinese adolescent girls. J Nutr. 2009; 139(5): 1002–1007.

60. Viard J, Souberbielle J, Kirk O, Reekie J, Knysz B, Losso M, Gatell J, Pedersen C, Bogner JR, Lundgre JD, Mocroft A, for the EuroSIDA Study Group. Vitamin D and clinical disease

progression in HIV infection: Results from the EuroSIDA study. AIDS. 2011; 25(10): 1305-1315.

61. Bienaimé F, Girard D, Anglicheau D, Canaud G, Souberbielle JC, Kreis H, Noël LH, Friedlander G, Elie C, Legendre C, Prié D. Vitamin D status and outcomes after renal transplantation. J Am Soc Nephrol. 2013; 24(5): 831-841.

62. HariharaHariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int. 2002; 62(1): 311-318.

63. Yu RW, Faull RJ, Coates PTH, Coates PS. Calcium supplements lower bone resorption after renal transplant. Clin Transplant. 2012; 26: 292–299.

64. Teruela JL, Lucas MF, Mendiola NR. Calcium supplements in chronic renal failure. Nefrologia. 2009; 29(1): 10-12.

65. Gallant KMH, Spiegel DM. Calcium balance in chronic kidney disease. Curr Osteoporos Rep. 2017; 15(3): 214–221.

66. Taal MW, Masud T, Green D, Cassidy MJD. Risk factors for reduced bone density in haemodialysis patients. Nephrol Dial Transplant. 1999; 14(8): 1922–1928.

67. Rho MR, Lim JH, Park JH, Han SS, Kim YS, Lee YH, Kim WG. Evaluation of nutrient intake in early post kidney transplant recipients. Clin Nutr Res. 2013; 2(1): 1-11.

68. Heaf J, Jakobsen U, Tvedegaard E, Kanstrup IL, Fogh-Andersen N. Dietary habits and nutritional status of renal transplant patients. J Ren Nutr. 2004; 14(1): 20-25.

69. de Sévaux RGL, Hoitsma AJ , Corstens FHM, Wetzels JFM. Treatment withVitamin D and calcium reduces bone loss after renal transplantation: A randomized study. J Am Soc Nephrol. 2002; 13(6): 1608-1614.

70. Compston J. HIV infection and osteoporosis. Bonekey Rep. 2015; 4(636). doi: 10.1038/bonekey.2015.3

CHAPTER 5
CORRELATION OF ANTHROPOMETRIC MEASURES WITH DUAL ENERGY X-RAY ABSORPTIOMETRY

ABSTRACT

Background: The evaluation of body composition (BC) is important for observing changes in musculature and adiposity. Obesity and low muscle mass are associated with adverse outcomes in kidney transplant candidates and recipients. Therefore, practical measures of BC, with a high degree of accuracy are essential in the assessment of nutritional status.

Objective: To correlate anthropometric measures with dual-energy X-ray absorptiometry (DEXA) as a reference standard in kidney transplant candidates and recipients.

Methods: 34 clinically stable kidney transplant candidates and recipients infected with HIV participated in this cross-sectional study. Body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) and mid arm muscle circumference (MAMC) were compared to DEXA derived percentage body fat (%BF), truncal fat (TF) and visceral adipose tissue (VAT). Mid arm muscle circumference (MAMC) was correlated with DEXA lean indices namely, lean mass (LM), lean mass index (LMI) and appendicular lean mass index (ALMI).

Results: Pearson's correlation coefficient between BMI and %BF was strong ($r = 0.773$, $p < 0.001$). There was a greater statistical significance in the association between WC with TF ($r = 0.799$, $p = 0.00$) and VAT ($r = 0.885$, $p < 0.001$), than WHtR with TF and VAT ($r = 0.778$, $p = 0.013$ and $r = 0.830$, $p < 0.001$). There was a lack of significant correlation between WHR and TF or VAT. MAMC correlated best with ALMI ($r = 0.511$, $p = 0.011$).

Conclusion: There was a strong significant correlation between anthropometric measures of adiposity and musculature with the reference standard DEXA. In particular, between BMI and %BF and WC with TF and VAT. MAMC correlated best with DEXA lean indices such as ALMI.

Keywords: Kidney transplant candidates, Kidney transplant recipients, Human immunodeficiency virus (HIV), dual-energy X-ray absorptiometry (DEXA), anthropometry, body composition

5.1 Introduction

Body composition (BC) is an important component of physical health (1). Substantial changes in BC are known to affect morbidity and mortality in kidney transplant candidates and recipients (2,3,4). BMI is the most widely used indicator of nutritional status and is a surrogate measure of adiposity. However, it is unable to distinguish fat from muscle mass or regional distribution of fat (5). This differentiation is important to identify transplant candidates and recipients at risk of adverse outcomes. For example, under-nutrition characterized by a low body mass index (BMI), predisposed candidates to an increased mortality risk while awaiting transplant (2), or greater graft loss and post-transplant mortality (6). A higher BMI was associated with a lower mortality risk (7,8). This protective advantage is attributed to a higher muscle mass (3).

Among transplant recipients, overall obesity negatively impacts graft and patient outcomes in some (4,9) although not all (10) transplant recipients. However, central obesity and excess visceral adipose tissue (VAT), is associated with increased cardio-metabolic risk in the general population (11,12) and is related to a higher all-cause mortality following transplantation (13). Less is known about the implications of co-existing human immunodeficiency virus (HIV) on BC in kidney transplant candidates and recipients. However, it is likely to be morphologically significant as HIV and antiretrovirals are related to muscle wasting and lipodystrophy (14).

These links between adiposity, muscularity and clinical outcomes that have an impact on kidney transplantation are well described, and clearly necessitates the inclusion of in-depth BC measures for assessment, monitoring and prognosis. It is therefore essential that the methods used, provide information with a high degree of accuracy (15). Anthropometry is one of the more common BC methods (16) and is known to provide valid information on fat and muscle composition when compared to magnetic resonance imaging (17). Waist circumference (WC), waist-to hip-ratio (WHR) and waist-to-height ratio (WHtR) are commonly used proxy measures of abdominal obesity and the health risks accompanying obesity (18). MAMC for example, is one of several proxy measures to estimate lean body mass (19). With the measurement of anthropometric indices however, there is potential for human error as it requires skill and equipment of a high quality (20).

Dual-energy X-ray absorptiometry (DEXA) accurately measures BC, in agreement with more detailed methods (21). However, it is costly, and not always feasible for use in bedside and field

investigations. Moreover it involves some, albeit slight, exposure to X-ray radiation (22). It is therefore often used as a reference, to verify less precise methods (23), as is the focus of the current study. Recognising that measurement accuracy is crucial to correctly identify and treat the individual, or to facilitate decisions and policy making at a group level (24), this study aimed to verify selected BC measures determined through anthropometry, against DEXA derived BC as the reference standard, in HIV-infected kidney transplant candidates and recipients.

5.2 Methods

5.2.1 Participants

For this cross-sectional study, prospective participants were recruited through the kidney transplant programme for HIV-infected patients at Groote Schuur Hospital, Cape Town. Participants were recruited based on whether they were transplant recipients or were awaiting a transplant and hence managed on who have received a kidney from a HIV-infected donor; and (ii) HIV-infected transplant candidates who were on the waiting list to receive a kidney from a HIV-infected donor. Prospective participants were contacted telephonically or at their respective outpatient clinics and invited to undergo a dual-energy X-ray absorptiometry (DEXA) evaluation. Participants were eligible for inclusion if they were clinically stable at the time of recruitment. Exclusion criteria included those who declined to participate, missed several DEXA appointments (typically two or more without reason) or were not willing to travel the distance to the radiology centre. Although 54 participants agreed to undergo the DEXA assessment, only three radiology centres were able to provide the measurement of body composition which 34 participants had access to. Before screening, written informed consent was obtained and participants were re-reimbursed for travel expenses incurred. This cross-sectional study was approved by the University of KwaZulu-Natal's Biomedical Research Ethics Committee (Approval number BE 327/13).

5.2.2 Socio-demographic and clinical information

Socio-demographic information was collected using an interviewer-administered structured questionnaire developed for the purpose of the study. Clinical information was obtained from medical records or during participant interviews.

5.2.3 DEXA Body composition measurements

Participants were assessed with the Hologic Discovery W (MA, USA) and the GE Lunar Prodigy (Advance, GE Healthcare, USA). All DEXA assessments were conducted by radiographers with relevant training and experience regarding the positioning of participants and machine operation according to standard procedures (1). DEXA provides information on bone, lean and fat mass with BC information based on X-ray beam variations as it passes through body matter of different densities. Two energy fields separates soft tissue into lean and fat components, thereby enabling the measurement of whole body and regional BC (25). This includes raw values and indices indicating total and regional fat and lean mass distribution. Adiposity indices used as reference values were percentage body fat (%BF), truncal fat (TF) and visceral adipose tissue (VAT). BF is calculated from fat mass divided by total mass and expressed as a percentage. TF in kg, representing abdominal fat, is presented in kilograms (kg) and VAT as area in cm^2. Lean mass reference values were lean mass (LM), lean mass index (LMI) and appendicular mass index (AMI). LM (kg) represents fat free and bone free mass, but includes muscle, skin, tendons, and connective tissue. LMI is LM adjusted for height and is defined as total LM divided by height (H) in m^2. ALMI is calculated from the lean mass of the arms and legs in kg divided by H (m^2). Appendicular lean mass refers to soft tissue found in arms and legs. A large percentage of whole body skeletal muscle is found in the arms and legs while a large percentage of appendicular lean tissue is present as skeletal muscle. This represents about 75% of whole body skeletal muscle (23).

5.2.4 Anthropometric measurements

Although dietitians that collected data for the study, served as fieldworkers, and were experienced in taking anthropometric measurements, they received a refresher training session which was followed by a post-training test to ensure standardisation of measurement techniques and thereby reduce inter fieldworker variability. Both the training and test were accredited for continuing education purposes with the Health Professions Council of South Africa. All body measurements namely weight (WT), height (Ht), triceps skinfold thickness (TSF), mid upper arm circumference (MUAC), waist circumference (WC) and hip circumference (HC) were measured using protocols described in the National Health and Nutrition Examination Survey (NHANES) and is described in detail in the NHANES anthropometry procedure manual (26). Heights in centimetres (cm) and weight (kg) were obtained using equipment already present at various outpatient and dialysis centres. Weight measurements on dialysis participants were

taken post dialysis (dry weight), on the non-access arm (19). Circumference measurements (cm) and TSF in millimetres (mm) were taken using standardized callipers (Slim Guide, USA) and measuring tape (SECA 201, Germany) on all participants. Measurements were taken to one decimal place and the mean value of three readings were recorded. BMI was calculated as WT divided by Ht squared (kg/m^2) and classified according to the World Health Organization categories: underweight (<18.5), normal (18.5-24.9), overweight (≥ 25.0-29.9), obese class I (30.0-34.9), obese class II (35.0-39.9) and obese class III (≥40) (27). WHR was calculated as WC divided by HC. WHtR was calculated as WC divided by Ht. TSF and mid upper arm circumference (MUAC) were used to determine MAMC using the equation:-

MAMC (cm) = MUAC (cm) – [3.1415 x TSF cm)] (28)

5.2.5 Statistics

Data was analysed using the Statistical Package for Social Sciences (SPSS®) version 25.0. Means and standard deviation were calculated for all continuous variables and frequencies with percentages for categorical variables. Independent samples *t*-test was used to determine differences between transplant candidates and recipients' clinical and nutritional variables. Pearson's coefficient was used for correlation analysis between the anthropometric values and corresponding DEXA measurements. A p value of <0.05 was taken as statistically significant.

5.3 Results

5.3.1 Participant characteristics

Of the 34 participants, 18 were undergoing haemodialysis while on the waiting list for a transplant and 16 were already recipients of a kidney donated from a HIV infected individual. Participant characteristics are summarized in table 5.1. The majority were male (61.8%) and 38.2% were female. The majority (91.2%) were black, with an average age of 43.9 ± 7.9 years. All participants were HIV positive, the majority were hypertensive (88.2 %), while two (5.9%) had hypercholesterolemia, and five (14.7%) had diabetes. The average CD4 count for the group was 374.85 ± 214.42 cells/µL. Transplant recipients had higher mean CD4 (417.69 ± 280.56 cells/µL versus 334.53 ± 120.85 cells/µL) when compared to transplant candidates All transplant recipients had viral loads (VL) levels that were lower than detectable limits (LDL), while 87.5% of transplant candidates had viral loads at LDL. The majority of transplant

recipients had a normal weight (87.5%), and two (12.5%) were categorized as obese class I. In the transplant candidate group, only 28.7% were classified as normal weight. The majority were either overweight (33.3%) or obese (38.9 %).

Table 5.1: Demographic, nutritional and clinical characteristics of the study group

Patient Characteristics	**Total group** N = 34	**Transplant candidates** n = 18	**Transplant recipients** n = 16
Gender			
Male	21 (61.8)	11 (61.1)	10 (62.5)
Female	13 (38.2)	7 (38.9)	6 (37.5)
Age (years)	43.9 ± 7.9	46.2 ± 7.6	41.2 ± 7.56
Ethnicity			
Black	31 (91.2)	16 (88.9)	15 (93.8)
Coloured[a]	3 (8.8)	2 (11.1)	1 (6.3)
Duration of current treatment (years)	3.7 ± 2.6		
Chronic illness			
Diabetes	5 (14.7)	5 (27.8)	0 (0.0)
Hypertension	30 (88.2)	17 (94.4)	13 (81.3)
Hypercholesterolaemia	2 (5.9)	1 (5.6)	1 (6.3)
CD4 (cells/µL)[b]	374.85 ± 214.42	334.53 ± 120.85	417.69 ± 280.56
Viral load (copies /ml)[c]			
Lower than detectable limit (LDL)	29 (93.5)	14 (87.5)	15 (100.0)
≤ 10000 copies/ml	2 (6.5)	2 (12.5)	(0.0)
BMI			
Normal (18.5-24.9)	19 (55.9)	5 (27.8)	14 (87.5)
Overweight (25.0-29.9)	6 (17.6)	6 (33.3)	-
Obese class I (30-34.0)	9 (26.5)	7 (38.9)	2 (12.5)

[a] In South Africa, refers to an individual of mixed race ancestry

[b]CD4: n = 33 (dialysis: n = 17 , transplant: n = 16), [c] Viral load: n = 31 (dialysis: n = 16 , transplant: n =15)

BMI: body mass index

Data expressed as means and standard deviation or frequencies with percentages

5.3.2 Body composition

Table 5.2 depicts the body composition values obtained from DEXA and anthropometric measurements for each treatment group respectively. Although there were no significant differences between transplant candidates and transplant recipients, there was a trend towards greater adipose and muscle mass values in candidates on dialysis when compared to transplant recipients. BMIs amongst transplant candidates versus transplant recipients were 27.9 ± 4.2 kg/m^2 and 23.4 ± 4.6 kg/m^2 respectively. WC and WHtR were also higher in the candidate group (93.5 ± 13.6 and 0.6 ± 0.1) compared to the recipient group (86.8 ± 11.4 and 0.5 ± 0.1). WHR ratio showed no significant difference between the two groups, with a mean value of 0.9 ± 0.1 recorded for both. Transplant candidates were also more muscular with a mean MAMC of 27.3 ± 4.4cm compared to 24.5 ± 4.4cm amongst transplant recipients.

Similarly, all DEXA measurements of adiposity were higher amongst transplant candidates compared to transplant recipients. %BF was 29.5 ± 11.4% versus 24.0 ± 11.8%. Mean TF among the transplant candidates was 11.4 ± 6.6 kg and 8.1± 5.1 kg among transplant recipients. VAT was 122.2 ± 57.5cm^2 versus 104.0 ± 55.2cm^2. LM and LM indices were also greater. LMI was 18.0 ± 1.53kg/m^2 and 16.8 ± 1.9kg/m^2 amongst transplant awaiting candidates and transplant recipients respectively.

Correlation coefficients between BC derived from anthropometry and DEXA were determined for the whole group, and are given in Table 5.3. Strong correlations were observed between BMI ($r = 0.773$, $p < 0.001$) and TSF ($r = 0.803$, $p < 0.001$) with %BF.

TF correlated strongly with WHtR ($r = 0.778$, $p = 0.000$), but even more so with WC ($r = 0.799$, $p = 0.000$). WC strongly correlated with the reference VAT ($r = 0.885$, $p \leq 0.001$), as did WHtR ($r = 0.802$, $p \leq 0.001$), and BMI ($r = 0.716$, $p \leq 0.001$). No significant association was observed between WHR and TF or VAT. The strength of association between MAMC and lean mass was moderate ($r = 0.403$, $p = 0.041$), but was stronger with ALMI ($r = 0.511$, $p = 0.011$).

Table 5.2: Anthropometry and DEXA derived body compositional characteristics of the dialysis and transplant group

Body composition		Transplant candidates		Transplant recipients	
		n		**n**	
Anthropometry	Weight (kg)	18	75.7 ± 11.5	16	64.9 ± 13.2
	Height (cm)	18	164.7 ± 10.3	16	166.6 ± 9.3
	BMI (kg/m^2)	18	27.9 ± 4.2	16	23.4 ± 4.6
	Waist circumference (cm)	13	93.5 ± 13.6	14	86.8 ± 11.4
	Waist to hip ratio	13	0.9 ± 0.1	14	0.9 ± 0.1
	Waist to height ratio	13	0.6 ± 0.1	14	0.5 ± 0.1
	Mid upper arm circumference (cm)	12	30.4 ± 4.6	14	27.3 ± 5.2
	Triceps skinfold thickness (mm)	12	10.8 ± 5.2	14	9.0 ± 4.8
	Mid arm muscle circumference (cm)	12	27.3 ± 4.4	14	24.5 ± 4.4
DEXA	Body fat (%)	18	29.5 ± 11.4	16	24.0 ± 11.8
	Fat mass (kg)	18	22.3 ± 10.8	16	16.3 ± 11.54
	Visceral adipose tissue (g)	13	589.31 ± 276.67	16	501.38 ± 266.28
	Visceral adipose tissue (cm^2)	13	122.18 ± 57.38	16	104.01 ± 55.22
	Truncal fat (kg)	18	8.4 ± 5.9	16	8.1 ± 5.1
	Lean mass (kg)	18	49.5 ± 7.78	16	46.4 ± 9.0
	lean mass index (kg/ht^2)	18	17.99 ± 1.53	14	16.84 ± 1.94
	Appendicular lean mass index (kg/Ht^2)	18	7.72 ± 0.93	14	7.08 ± 0.94

Data expressed as means and standard deviation
DEXA: dual-energy X-ray absorptiometry

Table 5.3: Pearson's correlation of anthropometric measurements with DEXA measurements for the whole group

	%BF			TF (kg)			VAT(cm^2)			LM (kg)			LMI (kg/Ht^2)			ALMI (kg/ Ht^2)		
	n	**r**	**p**	**n**	**r**	**p**	**n**	**r**	**p**	**n**	**r**	**p**	**n**	**r**	**p**	**n**	**r**	**p**
BMI	34	0.773**	<0.001	33	0.884**	0.000	29	0.716**	<0.001									
TSF	26	0.803**	<0.001															
WHR				27	0.131	0.515	23	0.238	0.275									
WHtR				27	0.0.778**	0.000	23	0.802**	<0.001									
WC				27	0.799**	0.000	23	0.885**	<0.001									
MAMC										26	0.403*	0.041	24	0.475*	0.019	24	0.511*	0.011

BMI: Body mass index, TSF: triceps skinfold thickness, WHR: waist to hip ratio, WHtR: waist to height ratio, WC: waist circumference, MAMC: mid arm muscle circumference, %BF: Percentage body fat, VAT: Visceral adipose tissue, LM: Lean mass, LMI: Lean mass index, ALMI: Appendicular lean mass index
**Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed)

5.4 Discussion

Accurate measurements of BC are essential for the assessment of nutritional status. DEXA accurately quantifies adipose and muscle tissue (29), and for this reason, was used as a reference standard to correlate BC determined by anthropometry.

BMI is a widely used indicator for whole body adiposity, based on the correlation that exists between BMI and direct measures of body fat such as underwater weighing and DEXA (5). The present study confirms this relationship, showing a strong correlation ($r = 0.773$, $p < 0.001$) between BMI and DEXA derived %BF. As to be expected, TSF showed a stronger relationship with %BF ($r = 0.803$, $p = <0.001$) than BMI in the current study, and other studies (30), as BMI is an indirect measure of adiposity (31). However, skinfolds provide a more direct measure of fat as they determine subcutaneous fat, which make up about 50.0% of whole body fat (32). In addition, skinfolds at the triceps site demonstrate a highly correlational relationship with whole body fat (32). Nonetheless, BMI is more routinely used, as skinfolds require skill and equipment that is not always available. It is therefore considered an expanded, rather than one of the core body measurements by the WHO (33). However, it could be considered in situations where the measurement of weight and height are not practical.

Central/ truncal adiposity is abdominally located adipose tissue that incorporates both the intra-abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) (34). The VAT component however, adversely affects the metabolic profile more so than the subcutaneous adipose tissue (SAT) (12). In recent years, it has become an increasingly important focus of research, since VAT was found to be associated with hypertension (35), pre-diabetes and diabetes (36), dyslipidaemia (37) and the metabolic syndrome (38). In the current study, the performance of WC, WHR and WHtR as proxy measures of central adiposity was assessed using their associations with TF and VAT. Of these three indicators, WC demonstrated the strongest correlation to both TF and VAT. WHtR also showed strong associations, although to a lesser extent. Although not investigated in the present study, researchers also report that WC correlates strongly with total abdominal fat, SAT and BMI (39,40).

The superior performance of WC in this study is an encouraging finding as numerous studies have shown its discriminative ability in predicting one's risk for type 2 diabetes (41), metabolic syndrome (42), and cardiovascular risk factors (43,44). Moreover, WC is also highly sensitive

in detecting BC changes following a WC reduction intervention without any change in BMI or weight following a year-long exercise program (45).

The current study found no correlation between WHR and TF or VAT. A possible reason for this finding is that unlike WC, WHR does not solely reflect adipose distribution in the truncal area, but also the hip area. The latter comprises pelvic bone structure and gluteal muscle and fat. Given the individual variations in these body components, hip measurements are likely to affect WHR (46).

Although BMI correlated well with %BF, there was also a similarly strong association with TF and VAT. This is probably due to the fact that increases in abdominal fat and total body fat occur simultaneously. Despite the correlation with overall and central adiposity, BMI is not a stand-alone indicator to be used for both, as it is not suitably predictive of disease risk (22). Evidence shows that measures of central obesity like WC is strongly associated with CVD risk, and is a better reflection than BMI, of adiposity in older individuals and is less affected by a loss of muscle associated with ageing. It is therefore and important indicator to include in nutritional assessment of adiposity (47).

In addition to adiposity, measures of musculature have become an increasingly important component of body composition (23), with important implications for strength, function, mobility and longevity (48,49).

In this study, MAMC was associated with LM. This finding is in agreement with other studies conducted among CKD and HIV-positive populations that also showed a good association with MAMC and LM (19,50). In the present study, the strength of association is greater with lean mass adjusted for height (LMI) with the strongest association documented for ALMI. This is not surprising, as whole body LM includes muscle, skin, tendons and connective tissues, whereas appendicular soft tissue (in arms and legs), is largely skeletal muscle, and represents approximately 75% of whole body skeletal muscle mass (23). Therefore, a stronger relationship would exist between ALMI and whole body skeletal muscle (21).

This study has strengths and limitations. The small sample size limits generalizability of the results as well as subgroup analysis according to gender or age, as is often seen in other studies (51,52). In addition, the time discrepancy between DEXA, anthropometric measurements and dialysis could be viewed as a limitation. However, logistical challenges such as the geographical

location of participants impaired the ability to schedule the DEXA scan and anthropometric measurements on the same day, in addition to conducting these measures after dialysis. This is an important consideration, as muscle tissue is influenced by the hydration status of dialysed patients (53), and reliable LM estimates can only be obtained when participants are at their ideal dry weight (54). It was therefore unlikely that the obtained values would be similar. Statistical analysis was limited to correlational analysis, examining the strength of association between two variables. Future studies should consider agreement analysis to confirm agreement between two methods of the same variable (55). However, previous validation studies (56), between %BF and BMI have demonstrated good agreement, confirming the use of BMI as a proxy measure of overall adiposity. It is also encouraging to note that despite these challenges, the results were not unlike those reported in more controlled studies (52). A possible reason for this finding was the recruitment of dietitians for taking anthropometric measurements, as they have extensive training and experience in anthropometry. Previous research showed good intra-observer precision, even among newly trained dietitians with limited experience (57).

An important strength of this study is that it is the first correlational study of this nature conducted among HIV-infected kidney transplant awaiting candidates and recipients from HIV-infected donors. Furthermore, this study was able to quantify the VAT component of abdominal fat. Previously, DEXA was unable to distinguish VAT from SAT (58,59). Only recently, have advances in DEXA analysis allowed differentiation and quantification of total abdominal adipose tissue into VAT and SAT components with a high degree of accuracy (25).

The present study concludes, that based on the correlations of BMI, WC and MAMC with DEXA derived %BF, VAT and ALMI respectively, these anthropometric measures suitably reflect overall and regional adiposity as well as musculature, and can confidently be used for nutritional assessment in this patient group.

5.5 References

1. Karli U, Ucan Y, Sozbir K, Aydin K, Yarar H. Validation of skinfold measurement method to DEXA for the assessment of body composition. IJSPE. 2016; 2(1): 20-26.

2. Schold JD, Srinivas TR, Guerra G, Reed AI, Johnson RJ, Weiner ID, Oberbauer R, Harman JS, Hemming AW, Meier-Kriesche HU. A ‘Weight-Listing’ paradox for candidates of renal transplantation? Am J Transplant. 2007; 7(3): 550-559.

3. Molnar MZ, Streja E, Kovesdy CP, Bunnapradist S, Sampaio MS, Jing J, Krishnan M, Nissenson AR, Danovitch GM, Kalantar-Zadeh K. Associations of body mass index and weight loss with mortality in transplant-waitlisted maintenance hemodialysis patients. Am J Transplant. 2011; 11(4): 725-736.

4. Aalten J, Christiaans MH, de Fijter H, Hené R, van der Heijde JH, Roodnat J, Surachno J, Hoitsma A. The influence of obesity on short- and long-term graft and patient survival after renal transplantation. Transpl Int. 2006; 19(7): 901-907.

5. Centers for Disease Control and Prevention. Body mass index: Considerations for practitioners. [Online]. 2008 [cited 15/12/2018]. Available from https://www.cdc.gov/obesity/downloads/bmiforpactitioners.pdf.

6. Streja E, Molnar MZ, Kovesdy CP, Bunnapradist S, Jing J, Nissenson AR, Mucsi I, Danovitch GM, Kalantar-Zadeh K. Associations of pretransplant weight and muscle mass with mortality in renal transplant recipients. Clin J Am Soc Nephrol. 2011; 6(6): 1463-1473.

7. Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. Am J Clin Nutr 2004;80: 324–332.

8. Neale J, Smith AC. Cardiovascular risk factors following renal transplant. World J Transplant. 2015; 5(4): 183-195.

9. Gore JL, Pham PT, Danovitch GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, Singer JS. Obesity and outcome following renal transplantation. Am J Transplant. 2006; 6(2): 357–363.

10. Marcén R, Fernández A, Pascual J, Teruel JL, Villafruela JJ, Rodriguez N, Martins J, Burgos FJ, Ortuño J. High body mass index and post transplant weight gain are not risk factors for kidney graft and patient outcome. Transplant Proc. 2007; 39(7): 2205-2207.

11. de Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. Eur Heart J. 2007; 28(7): 850–856.

12. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu C, Vasan RS, Murabito JM, Meigs JB, Cupples LA, D'Agostino Sr RB, O'Donnell CJ. Abdominal visceral and subcutaneous adipose tissue compartments. Association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007; 116(1): 39-48.

13. Kovesdy CP, Czira ME, Rudas A, Ujszaszi A, Rosivall L, Novak M, Kalantar-Zadeh K, Molnar MZ, Mucsi I. Body mass index, waist circumference and mortality in kidney transplant recipients. Am J Transplant. 2010; 10(12): 2644-2651.

14. Knox TA, Zafonte-Sanders M, Fields-Gardner C, Moen K, Johansen D, Paton N. Assessment of nutritional status, body composition, and human immunodeficiency virus–

associated morphologic changes. Clin Infect Dis. 2003; 36(Suppl 2):. S63–S68.

15. Lentine KL, Axelrod D, Abbott KC. Interpreting body composition in kidney transplantation: weighing candidate selection, prognostication, and interventional strategies to optimize health. Clin J Am Soc Nephrol. 2011; 6(6): 1238-1240.

16. Duren DL, Sherwood RJ, Czerwinski SA, Lee M, Choh AC, Siervogel RM, Cameron Chumlea WM. Body composition methods: comparisons and interpretation. J Diabetes Sci Technol. 2008; 2(6): 1139–1146.

17. Rolland-Cachera M, & Brambilla P, Manzoni P, Akrout M, Sironi S, Del Maschio A, Chiumello G. Body composition assessed on the basis of arm circumference and triceps skinfold thickness: a new index validated in children by magnetic resonance imaging. Am J Clin Nutr. 1997; 65(6): 1709-1713.

18. Schneider HJ, Friedrich N, Klotsche J, Pieper L, Nauck M, John U, Dörr M, Felix S, Lehnert H, Pittrow D, Silber S, Völzke H, Stalla GK, Wallaschofski H, Wittchen H. The predictive value of different measures of obesity for incident cardiovascular events and mortality. J Clin Endocrinol Metab. 2010; 95(4): 1777–1785.

19. Noori N, Kopple JD, Kovesdy CP, Feroze U, Sim, JJ, Murali SB, Luna A, Gomez M, Luna C, Bross R, Nissenson AR, Kalantar-Zadeh K. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. Clin J Am Soc Nephrol. 2010; 5(12): 2258–2268.

20. Wang J, Thornton JC, Kolesnik S, Pierson RN (Jr). Anthropometry in body composition. An overview. Ann N Y Acad Sci. 2000; 904(1): 317-326.

21. Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D. Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr. 2002; 76(2): 378–383.

22. Browning LM, Mugridge O, Dixon AK, Aitken SW, Prentice AM, Jebba SA. Measuring abdominal adipose tissue: Comparison of simpler methods with MRI. Obes Facts 2011;4: 9–15.

23. Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, Maggi S, Dennison E, Al-Daghri NM, Allepaerts S, Bauer J, Bautmans I, Brandi ML, Bruyère O, Cederholm T, Cerreta F, Cherubini A, Cooper C, Cruz-Jentoft A, McCloskey E, Dawson-Hughes B, Kau. Pitfalls in the measurement of muscle mass: A need for a reference standard. J Cachexia, Sarcopenia Muscle. 2018; 9(2): 269–278.

24. Adab P, Pallan M, Whincup P. Is BMI the best measure of obesity? BMJ. 2018; 360: k1274. doi: 10.1136/bmj.k1274.

25. Kaul S, Rothney MP , Peters DM, Wacker WK, Davis CE ,Shapiro MD, Ergun DL. Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity (Silver Spring).

2012; 20(6): 1313–1318.

26. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) Anthropometry Procedures Manual. [Online]; 2009 [cited 22/02/2014]. Available from: https://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf.

27. World Health Organization. Obesity: Preventing and managing the global epidemic. [Online]; 2000. [cited 12/03/2018]. Available from: https//Obesity: preventing and managing the global epidemic. Report of a WHO Consultation (WHO Technical Report Series 894). Geneva:; 2000.

28. Frisancho AR. Triceps skin fold and upper arm muscle size norms for assessment of nutritional status. J. Clin. Nutr. 1974; 27(10): 1052-1058.

29. Katz P, Gregorich S, Yazdany J, Trupin L, Julian L, Yelin E, Criswell LA. Obesity and its measurement in a community-based sample of women with systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2011; 63(2): 261–268.

30. Sarría A, Moreno LA, García-Llop LA, Fleta J, Morellón MP, Bueno M. Body mass index, triceps skinfold and waist circumference in screening for adiposity in male children and adolescents. Acta Paediatr. 2001; 90(4): 387-392.

31. Centers for Disease Control and Prevention. Overweight and Obesity. [Online]; 2016 [cited 11/01/2019]. Available from: https://www.cdc.gov/obesity/adult/defining.html.

32. National Center for Health Statistics. Vital and health statistics; Series 11, No. 35 (2/70). [Online];1970 [cited 12/03/2019]. Available from: https://www.cdc.gov/nchs/data/series/sr_11/sr11_035acc.pdf

33. World Health Organization. WHO STEPS Surveillance Manual, part 4. [Online]; [cited 21/11/2018]. Available from: http://www1.paho.org/hq/dmdocuments/2009/STEPSmanual.pdf.

34. Montague CT, O' Rahilly S. The perils of portliness causes and consequences of visceral adiposity. Diabetes. 2000; 49(6): 883–888.

35. Chandra A, Neeland IJ, Berry JD, Ayers CR, Rohatgi A, Das SR, Khera A, McGuire DK, de Lemos JA, Turer AT. The relationship of body mass and fat istribution with incident hypertension: observations from the Dallas Heart Study. J Am Coll of Cardiol. 2014; 64(10): 997-1002.

36. Jung SH, Ha KH, Kim DJ. Visceral fat mass has stronger associations with diabetes and prediabetes than other anthropometric obesity indicators among Korean adults. Yonsei Med J. 2016; 57(3): 674–680.

37. Hwang YC, Fujimoto WY, Hayashi T, Kahn SE, Leonetti DL, Boyko EJ. Increased visceral adipose tissue is an independent predictor for future development of atherogenic dyslipidemia. J Clin Endocrinol Metab. 2016; 101(2): 678–685.

38. Demerath EW, Reed D, Rogers N, Sun SS, Lee M, Choh AC, Couch W, Czerwinski SA, Chumlea WC, Siervogel RM, Towne B. Visceral adiposity and its anatomical distribution as predictors of the metabolic syndrome and cardiometabolic risk factor levels. Am J Clin Nutr. 2008; 88(5): 1263–1271.

39. Grundy SM, Neeland IJ, Turer AT, Vega GL. Waist circumference as measure of abdominal fat compartments. J Obes. 2013; 2013::454285. doi: 10.1155/2013/454285.

40. Ahmad N, Adam SI, Nawi AM, Hassan MR, Ghazi HF. Abdominal obesity indicators: Waist circumference or waist-to-hip ratio in Malaysian adult population. Int J Prev Med. 2016; 7: 82. doi: 10.4103/2008-7802.183654.

41. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr. 2005; 81(3): 555-563.

42. Cheong KC, Ghazali SM, Hock LK, Subenthiran S, Huey TC, Kuay LK, Mustapha FI, Yusoff AF, Mustafa AN. The discriminative ability of waist circumference, body mass index and waist-to-hip ratio in identifying metabolic syndrome: Variations by age, sex and race. Diabetes Metab Syndr. 2015; 9(2): 74-78.

43. Dobbelsteyn CJ, Joffres MR, MacLean DR, Flowerdew G & The Canadian Heart Health Surveys Research Group. A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The Canadian Heart Health Surveys. Int J Obes Relat Metab Discord 2001; 25: 652–661.

44. van Dijk SB, Takken T, Prinsen EC, Wittink H. Different anthropometric adiposity measures and their association with cardiovascular disease risk factors: a meta-analysis. Neth Heart J. 2012; 20(5): 208–218.

45. Velthuis MJ, Schuit AJ, Peeters PHM, Monninkhof EM. Exercise program affects body composition but not weight in postmenopausal women. Menopause. 2009; 16(4): 777-784.

46. Seidell JC, Pérusse L, Després J, Bouchard C. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. AJCN. 2001; 74(3): 315–321.

47. Flint AJ, Rexrode KM, Hu FB, Glynn RJ, Caspard H, Manson JE, Willett WC, Rimm EB. Body mass index, waist circumference, and risk of coronary heart disease: a prospective study among men and women. Obes Res Clin Pract. 2010; 4(3): e171–e181. doi: 10.1016/j.orcp.2010.01.001

48. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: The effect of diabetes, obesity, and other diseases. Lancet Diabetes Endocrinol. 2014; 2(10): 819–829.

49. Brown JC, Harhay MO, Harhay MN. Appendicular lean mass and mortality among prefrail and frail older adults. J Nutr Health Aging. 2017; 21(3): 342–345.

50. Vassimon HS, Jordão AA, F. J. de Paula FJA, Machado AA, Monteiro JP. Comparison of bioelectrical impedance with skinfold thickness and X-ray absorptiometry to measure body composition in HIV-infected with lipodistrophy. Nutr Hosp. 2011; 26(3): 458-464.

51. Ojo G, Adetola O. The Relationship between skinfold thickness and body mass index in estimating body fat percentage on Bowen University students. Int. Biol. Biomed. J. 2017; 3(3): 138-144.

52. Ranasinghe C, Gamage P, Katulanda P, Andraweera N, Thilakarathne S, Tharanga P. Relationship between body mass index (BMI) and body fat percentage, estimated by bioelectrical impedance, in a group of Sri Lankan adults: a cross sectional study. BMC Public Health. 2013;13:797. doi.org/10.1186/1471-2458-13-797

53. Razak K, Gupta S, Razak UH, Meena GL. Impact of hydration on body status pre & post dialysis: a radiological appraisal by DEXA scan. J of Biosens Biomark Diagn 2017; 2(2): 1-3. doi:10.15226/2575-6303/2/2/0117

54. de Fijter CW1, de Fijter MM, Oe LP, Donker AJ, de Vries PM. The impact of hydration status on the assessment of lean body mass by body electrical impedance in dialysis patients. Adv Perit Dial. 1993; 9: 101-104.

55. Bland JM, Altman DG. Statistical methods for testing agreement between two methods of clinical measurement. Lancet. 1986; 1(8476): 307-310.

56. Kamimura MA, Avesani CM, Cendoroglo M, Canziani MEF, Draibe SA, Cuppari L. Comparison of skinfold thicknesses and bioelectrical impedance analysis with dual-energy X-ray absorptiometry for the assessment of body fat in patients on long-term haemodialysis therapy. Nephrol Dial Transplant. 2003; 18(1): 101-105.

57. Arroyo M, Freire M, Ansotegui L, Rocandio AM. Intraobserver error associated with anthropometric measurements made by dietitians. Nutr Hosp. 2010; 25(6): 1053-1056.

58. Sun Q, van Dam RM, Spiegelman D,Heymsfield SB, Willett WC, Hu FB. Comparison of dual-energy X-ray absorptiometric and anthropometric measures of adiposity in relation to adiposity-related biologic factors. Am J Epidemiol. 2010; 172(12): 1442–1454.

59. Taylor RW, Jones IE, Williams SM, Goulding A. Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3–19 y. Am J Clin Nutr 2000; 72:4. 2000; 72(2): 490–495.

CHAPTER 6

ASSESSMENT OF OVERALL AND CENTRAL ADIPOSITY IN HIV-POSITIVE TRANSPLANT CANDIDATES AND RECIPIENTS FROM HIV-POSITIVE DONORS

ABSTRACT

Background: Overall and abdominal obesity are closely related to health outcomes in kidney transplant candidates and recipients. Diet is one of several determinants of obesity. However, this has not been investigated in HIV-infected transplant candidates and recipients from a HIV-infected donor.

Objectives: 1) To determine weight, body mass index (BMI) and waist circumference (WC) at baseline and the changes in these indicators after six months; 2) To determine the prevalence of obesity, central obesity and the metabolic syndrome (MetS), and 3) to determine the relationship between dietary macronutrient composition, weight and WC.

Methods: Weight, BMI, WC and biochemical parameters for the assessment of MetS were collected at baseline and six months.

Results: Transplant candidates: The mean baseline BMI was 26.3 ± 4.8kg/m^2. The majority (38.5%) were overweight, followed by 36.5% with a normal BMI. At six months, 62.7% had lost weight. The mean weight lost was statistically significant t (50) = 2.072, p = 0.043). Mean WC from baseline to six months also decreased slightly although non-significantly. The WHO cut-offs (WC ≥ 88cm for women and ≥ 102cm for men), classified 33.3% with central obesity at baseline and 30.4% at six months. MetS was present in 47.5% and 51.0% of candidates at baseline and six months respectively. The mean daily energy and protein intake at baseline and six months was 25.9 ± 7.8 and 26.4 ± 8.4 kcal/kg/day, and 1.0 ± 0.4g/kg/day and 1.1 ± 0.4 g/kg/day respectively. Both were lower than that recommended by the South African (SA) Renal guidelines. There was a lack of association between macronutrient intake and weight or WC at either time point or with the weight change over six months.

Transplant recipients: The mean BMI was 24.5 ± 4.6 kg/m^2. The majority had a normal BMI (71.4%). At six months, 52.4% had gained weight. The increase in weight and BMI was non-significant. However, mean increases in WC were statistically significantly (t (14) = -2.861, p 0.013). WC cut-offs classified 33.3% with central obesity at baseline and 44.4% at six months. MetS was present in 35.3% of transplant recipients at baseline and 35.0% at six months. The macronutrient content of the diet was within recommended guidelines, at 28.6 ± 7.8 and 27.7 ± 9.1kcal/kg/day, and 1.0 ± 0.3g and 1.1 ± 0.3g. At baseline, weight correlated with total protein

(r = 0.609, p = 0.003), animal (r = 0.513, p = 0.017) and plant protein (r = 0.534, p = 0.013) intake. At six months, WC correlated with animal protein (r = 0.517, p = 0.028) intake.
Conclusion: Transplant candidates had significant weight loss after six months. Transplant recipients experienced a significant increase in waist circumference from baseline to six months. At baseline, weight correlated with total protein, animal and plant protein. At six months, WC correlated with animal protein.

Keywords: Kidney transplant candidates, Kidney transplant recipients, Human immunodeficiency virus (HIV), Adiposity, BMI, Waist circumference, Weight, Metabolic syndrome, Dietary intake

6.1 Introduction

The increasing prevalence of overweight and obesity in the general population over the past three decades is of global health concern. Increasing body mass index (BMI) corresponds to a greater risk of certain cancers, cardiovascular disease (CVD), Type 2 diabetes mellitus and higher rates of mortality (1). In end stage renal disease (ESRD), overweight and obesity, defined by BMI are also related to health, although the implications in the pre- and post-transplant population are more complex.

In candidates, wait-listed for a transplant, BMI has an inverse relationship with mortality. Higher BMIs afford greater survival benefits when compared to normal or underweight candidates. The lowest mortality rates have been observed among those in the >35 kg/m^2 BMI category, while a low BMI (< 20 kg/m^2), or muscle mass, and reductions in either of these indicators over time are associated with a higher mortality risk whilst on dialysis (2). The effects of pre-transplant BMI on post-transplant outcomes are less consistent. Obesity at the time of transplantation has been associated with delayed graft function (3), a higher risk of graft and death-censored graft failure at BMI above 22–25 kg/m^2, with the highest risk observed at BMI ≥ 34 kg/m^2 (4). Other researchers however, failed to show any long term impact of pre-transplant obesity on post-transplant outcomes (5).

Following a transplant, increases in body weight of 10% to 35% are known to occur mainly during the first year post-transplant (6) and are usually attributable to increases in fat mass (7). Weight gain after the first year, is associated with chronic allograft nephropathy (8), new onset diabetes after transplantation (NODAT), and a greater risk of graft failure and death (9,10).

Abdominal obesity determined by regional measurements such as waist circumference (WC) is also common in transplant recipients (11). It is associated with cardiovascular risk factors (11), and is predictive of recipients at high mortality risk (12). Together with CVD risk factors, hypertension, hyperglycaemia and dyslipidaemia, it constitutes the metabolic syndrome (MetS) (13), which is present in 52.8% of kidney transplant recipients (14). In the general population, MetS increases the risk of CVD, coronary heart disease (CHD) and overall mortality (15), impaired graft function in transplant recipients (16), and significantly reduces graft and recipient survival (17).

Post-transplant weight gain is likely to be influenced by a number of factors including demographic clinical variables and lifestyle variables (18-20). Diet is an aspect of the latter and

is important in its influence on graft function and CVD risk factors (21). Diet is an important modifiable component of weight gain (7), and has previously been studied in transplant recipients (18,22,23), but not in the HIV infected population. Therefore the objectives in this study population were 1) to determine participants' weight, BMI and WC at baseline and observe changes in these anthropometric indicators after six months, 2) to classify BMI and WC in order to determine the prevalence of obesity and MetS, and 3) to determine the relationship between the macronutrient composition of the diet, weight and WC.

6.2 Methods

6.2.1 Participants

For this longitudinal study, observational study, prospective participants were recruited through the kidney transplant programme for HIV-infected patients at Groote Schuur Hospital, Cape Town. Participants were recruited based on whether they were transplant recipients or transplant candidates awaiting a transplant and hence managed on dialysis. From the outset they were therefore categorised as: (i) HIV-infected kidney transplant recipients who have received a kidney from a HIV-infected donor and (ii) HIV-infected transplant candidates on the waiting list to receive a kidney from a HIV-infected donor. Prospective participants were contacted telephonically or at their respective outpatient clinics and invited to participate in the study which ran from May 2015 to June 2016. Participants were included if they were clinically stable at the time of recruitment. Participants were excluded if they declined participation, were severely ill, were not contactable, uncooperative or had missed several interview appointments (typically two or more without reason). In total, seventy six patients agreed to participate, from whom written informed consent was obtained. The study was approved by The University of KwaZulu-Natal's Biomedical Research Ethics Committee (Approval number BE 327/13).

6.2.2 Socio-demographic and clinical information

Socio-demographic information was collected using an interviewer-administered structured questionnaire, developed for the purpose of the study. Clinical information was obtained from medical records or during participant interviews. The socio-demographic questionnaire was reviewed by researchers experienced in questionnaire design, and then pilot tested for comprehension.

6.2.3 Anthropometry

Dietitians were recruited to take anthropometric measurements due to their training and experience in this area. In addition, all dietitians received a brief refresher training session which was followed by a post-training test. To ensure uniformity and appropriate standards of training, both the training and the test were accredited for continuing professional development (CPD) purposes with the Health Professions Council of South Africa (HPCSA). All body measurements namely weight (WT), height (Ht) and waist circumference (WC) were taken using protocols described in the National Health and Nutrition Examination Survey (NHANES) anthropometry procedure manual (24). Height in centimetres (cm) and weight in kilograms (kg) were obtained using equipment present at various outpatient and dialysis centres. Weights measurements of dialysis patients were taken post-dialysis (dry weight). WC (cm) was measured using standardised measuring tapes (SECA 201, Germany). A mean of three readings were recorded. BMI and WC were used as measures of overall and central adiposity respectively. BMI was calculated as WT divided by Ht squared (kg/m^2) and classified according to the World Health Organization categories: Underweight (<18.5), normal (18.5 – 24.9), overweight (≥ 25.0-29.9), obese class I (30.0-34.9), obese class II (35.0-39.9) and obese class III (≥ 40) (1). WC cut-offs used, were WC ≥ 88cm for women and ≥ 102cm for men that indicated a substantially increased risk for metabolic complications (25).

6.2.4 Biochemical metabolic parameters

Participants had their blood samples tested through the National Health Laboratory Services (NHLS) or through any one of three private laboratories across the six provinces. The choice of laboratory was based on their proximity to the laboratory to their place of work or place of residence, whether they were state or private patients or whether the laboratory was their usual laboratory service provider. Serum glucose and lipids were measured in the morning after an overnight fast. Serum total cholesterol (TC) and glucose were determined enzymatically using cholesterol oxidase and glucose hexokinase respectively. Triglycerides (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) were determined using the enzymatic colour test on Beckman Coulter analysers. Serum albumin was measured using the bromocresol green colour reaction method, with a cut-off of < 38g/l set as a criterion for hypoalbuminaemia (26)

6.2.5 The metabolic syndrome

The presence of MetS was based on a recent consensus definition of MetS that encompasses the MetS definitions of the International Diabetes Federation (IDF), American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI) (13). Using this definition, MetS is diagnosed as the presence of any three of five given criteria listed in Table 6.1. It should be noted that the WC used in this MetS definition differs from the general WC cut-offs (paragraph 6.2.3).

Table 6.1: Consensus definition of the metabolic syndrome

Metabolic Syndrome Criteria
Raised WC using ethnic specific cut-offs [a, b]
Triglycerides ≥ 1.7 mmol/l
HDL-Cholesterol < 1.03 mmol/l for males and < 1.29 mmol/l for females
Blood pressure ≥ 130/85mm/Hg
Fasting plasma glucose ≥ 5.6 mmol/l

[a] WC ≥ 94cm for males or ≥ 80cm for females, based on European data in the absence of suitable WC cut-offs for African ethnic groups.
[b] In the absence of a WC measurement, BMI > 30kg/m^2 assumed the presence of central obesity (27)
Participants also met the criteria if they were receiving medication to manage hypertension, diabetes or were on treatment for lipid abnormalities (27)

6.2.6 Dietary intake

Macronutrient intake was obtained from a single quantified 24-hour recall. These were administered by registered dietitians with experience in recording of dietary intake data. Additional training was provided to ensure the use of standardized protocols during the dietary interview technique such as the use of similar probing questions to minimise interviewer bias. (28). Portion size estimation was improved through the use of household measuring utensils and a food-portion booklet that referenced food portions against common household objects, applicable to the South African context (29). All dietary data was analysed using Foodfinder 3 for Windows^R (The South African Medical Research Council), and macronutrient content of the diet was compared to the recommendations of the renal nutrition guidelines for South Africans (30).

6.2.7 Statistics

Data was analysed using the Statistical package for Social Sciences (SPSS®) version 25.0. Means and standard deviation were calculated for all continuous variables, while frequencies and percentages were calculated for categorical variables. A p value of <0.05 was taken as statistically significant.

Chi-square test of independence or Fisher's exact test was used to test for differences in categorical variables between the two treatment groups. The means of groups were compared at baseline and 6 months using the independent samples *t*-test. The change in weight and WC from baseline to six months was calculated for all participants with both sets of weights, and expressed as a percentage. Paired samples t-test was used to determine whether the changes in weight between the two assessment points differed significantly. Pearson's correlation coefficients were used to calculate the strength of the associations between macronutrients, weight and WC.

6.3 Results

6.3.1 Participant baseline characteristics

Participants were divided into two groups. There were 22 HIV-infected kidney transplant recipients who had already received a kidney from a HIV-infected donor, and 54 HIV-infected kidney transplant candidates on the waiting list to receive a kidney from a HIV-infected donor. The latter were managed on haemodialysis (HD) (n = 51) or peritoneal dialysis (PD) (n =3).

Demographic and nutritional characteristics of the study population are given in Table 6.2. The study population, who were predominantly black (93.4 %), had an average age of 43.6 ± 8.1 years. More participants were male (60.5%) than female (39.5%). Transplant candidates were on dialysis for an average of 3.9 ± 3.0 years (range: 0.3 - 11.5 years), while transplant recipients averaged 2.7 ± 2.3 years (range: 0.0 – 6.8 years) since transplantation. In terms of pre-existing comorbidities, most participants were hypertensive (92.1%), while only four had hypercholesterolemia. There were significantly more patients with diabetes amongst the candidates compared to the transplant recipients (29.6% versus 4.5%, p = 0.017). Transplant recipients had higher mean CD4 cell count (447.3 ± 282.70 cells/µL versus 382.1 ± 178.02 cells/µL), and higher viral loads with 94.7% versus 79.6% of patients with levels lower than

detectable limits. There were no other significant differences in demographic and clinical characteristics between the two groups.

Table 6.2: Socio-demographic and clinical characteristics of the study sample

Patient Characteristics	Whole group N = 76	Transplant candidates n = 54	Transplant recipients n = 22
Age (years)	43.6 ± 8.1 (28.0 – 63.0)		
Gender			
Male	46 (60.5)		
Female	30 (39.5)		
Ethnicity			
Black	71 (93.4)		
Coloured[a]	4 (5.3)		
White	1 (1.3)		
Type of treatment			
Transplant			22 (28.9)
Haemodialysis		51 (67.1)	
Peritoneal dialysis		3 (3.9)	
Length of time on current treatment (years)		3.9 ± 3.0 range: 0.3 - 11.5	2.7 ± 2.3 range: 0.0 – 6.8
Chronic illness			
Diabetes		16 (29.6) [a]	1 (4.5) [b]
Hypertension		51 (94.4)	19 (86.4)
Hypercholesteraemia		3 (5.6)	1 (4.5)
CD4 cell count (cells/mm^3)[c]		382.1 ± 178.0	447.3 ± 282.7
Viral load (copies /ml) [d]			
LDL		39 (79.6)	18 (94.7)
≤ 10 000		7 (14.3)	1 (5.3)
> 10 000		3 (6.1)	0 (0.0)

Data expressed as percentages or means with standard deviation, LDL: lower than detectable limit
[a] In South Africa, refers to individuals of mixed race ancestry
[b] Significantly more transplant candidates than recipients were diabetic Fischer's exact test, $p = 0.017$
[c] transplant patients: $n = 20$, dialysis patients: $n = 52$
[d] transplant patients: $n = 19$, dialysis patients: $n = 49$

6.3.2 Clinical and nutritional characteristics of transplant candidates

Transplant candidates had a lower mean serum albumin than transplant recipients (35.9 ± 4.5g/L and 37.2 ± 4.8g/L versus 43.1 ± 4.1g/L and 41.3 ± 4.1g/L) at baseline and six months respectively. The low mean values of the candidates classified the majority as hypoalbuminaemic, especially at baseline when significantly more had hypoalbuminaemia (62.5%), compared to transplant recipients (10.0%) with hypoalbuminaemia (χ^2 (1) = 15.619, p < 0.0005).

The mean weights and BMIs for transplant candidates at baseline was 73.9 ± 13.1kg and 26.3 ± 4.8kg/m^2 respectively. This classified 20/52 (38.5%) as overweight and 19/52 (36.5%) as normal weight. There were 11/52 (21.2%) in the obese class I category and one participant each (1.9%) who was underweight and obese class II. At six months, mean weights and BMIs decreased to 72.4 ± 13.1kg and 25.7 ± 4.8 kg/m^2 respectively. Fifty one transplant candidates had weights at baseline and six month follow-up, to enable the longitudinal calculation of weight change from baseline to six months (figure 6.1). Eighteen out of fifty one (35.3%) experienced weight gain, while weight remained static in one candidate (1/51, 2.0%). The majority of candidates 32/51 (62.7%) had lost weight. Paired samples t-test which was applied to analyse the weight change between the two time points, determined the mean weight lost from 73.1 ± 12.9 kg to 72.4 ± 13.1 kg, as statistically significant (t(50) = 2.072, p = 0.043).

Only 36 and 46 patients had WC values at baseline and six months respectively. Mean WC from baseline to six months also decreased slightly from 92.2 ± 14.1cm to 90.7 ± 14.2cm, although no significant difference in WC between the two time points could be found. The WHO cut-offs (WC ≥ 88cm for women and ≥ 102cm for men), classified 33.3% with central obesity at baseline and 30.4% at six months, whereas BMI (> 30.0 kg/m^2) classified 23.1% as obese at baseline and 18.3% at six months. MetS was present in 19/40 (47.5%) of transplant candidates at baseline, and 25/49 (51.0%) of transplant candidates at six months (Figure 6.2).

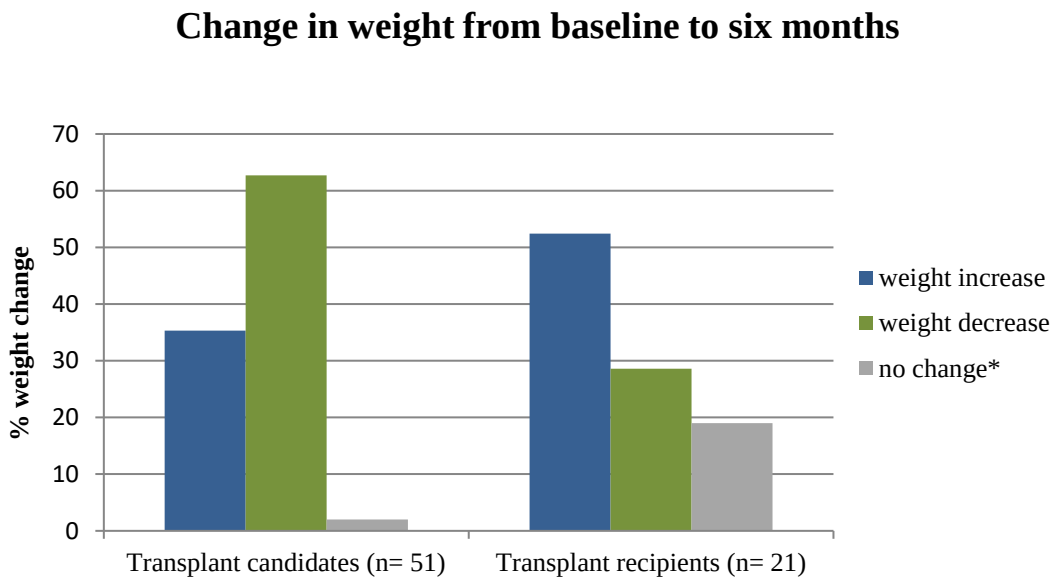

Figure 6.1: Percentage change in weight after six months in the transplant candidates and recipients

*Significantly more transplant recipients' weight remained static (f = 9.918, p = 0.005)

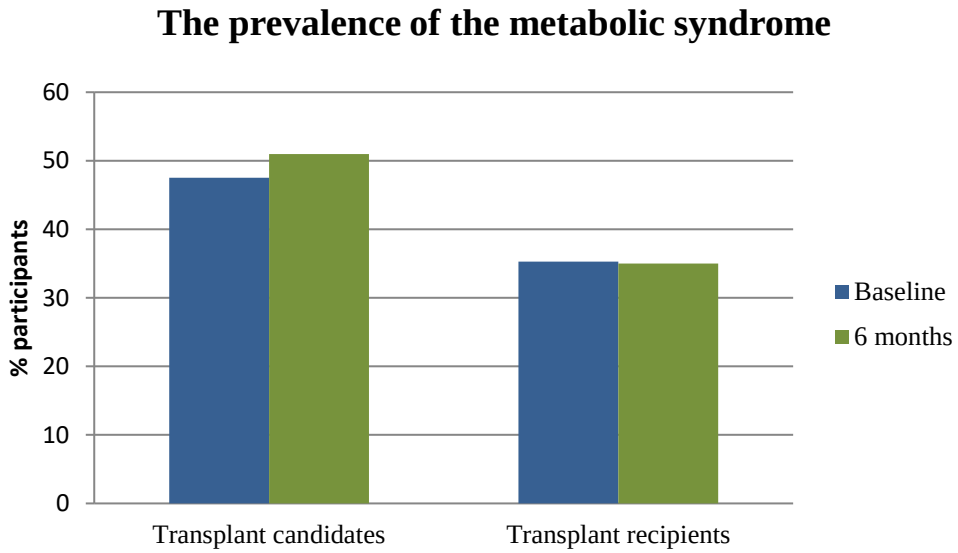

Figure 6.2: The prevalence of the metabolic syndrome in transplant candidates and recipients at baseline and six months

Dietary intake of both treatment groups are shown in Table 6.4. The mean daily energy intake of transplant candidates was similar at baseline and six months (7786.2 ± 1919.1 kJ/day and

7849.0 ± 2093.9 kj/day). This amounted to 25.9 ± 7.8 and 26.4 ± 8.4 kcal/kg/day; lower than that recommended by the South African (SA) renal guidelines. Mean daily protein intake was 72.5 ± 27.5g at baseline and increased to 76.3 ± 31.4g/day at six months, contributing 15.3 ± 4.2 % and 15.9 ± 4.2 % of total energy respectively. Plant protein contributed about a third, while two thirds was sourced from animal protein. The mean daily protein intake was calculated at 1.0 ± 0.4g/kg/day and 1.1 ± 0.4 g/kg/day, which was lower than recommendations by the SA renal guidelines for HD (1.2g/kg/day) and PD (1.2-1.3g/kg/day). At baseline and at six months, the percentage carbohydrate intake was 54.0 ± 10.6 % and 51.2 ± 10.7 %, while fat contributed 28.5 ± 9.1 % and 30.6 ± 9.1 % towards daily energy. Both the percentage distribution of total carbohydrate and total fat were within the 50% to 60% and 25% to 35% recommended guidelines. There were no significant difference between nutrients at baseline and six months. Correlation analysis showed no significant relationships between macronutrients and weight or WC at either time point or with the weight change over six months.

6.3.3 Clinical and nutritional characteristics of transplant recipients

The mean weight and BMI of recipients at baseline was 70.2 ± 17.2kg and 24.5 ± 4.6 kg/m^2 respectively, classifying the majority as having a normal BMI (71.4%) (Table 6.3). Compared to transplant candidates, the difference in BMI classification was most pronounced at baseline, when significantly more transplant recipients had a normal BMI (71.4%) while more transplant candidates were overweight (Fisher's exact = 9.004, p = 0.033). No transplant recipient was underweight at baseline, while 2/21 (9.5%) and 4/21 (19.0%) were overweight and obese class I respectively.

At six months, the majority of transplant recipients 11/21 (52.4%) experienced an increase in weight, while 6/21 (28.6%) lost weight and 4/21 (19.0%) showed no change in weight (Figure 6.1). Significantly more transplant recipients' weight remained static (f = 9.918, p = 0.005), compared to candidates. Consequently, mean weights and BMIs were higher from 70.2 ± 17.2 kg to 71.1 ± 18.3 kg and from 24.5 ± 4.6 kg/m^2 to 25.6 ± 5.8 kg/m^2, although this increase from baseline was not significant. At six months however, one transplant recipient was classified as underweight and fewer patients had normal BMIs (59.1%). Six out of twenty two recipients (27.3%) were classified as obese class I.

WC values were available for 18 recipients. Mean WC increased from 89.6 ± 13.1cm to 95.8 ± 12.3 cm. This increase in WC from baseline to six months was found to be statistically

significantly, paired samples t-test: t(14) = -2.861, p 0.013. WC cut-offs classified 33.3% as obese at baseline and 44.4% as obese at six months, whereas BMI only classified obesity at 19.0% and 27.3% at baseline and six months respectively. MetS was less prevalent among transplant recipients than candidates (Figure 6.3), with 6/17 (35.3%) transplant recipients meeting the criteria for MetS at baseline and 7/20 (35.0%) at six months.

The macronutrient intake of transplant recipients was very similar to that of transplant candidates with the mean daily intake of total energy and protein falling within the 25 - 30 kcal/day and 1.0 -1.1g protein (maintenance)/kg/day recommendations. The mean daily energy intake of transplant recipients was slightly higher than transplant candidates with baseline and six months values respectively being 8142.5 ± 2067.8 kj/day and 8029.9 ± 2361.6 kj/day. At 28.6 ± 7.8 and 27.7 ± 9.1 kcal/kg/day, total energy requirements fell within the recommendations of 25 - 30 kcal/kg/day. Mean daily protein intake was 72.7 ± 26.8g at baseline and increased to 78.0 ± 22.2g/day at six months, contributing 14.6 ± 3.9% and 16.4 ± 3.8% of total energy respectively. Per kg per day, the mean value at baseline was 1.0 ± 0.3g, which met the guideline protein amount required for maintenance, namely 0.8-1.0g/kg/day. At six months, mean daily intake increased to 1.1 ± 0.3g/kg/day exceeding these recommendations. Plant protein intake was 28.3 ± 14.6g/day and decreased slightly to 26.3 ± 13.7g at six months. Mean daily animal protein intake was 39.0 ± 19.2g/day increasing to 48.6 ± 20.0g/day. At baseline and six months, percentage carbohydrate intake was 55.0 ± 10.7% and 51.3 ± 8.9%. Fat contributed 28.3 ± 9.3% and 30.2 ± 8.0% towards daily energy. Both the percentage distribution of total carbohydrate and total fat met the 50% - 60% and 25% - 30% recommended guidelines. There were no significant differences between nutrients at baseline and six months.

The independent samples t-test was conducted to test if mean values differ across each group. There were no significant differences in any nutrient between the two treatment groups. Pearson's correlation was used to identify relationships between macronutrient intake and anthropometric indices. Although none were found in the transplant candidate group, several correlations were identified among transplant recipients. At baseline, weight correlated with total protein (r = 0.609, p = 0.003), animal (r = 0.513, p = 0.017) and plant protein (r = 0.534, p = 0.013). At six months, a moderate to strong correlation was established between WC and animal protein (r = 0.517, p = 0.028). There was no correlation between any of the macronutrients and change in weight or WC. There was also no relationship between energy, total fat and carbohydrate with weight or WC.

Table 6.3: Nutritional and clinical characteristics of transplant candidates and recipients

Nutritional Characteristics	**Transplant candidates**				**Transplant recipients**			
	n	Baseline	**n**	6 months	**n**	Baseline	**n**	6 months
Albumin (g/L)	48	35.9 ± 4.5	52	37.2 ± 4.8	20	43.1 ± 4.1	22	41.3 ± 4.1
Hypoalbuminaemia (<38g/L)		30 (62.5) [a]		26 (50.0) [a]		2 (10.0)		3 (13.6)
Normal albumin (≥38g/L)		18 (37.5)		26 (50.0)		18 (90.0)		19 (86.4)
Weight (kg)	54	73.9 ± 13.1	51	72.4 ± 13.1	21	70.2 ± 17.2	22	72.6 ± 19.1
Weight change	51	73.1 ± 12.9[b]	51	72.4 ± 13.1[b]	21	70.2 ± 17.2	21	71.1 ± 18.3
Height (cm)	52	167.4 ± 8.3			22	168.4 ±10.1		
BMI (kg/m^2)	52	26.3 ± 4.8	49	25.7 ± 4.8	21	24.5 ± 4.6	22	25.6 ± 5.8
Underweight		1 (1.9)		1 (2.0)				1 (4.5)
Normal		19 (36.5)		19 (38.8)		15 (71.4) [c]		13 (59.1)
Overweight		20 (38.5) [c]		20 (40.8)		2 (9.5)		2 (9.1)
Obese Class I		11 (21.2)		8 (16.3)		4 (19.0)		6 (27.3)
Obese Class II		1 (1.9)		1 (2.0)				
WC (cm)	36	92.2 ± 14.1	46	90.7 ± 14.2	18	89.6 ± 13.1[c]	18	95.8 ± 12.3[c]
Central obesity prevalence	36	12 (33.3)	46	14 (30.4)	18	6 (33.3)	18	8 (44.4)
Total cholesterol (mmol/l)	43	4.2 ± 0.9	49	4.1 ± 0.9	19	4.5 ± 1.2	21	4.4 ± 1.3
HDL cholesterol (mmol/l)	37	1.2 ± 0.3	48	1.2 ± 0.4	17	1.3 ± 0.3	20	1.3 ± 0.5
LDL cholesterol (mmol/l)	37	2.4 ± 0.8	48	2.3 ± 0.7	15	2.4 ± 1.0	18	2.2 ± 1.1
Triglycerides (mmol/l)	37	1.57 ± 1.08	48	1.47 ± 0.96	17	2.09 ± 1.85	20	1.86 ± 1.34
Fasting glucose (mmol/l)	41	5.5 ± 2.4	47	5.23 ± 1.9	21	5.4 ± 1.1	21	5.0 ± 0.7
Metabolic syndrome	40	19 (47.5)	49	25 (51.0)	17	6 (35.3)	20	7 (35.0)

Data expressed as means with standard deviation or frequencies with percentages

[a] At baseline, significantly more candidates had hypoalbuminaemia than recipients, chi Square test: χ^2 (1) = 15.619, p <0.005)

[b] Significant weight loss, paired samples t-test: t (50) = 2.072, p = 0.043

[c] Significant WC increase, paired samples t-test: t (14) = - 2.861, p = 0.013

Significantly more transplant recipients had normal BMI at baseline while transplant candidates were overweight, Fisher's exact = 9.004, p=0.033.

[d] Central obesity and increased risk obesity (WC ≥ 88cm for women & ≥ 102 for men (25)

Table 6.4: Macronutrient intake of transplant candidates and recipients at baseline and six months

	Transplant candidates			Transplant recipients		
	Baseline n = 53	**6 months n = 51**	**SA reference values†**	**Baseline n = 22**	**6 months n = 22**	**SA reference values†**
Total energy (kj/day)	7786.2 ± 1919.1	7849.0 ± 2093.9		8142.5 ± 2067.8	8029.9 ± 2361.6	
Energy (kj/ kg BW/day)	108.1 ± 32.4	110.5 ± 35.0		119.6 ± 32.5	115.7 ± 38.1	
Energy (kcal)/ kg BW / day	25.9 ± 7.8	26.4 ± 8.4	30 – 35 kcal/kg/day	28.6 ± 7.8	27.7 ± 9.1	25 -30 kcal/kg/day
% Protein energy	15.3 ± 4.2	15.9 ± 4.2		14.6 ± 3.9	16.4 ± 3.8	
Total protein (g/day)	72.5 ± 27.5	76.3 ± 31.4		72.7 ± 26.8	78.0 ± 22.2	
Plant protein (g/day)	23.7 ± 9.2	23.1 ± 9.3		28.3 ± 14.6	26.3 ± 13.7	
Animal protein (g/day)	45.7 ± 29.4	51.5 ± 30.8		39.0 ± 19.2	48.6 ± 20.0	
Total protein /kg BW/day	1.0 ± 0.4	1.1 ± 0.4	HD: 1.2g/kg/day PD: 1.2-1.3g/kg/day	1.0 ± 0.3	1.1 ± 0.3	0.8-1.0g/ kg/ day
Fat energy (%)	28.5 ± 9.1	30.6 ± 9.1	25 -35 %/day	28.3 ± 9.3	30.2 ± 8.0	25 -30 %/day
Total fat (g/day)	62.3 ± 27.9	66.9 ± 27.3		64.6 ± 26.8	67.3 ± 30.6	
CHO energy (%)	54.0 ± 10.6	51.2 ± 10.7	50-60%/ day	55.0 ± 10.7	51.3 ± 8.9	50-60%/ day
Total CHO (g/day)	229.9 ± 63.0	220.0 ± 66.6		245.0 ± 75.0	228.8 ± 79.3	

Data expressed as means with standard deviation

kj: kilojoule, BW: body weight, CHO: carbohydrate

† (30)

Table 6.5: Correlation coefficients between macronutrients and weight and waist circumference in transplant recipients

	Weight (n = 21)		**Waist circumference** (n = 18)	
	r	**p**	**r**	**p**
Total energy (kj/day)	0.252	0.270	0.114	0.652
Total protein (g) /day	**0.609****	**0.003**	0.428	0.076
Plant protein (g) /day	**0.534***	**0.013**	- 0.158	0.532
Animal protein (g) /day	**0.513***	**0.017**	**0.517***	**0.028**
Total fat (g) / day	0.065	0.778	0.214	0.393
Total CHO (g) /day	0.084	0.718	- 0.074	0.772

r =Pearson's correlation
kj: kilojoule, CHO: carbohydrate
*correlation is significant at $p < 0.05$, ** correlation is significant at $p < 0.01$

6.4 Discussion

The present study investigated overall and central obesity, through longitudinal observation of weight, BMI and WC in HIV-infected kidney transplant candidates and recipients from a HIV-infected donor. In addition, the macronutrient composition of the diet and their association with weight, WC and their respective changes after six months, was also explored.

6.4.1 Transplant candidates

In the present study, more transplant candidates were overweight than normal weight, which is in line with anthropometric characteristics of dialysis patients elsewhere (31), and is reflective of the trend, both globally and in South Africa, of increasing BMI in the general population (32-34).

Due to the paradoxical association between a high BMI and enhanced survival in the dialysis populations (35), a more pressing concern would be to patients with a low BMI or weight loss while on dialysis. A low BMI carries a two-fold higher mortality risk than HD patients with normal BMI (36), as weight loss and muscle loss over time is associated with a higher mortality rate. Furthermore, it has also been shown that of the two indicators, muscle loss is more serious as it is a stronger predictor of mortality than overall weight loss (35). In the current study, weight loss was experienced by the majority of candidates over the six month follow-up period. Furthermore, the magnitude of weight lost between the two assessment points was found to be statistically significant. Although, weight loss could mean a reduction in either fat, muscle, or

both, it is highly likely that in the current study, the loss of weight seen at six months was not limited to adipose tissue. The reasoning behind this is that decreases in weight are typically accompanied by decreases in WC when there is a reduction in body fat (37). In the present study, the decrease in overall weight was significant, while the decrease in WC after six months, was slight and not statistically significant. Therefore, the probability that some of the weight loss could be attributed to muscle mass is high, and would be important to investigate to enable the initiation of appropriate interventions.

Abdominal obesity using the WHO WC cut-offs (WC ≥ 88cm for women and ≥ 102cm for men), identified 33.3% and 30.4% of transplant candidates, at both time points, with a high WC in the current study. An Italian cohort of dialysis patients reported an even higher prevalence of abdominal obesity (39%) using the same cut-offs (38). The authors also documented that a WC of ten centimetres above the male and female cut-offs of 102 cm and 88 cm respectively, corresponded to a 26% and 38% higher risk for general and CVD-related mortality respectively. Moreover, it was noted that since BMI was inversely related to both these outcomes, patients at the greatest mortality risk had a low BMI and high WC. Conversely, better survival was observed in patients with a higher BMIs and a lower WC (38).

The MetS definition used in the current study, stipulates an even lower cut-off than the WHO for WC, i.e ≥ 94cm for males and ≥ 80cm for females, which classified 47.5% and 51.0% of candidates with MetS at baseline and six months respectively. Differences in MetS definitions notwithstanding, the prevalence of MetS in other dialysis groups has been reported to range from 34.0% to 67% HD patients (39,40), and between 53.2% and 66.3% in PD patients (41). Wait-listed candidates with MetS are at a 2.6 fold risk of new-onset diabetes mellitus (NODAT) (39), which by itself is associated with graft loss and CVD risk and mortality (42), highlighting the importance of controlling individual MetS components (39).

In terms of dietary adequacy, neither mean total energy nor protein intake met the recommended daily energy and protein intake for HD and PD (30), falling short in these nutrients at both assessments, despite a slight increase in protein intake at six months. Correlational analysis showed no relationship between macronutrients and weight, WC or weight change. This is not unusual, as weight loss in disease states is known to occur for reasons other than dietary intake. In CKD, a host of factors, including chronic inflammation, hypercatabolism, endocrine abnormalities and metabolic acidosis contribute to malnutrition (43), as does the presence of comorbidity (26). HIV-positive individuals in particular, even in the era of antiretroviral

therapy, are known to live with chronic low grade inflammation (44). The possibility of illness related weight loss is further evidenced by the presence of hypoalbuminaemia, found in the majority of the present study's transplant candidates. Hypoalbuminaemia is a recognised marker of illness and is usually not related to diet in CKD (45). It fact it is a poor indicator of nutritional status due to poor correlation with other nutritional markers in dialysed patients (46). It is however a useful predictor of CVD. De Mustert and colleagues noted that in dialysis patients, each 1g/dL decrease in serum albumin increases the risk of mortality by 47% and 38% in HD and PD patients respectively (47), and as such, is an important marker to observe in terms of disease status. Although diet was not linked to weight loss in the present study, a poor intake will no doubt exacerbate it (43), and will require attention to minimise weight loss and preserve muscle mass.

6.4.2 Transplant recipients

With a mean BMI of 24.5 ± 4.6 kg/m^2, the majority of recipients (71.4%) fell within the normal BMI category. After six months, 59.1% had a normal BMI, due to weight changes in all but 19.0% of recipients, whose weight remained static. The proportion of recipients with weight gain was not unlike that seen in kidney transplant recipients in the general population. The majority of recipients, (52.4%) showed increases in weight after six months, similar to previous studies that reported weight gain in 50.0% and 55.9% of recipients respectively (18,48). Twenty eight percent (28.0%) of transplant recipients lost weight at six month follow-up. Some weight loss occurs immediately following a transplant, due to increased surgery-related catabolism, fluid loss and inadequate dietary intake, although this is quickly restored (49). According to Dujovonic et al, comorbidity is an important determinant of malnutrition following a transplant (50). Indeed, HIV-related factors may have also contributed to the weight loss documented. In the current study, recipients appear to be well managed, as was evident from their favourable HIV parameters (CD4 and VL), indicative of disease progression and response to anti-retroviral therapy (51).

In the present study, WC identified 33.3% and 44.4% with central adiposity and high metabolic risk, whereas BMI classified 19.0% and 27.3% as obese at baseline and six months respectively. This increase in mean WC observed from baseline to six months was found to be statistically significant, and was a noteworthy finding in this study. Interestingly, this occurred without significant increases in BMI over the same period. Similar outcomes were reported by Harada and colleagues who noted near static BMIs, despite significant increases in percentage body fat (%BF) (52). Increases in abdominal fat in the current study and others (11,53) are common in

transplant recipients. According to Romegurro et al, when changes in WC occur independent of corresponding changes in weight or BMI, they are in all likelihood, reflective of changes in visceral adipose tissue (VAT) (54). This poses a concern for the present transplant recipients as VAT is metabolically active, and is associated with lipid abnormalities, hypertension and hyperglycaemia which are all risk factors for CVD (55,56). The clustering of these risk factors and central obesity identified about 35.0% of transplant recipients with MetS, which falls within the prevalence values of MetS in the HIV infected population (11.2% - 45.4%) (57). Moreover, in the transplant population, it appears that the prevalence of MetS increases over time (58). MetS was identified in 28.6% of recipients at one year post transplant (59), 37.7% at 18 months (17), and 63.0 % at six years post-transplant (16). In comparison, it appears that the 35.0% prevalence of MetS among the current study's transplant recipients at a mean post-transplant time of 2.7 ± 2.3 years is seemingly in line, if not lower than the prevalence of MetS in transplant recipients in the general population.

In the present study, the mean daily intake of total energy and protein was within the 25 - 30kcal/day and 1.0 - 1.1g protein (maintenance)/kg/day recommendations (30). At six months, there was an increase in total protein intake. This increase was not statistically significant, and still within the recommended limits. Total fat also increased, especially saturated fat, probably due to the greater proportion of animal protein consumed at the six month assessment. Unlike the transplant candidates, there was a significant association between total protein, animal and plant protein and weight at baseline. At six months, only animal protein showed a significant correlation with WC. There was no association between protein and change in weight or WC.

The association between protein and weight has previously been described in the general population. In a small number of healthy subjects, a longitudinal study spanning six years found that higher intakes of protein was associated with weight gain. Using bioelectrical impedance, researchers also showed that most of the weight gained was fat mass (60). Similarly, in the larger European EPIC-PANACEA cohort with 373 803 healthy participants, a positive correlation with protein and weight over a five year follow-up period was also found. Specifically, it was noted that 5.0% more protein energy that replaced either fat or carbohydrate energy, was positively associated with weight gain when intakes exceeded 22.0% of energy, normal weight and overweight participants had a 23 % - 24% greater chance of becoming overweight or obese (61). In the current study, the mean intake of 14.6 ± 3.9% at baseline increased to 16.4 ± 3.8% at six months. Although the latter was still within the recommended

guidelines, it would be an important to ensure that total protein does not exceed the guideline limits, given the greater dietary freedom after the restricted protein intake while on dialysis.

Bujnowski and colleagues, further investigated the source of protein linked to weight gain. Their results found a statistically significant positive association between dietary protein obtained from animal sources and obesity (62). Halkjaer et al found that weight increases over the long term, was linked to a higher overall protein intake, and protein sourced from animal products, specifically red meat and processed meat as opposed to protein derived from fish and dairy produce (63). Unlike the results of the current study, these authors did not find any relationship between protein and WC (63). However, this association was observed in other research. Moslehi et al, investigated the association between macronutrients and changes in visceral fat over three years. Their results showed that independent of total energy, higher overall protein intake as well as monounsaturated fats from animal sources may contribute to increases in harmful visceral fat (64). Results from the EPIC study also point to dietary patterns that are important to consider in preventing harmful increases in WC. Foods with a high energy density and a high glycaemic index are most likely to contribute to the deposition of VAT (54). Therefore to reduce abdominal obesity, the diet should include low glycaemic index, low energy density, and high fibre foods. Dietary intakes high in fruit and dairy and low in white bread, processed meat, margarine, and soft drinks may also help to prevent abdominal fat accumulation (54,65).

What is promising, is that diet is modifiable and long term interventions have shown some success. Transplant recipients that receive rigorous nutritional assessment and regular follow-up, gain less weight after ten years than those who receive standard nutrition education immediately following the transplant (66). The results in the current study and the aforementioned research are useful in highlighting key areas for nutrition education. With the exception of very low calorie diets (67), interventions that target diet only, have proven effective in decreasing weight and VAT by up to 35%, similar to interventions that include both diet and exercise (68). The authors caution, though, that interventions that only centre on diet, may produce undesired reductions in both lean tissue and skeletal muscle, which can be preserved if diet is combined with exercise (68). Moreover, exercise is important in that it helps maintain the weight lost. Hunter and colleagues specified that engaging in 80 minutes/week of aerobic or resistance activity prevented regain of VAT one year after weight loss, even if small regains in weight occurred. On the other hand, the diet-only group who did not include exercise as part of their weight loss programme, showed a 25% gain in VAT after one year (69). Although the present study did not include the assessment of activity or exercise, previous

research conducted on transplant recipients found very little change activity levels after six months (70). Indiscriminate dietary intake, and a sedentary lifestyle could result in unchecked increases in weight, WC and harmful VAT.

Limitations inherent to dietary intake studies are also applicable to the current study. This includes the inaccurate estimation of quantity, recall bias and misreporting (28). Furthermore, a single 24-hour recall is less likely to be a valid reflection of habitual intake, lowering the likelihood of significant correlations with individual nutrients. On the other hand however, intake information provided some constructive dietary insight for this study and for future research. For example, plant versus animal protein intake is important and was briefly mentioned within the scope of this study. However, given the emerging literature on animal versus plant protein distribution in CKD, future research with a focus in this area would be beneficial. Another drawback is that data on lipodystrophy was not collected, which could have affected the interpretation of the anthropometric measurement taken. Strengths of this study are the inclusion of WC, which is a more valid measurement of abdominal obesity than BMI alone and the associated health risks. This study is the first to investigate adiposity in HIV infected pre- and post-transplant recipients from HIV infected donors.

To summarise the present study, transplant candidates experienced significant weight loss. The underlying causes should be investigated and individual intervention planned accordingly. WC increased significantly for transplant recipients over the six month follow-up period, Furthermore, as WC increased without significant changes in BMI, it is possibly the result of increases in VAT. These results reinforce the importance of including WC as a routine anthropometric indicator when screening. Regular exercise and on-going nutrition assessment and education should aim not only to maintain a healthy BMI, but also to keep WC within healthy limits. The correlations of overall protein intake with weight at baseline, and animal protein with WC at six months amongst transplant recipients, is important for counselling.

6.5 References

1. World Health Organization. Obesity situation and trends. Global Health Observatory (GHO) data. [Online]; [cited 02/03/2019] Available from https://www.who.int/gho/en/

2. Molnar MZ, Streja E, Kovesdy CP, Bunnapradist S, Sampaio MS, Jing J, Krishnan M, Nissenson AR, Danovitch GM, Kalantar-Zadeh K. Associations of body mass index and weight loss with mortality in transplant-waitlisted maintenance hemodialysis patients. Am J Transplant. 2011; 11(4): 725-736.

3. Gore JL, Pham PT, Danovitch GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, Singer JS. Obesity and outcome following renal transplantation. Am J Transplant. 2006; 6(2): 357–363.

4. Aalten J, Christiaans MH, de Fijter H, Hené R, van der Heijde JH, Roodnat J, Surachno J, Hoitsma A. The influence of obesity on short- and long-term graft and patient survival after renal transplantation. Transpl Int. 2006; 19(7): 901-907.

5. Marcén R, Fernández A, Pascual J, Teruel JL, Villafruela JJ, Rodriguez N, Martins J, Burgos FJ, Ortuño J. High body mass index and posttransplant weight gain are not risk factors for kidney graft and patient outcome. Transplant Proc. 2007; 39(7): 2205-7.

6. Chadban S, Chan M, Fry K, Patwardhan A, Ryan C, Trevillain P, Westgarth F. Nutritional management of overweight and obesity in adult kidney transplant recipients. Nephrology. 2010; 15(S1): S52–S55.

7. Zelle DM1, Kok T, Dontje ML, Danchell EI, Navis G, van Son WJ, Bakker SJ, Corpeleijn E. The role of diet and physical activity in post-transplant weight gain after renal transplantation. Clin Transplant. 2013; 27(4): E484-490. doi: 10.1111/ctr.12149.

8. Micozkadioglu H, Ozdemir FN, Sezer S, Arat Z, Haberal M. Weight gain after living-related renal transplantation affects long-term graft function. Transplant Proc. 2005; 37(2): 1029-1032.

9. Gumber MR, Jain SH, Kute VB, Gireesh MS, Shah PR, Patel HV, Goplani KR, Vanikar AV, Trivedi HL. Effect of post-transplant weight at one year on renal allograft function. Saudi J Kidney Dis Transpl. 2011; 22(4): 799-801.

10. Hoogeveen EK, Aalten J, Rothman KJ, Roodnat JI, Mallat MJ, Borm G, Weimar W, Hoitsma AJ, de Fijter JW. Effect of obesity on the outcome of kidney transplantation: a 20-year follow-up. Transplantation. 2011; 91(8): 869-874.

11. Orazio L, Armstrong K, Banks M, Johnson D, Isbel N, Hickman I. Central obesity is common in renal transplant recipients and is associated with increased prevalence of cardiovascular risk factors. Nutr Diet. 2007; 64(3): 200-206.

12. Kovesdy CP, Czira ME, Rudas A, Ujszaszi A, Rosivall L, Novak M, Kalantar-Zadeh K, Molnar MZ, Mucsi I. Body mass index, waist circumference and mortality in kidney transplant recipients. Am J Transplant. 2010; 10(12): 2644-2651.

13. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: Definitions and controversies. BMC Med. 2011; 9(48). doi: 10.1186/1741-7015-9-48.

14. Hami M, M Sabbagh MG, Sefidgaran A, Mojahedi MJ. Prevalence of the metabolic syndrome in kidney transplant recipients: A single-center study. Saudi J Kidney Dis Transpl. 2017; 28(2): 362-367.

15. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation. 2004 Sep 7;110(10):1245-50. 2004; 110(10): 1245-1250.

16. de Vries AP, Bakker SJ, van Son WJ, van der Heide JJ, Ploeg RJ, The HT, de Jong PE, Gans RO. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. Am J Transplant. 2004; 4(10): 1675-1683.

17. Porrini E, Delgado P, Bigo C, Alvarez A, Cobo M, Checa MD, Hortal L, Fernández A, García JJ, Velázquez S, Hernández D, Salido E, Torres A. Impact of metabolic syndrome on graft function and survival after cadaveric renal transplantation. Am J Kidney Dis. 2006; 48(1): 134-142.

18. Cashion AK, Hathaway DK, Stanfill A, Thomas F, Ziebarth JD, Cui Y, Cowan PA, Eason J. Pre-transplant ppredictors of one year weight gain after kidney transplantation. Clin Transplant. 2014; 28(11): 1271–1278.

19. Johnson CP, Gallagher-Lepak S, Zhu YR, Porth C, Kelber S, Roza AM, Adams MB. Factors influencing weight gain after renal transplantation. Transplantation. 1993; 56(4): 822-827.

20. Clunk JM, Lin CY, Curtis JJ. Variables affecting weight gain in renal transplant recipients. Am J Kidney Dis. 2001; 38(2): 349-353.

21. Nolte Fong JV, Moore LW. Nutrition trends in kidney transplant recipients: the importance of dietary monitoring and need for evidence-based recommendations. Front Med (Lausanne). 2018; 5: 302. doi: 10.3389/fmed.2018.00302.

22. Heaf J, Jakobsen U, Tvedegaard E, Kanstrup I, Fogh-Andersen N. Dietary habits and nutritional status of renal transplant patients. J Ren Nutr. 2004; 14(1): 20-25.

23. Rho MR, Lim JH, Park JH, Han SS, Kim YS, Lee YH, Kim WG. Evaluation of nutrient intake in early post kidney transplant recipients. Clin Nutr Res. 2013; 2: 1-11.

24. Centers of Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) Anthropometry Procedures Manual. [Online]; 2009 [cited 22/02/2014]. Available from: https://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf.

25. World Health Organization. Preventing and managing the global epidemic. Geneva: Report of a WHO Consultation. Technical report series 894. [Online]; 2000. [cited 13/03.2019]. Available from: http://www.who.int/iris/handle/10665/42330

26. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevinho-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for

protein–energy wasting in acute and chronic kidney disease. Kidney Int. 2008; 73(4): 391-398.

27. Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: A global public health problem and a new definition. J Atheroscler Thromb. 2005; 12(6): 295-300.

28. Nelson M, Bingham SA. Assessment of food consumption and nutrient intake. In: Margetts BM, Nelson M, editors. Design concepts in nutritional epidemiology. Oxford: Oxford University Press; 1997. p. 123-169.

29. Senekal M, Steyn NP. Food Photo Manal. Parow: Medical Research Council. 2004

30. National Department of Health, Directorate: Nutrition. National renal nutrition practice guidelines for adults [Online];2018 [cited 24/01/2019]. Available from: http://www.saspen.com/Websites/saspen/images/Renal%20Nutrition%20web.pdf

31. Zoccali C. The obesity epidemics in ESRD: From wasting to waist? Nephrol Dial Transplant. (2009) 24: 376–380. 2009; 24(2): 376–380.

32. Hales CM, Carroll MD, Fryar CD, Ogden CL. Adult obesity facts. [Online]; 2017 [cited 14/02/2019]. Available from: https://www.cdc.gov/nchs/data/databriefs/db288.pdf.

33. Cois A, Day C. Obesity trends and risk factors in the South African adult population. BMC Obesity. 2015; 2(42). doi.org/10.1186/s40608-015-0072-2

34. World Health Organization. Obesity and overweight (fact sheet).[Online]; 2018. [cited 14/02/2019]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

35. Park J, Ahmadi SF, Streja E, Molnar MZ, Flegal KM, Gillen D, Kovesdy CP, Kalantar-Zadeh K. Obesity paradox in end-stage kidney disease patients. Prog Cardiovasc Dis. 2014; 56(4): 415-425.

36. de Mutsert R, Snijder MB, van der Sman-de Beer F, Seidell JC, Boeschoten EW, Krediet RT, Dekker JM, Vandenbroucke JP, Dekker FW. Association between body mass index and mortality is similar in the hemodialysis population and the general population at high age and equal duration of follow-up. J Am Soc Nephrol. 2007; 18(3): 967-974.

37. Miyatake N, Matsumoto S, Miyachi M, Fujii M, Numata T. Relationship between changes in body weight and waist circumference in Japanese. Environ Health Prev Med. 2007; 12(5): 220–223.

38. Postorino M, Marino C, Tripepi G, Zoccali C; CREDIT (Calabria Registry of Dialysis and Transplantation) Working Group. Abdominal obesity and all-cause and cardiovascular mortality in end-stage renal disease. J Am Coll Cardiol. 2009; 53(15): 1265-1272.

39. Bonet J, Martinez-Castelao A, Bayés B. Metabolic syndrome in hemodialysis patients as a risk factor for new-onset diabetes mellitus after renal transplant: a prospective observational study. Diabetes Metab Syndr Obes. 2013; 6: 339–346.

40. Al Saran K, Elsayed S, Sabry A, Hamada M. Obesity and metabolic syndrome in hemodialysis patients: Single center experience. Saudi J Kidney Dis Transpl. 2011; 22(6): 1193-1198.

41. Szeto CC, Kwan BC, Chow KM, Leung CB, Cheng MS, Law MC, Li PK. Metabolic syndrome in peritoneal dialysis patients: choice of diagnostic criteria and prognostic implications. Clin J Am Soc Nephrol. 2014; 9(4): 779-787.

42. Juan Khong M1, Ping Chong Ch. Prevention and management of new-onset diabetes mellitus in kidney transplantation. Neth J Med. 2014; 72(3): 127-134.

43. Yasui S, Shirai Y, Tanimura M, Matsuura S, Saito Y, Miyata K, Ishikawa E, Miki C, Hamada Y. Prevalence of protein-energy wasting (PEW) and evaluation of diagnostic criteria in Japanese maintenance hemodialysis patients. Asia Pac J Clin Nutr. 2016; 25(2): 292-299.

44. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. Immunity. 2013; 39(4): 633–645.

45. Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. JASN. 2010; 21(2): 223-230.

46. Gama-Axelsson T, Heimbürger O, Stenvinkel P, Bárány P, Lindholm B, Qureshi AR. Serum albumin as predictor of nutritional status in patients with ESRD. Clin J Am Soc Nephrol. 2012; 7(9): 1446-1453.

47. de Mutsert R (b), Grootendorst DC, Indemans F, Boeschoten EW, Krediet RT, Dekker FW; Netherlands Cooperative Study on the Adequacy of Dialysis-II Study Group. Association between serum albumin and mortality in dialysis patients is partly explained by inflammation, and not by malnutrition. J Ren Nutr. 2009; 19(2): 127-135.

48. Baum CL, Thielke K, Westin E, Kogan E, Cicalese L, Benedetti E. Predictors of weight gain and cardiovascular risk in a cohort of racially diverse kidney transplant recipients. Nutrition. 2002; 18: 139-146.

49. van den Ham EC (b), Kooman JP, Christiaans MH, Nieman FH, van Hooff JP. Weight changes after renal transplantation: A comparison between patients on 5-mg maintenance steroid therapy and those on steroid-free immunosuppressive therapy. Transpl Int. 2003; 16(5): 300-306.

50. Djukanović L, Lezaić V, Blagojević R, Radivojević D, Stosović M, Jovanović N, Ristić S, Simić-Ogrizović S. Co-morbidity and kidney graft failure-two main causes of malnutrition

in kidney transplant patients. Nephrol Dial Transplant. 2003; 18(Suppl 5): v68-70.

51. Panel on antiretroviral guidelines for adults and adolescents - Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. [Online]; 2018. [cited 05/04.2019]. Available from: https://aidsinfo.nih.gov/guidelines

52. Harada H, Nakamura M, Hotta K, Iwami D, Seki T, Togashi M, Hirano T, Miyazaki C. Percentages of water, muscle, and bone decrease and lipid increases in early period after successful kidney transplantation: A body composition analysis. Transplant Proc. 2012; 44(3): 672–675.

53. van den Ham EC, Kooman JP, Christiaans MH, Leunissen KM, van Hooff JP. Post transplantation weight gain is predominantly due to an increase in body fat mass. Transplantation. 2000; 70(1): 241-242.

54. Romaguera D, Angquist L, Du H, Jakobsen MU, Forouhi NG, Halkjaer J, Feskens EJ, van der A DL, Masala G, Steffen A, Palli D, Wareham NJ, Overvad K, Tjønneland A, Boeing H, Riboli E, Sørensen TI. Dietary determinants of changes in waist circumference adjusted for body mass index – a proxy measure of visceral adiposity. PLoS One. 2010; 5(7): e11588. doi: 10.1371/journal.pone.0011588.

55. Li X, Katashima M, Yasumasu T, Li KJ. Visceral fat area, waist circumference and metabolic risk factors in abdominally obese Chinese adults. Biomed Environ Sci. 2012; 25(2): 141-148.

56. Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD, Ergun DL. Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity (Silver Spring). 2012; 20(6): 1313–1318.

57. Paula AA, Falcão MC, Pacheco AG. Metabolic syndrome in HIV-infected individuals: Underlying mechanisms and epidemiological aspects. AIDS Res Ther. 2013; 10(32). doi: 10.1186/1742-6405-10-32.

58. Hricik DE. Metabolic syndrome in kidney transplantation: management of risk factors. CJASN. 2011; 6(7):1781-1785.

59. Ozdemir FN, Karakan S, Akgul A, Haberal M. Metabolic syndrome is related to long-term graft function in renal transplant recipients. Transplant Proc. 2009; 41(7): 2808-2810.

60. Ankarfeldt MZ, Gottliebsen K, Ängquist L, Astrup A, Heitmann BL, Sørensen TI. Dietary protein and urinary nitrogen in relation to 6-year changes in fat mass and fat-free mass. Int J Obes (Lond). 2015; 39(1): 162-168.

61. Vergnaud AC, Norat T, Mouw T, Romaguera D, May AM, Bueno-de-Mesquita HB, van der A D, Agudo A, Wareham N, Khaw KT, Romieu I, Freisling H, Slimani N, Perquier F,

Boutron-Ruault MC, Clavel-Chapelon F, Palli D, Berrino F, Mattiello A, Tumino R, Ricceri F, Macronutrient composition of the diet and prospective weight change in participants of the EPIC-PANACEA Study. PLoS One. 2013; 8(3): e57300. doi: 10.1371/journal.pone.0057300.

62. Bujnowski D, Xun P, Daviglus ML, Van Horn L, He K, Stamler J. Longitudinal association between animal and vegetable protein intake and obesity among men in the United States: the Chicago Western Electric Study. J Am Diet Assoc. 2011; 111(8): 1150-1155.

63. Halkjær J, Olsen A, Overvad K, Jakobsen MU, Boeing H, Buijsse B, Palli D, Tognon G, Du H, van der A DL, Forouhi NG, Wareham NJ, Feskens EJ, Sørensen TI, Tjønneland A. Intake of total, animal and plant protein and subsequent changes in weight or waist circumference in European men and women: The Diogenes project. Int J Obes (Lond). 2011 Aug;35(8). 2011; 35(8): 1104-13.

64. Moslehi N, Ehsani B, Mirmiran P, Hojjat P, Azizi F. Association of Dietary Proportions of Macronutrients with visceral adiposity index: non-substitution and iso-energetic substitution models in a prospective study. Nutrients. 2015; 7(10): 8859–8870.

65. Romaguera D(b), Ängquist L, Du H, Jakobsen MU, Forouhi NG, Halkjær J, Feskens EJ, van der A DL, Masala G, Steffen A, Palli D, Wareham NJ, Overvad K, Tjønneland A, Boeing H, Riboli E, Sørensen TI. PLoS One. 2011. PLoS One. 2011; 6(8): e23384. doi: 10.1371/journal.pone.0023384.

66. Kiisk L, Ots-Rosenberg M. Intensive nutritional counselling obviates a weight gain in kidney transplant recipients with long-term graft survival in Estonia [version 1; referees: 2 approved with reservations]. F1000Research. 2016; 5(2658). doi.org/10.12688/f1000research.10035.1

67. Chaston TB, Dixon JB. Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review. nt J Obes (Lond). 2008; 32(4): 619–628.

68. Ross R, Rissanen J, Pedwell H, Clifford J, Shragge P. Influence of diet and exercise on skeletal muscle and visceral adipose tissue in men. J. Appl. Physiol. 1996; 81(6): 2445–2455.

69. Hunter GR, Brock DW, Byrne NM, Chandler-Laney P, Del Coral P, Gower BA. Exercise training prevents regain of visceral fat for 1-year following weight loss. Obesity (Silver Spring). 2010; 18(4): 690–695.

70. Cupples CK, Cashion AK, Cowan PA, Tutor RS, Wicks MN, Williams R, Eason JD. Characterizing dietary intake and physical activity affecting weight gain in kidney transplant recipients. Prog Transplant. 2012; 22(1): 62-70.

CHAPTER 7

HEALTH RELATED QUALITY OF LIFE AND ASSOCIATED FACTORS IN HIV-POSITIVE TRANSPLANT CANDIDATES AND RECIPIENTS FROM A HIV-POSITIVE DONOR

ABSTRACT

Background: The assessment of health-related quality of life (HRQOL) furthers the understanding of living with a disease and its treatment, beyond clinical indicators of health. A better HRQOL has been reported in kidney transplant recipients compared to transplant candidates on dialysis. Globally, HRQOL in transplant candidates and recipients who are also infected with HIV and are awaiting a kidney, or have received one from a HIV-positive donor, has not been previously investigated.

Objective: To evaluate the HRQOL of HIV-positive kidney transplant candidates and recipients from HIV-positive donors at baseline and six months, and to determine the relationship between socio-demographic, clinical and nutritional status and HRQOL indicators.

Methods: A six month longitudinal study was undertaken using a mixed methodology approach. The Short Form-36 (SF-36) questionnaire was used to quantitatively score patients' perceptions of HRQOL. Face-to-face interviews provided a more in-depth understanding of the SF-36 scores. Nutritional status indicators were determined by mid arm muscle circumference, prealbumin and BMI.

Results: 68 patients completed the SF-36 at baseline and 6 months.

Transplant candidates: Transplant candidates had lower HRQOL than recipients. The main mental stressors were income, employment and waiting for a donor. Physical health complaints were body pain and fatigue. Prealbumin and BMI was positively correlated with general health (GH) at baseline ($r = 0.401$, $p = 0.031$ and $r = 0.338$, $p = 0.025$). Besides a positive association with role physical (RP) and body pain (BP), albumin was associated with overall physical composite score (PCS) ($r = 0.329$, $p = 0.024$) at six months.

Transplant recipients: Transplant recipients had high HRQOL scores. The PCS and mental composite score (MCS) was above the average of 50 for the general population, with PCS being 53.8 ± 10.0 and 56.6 ± 6.5 at baseline and six months respectively. MCS was 51.3 ± 11.5 and 54.2 ± 8.5 at baseline and six months respectively. Albumin correlated positively with PCS ($r = 0.464$, $p = 0.034$) at six months and role emotional (RE) ($r = 0.492$, $p = 0.024$). Higher prealbumin was associated with better RE and RP abilities and MCS ($r = 0.495$, $p = 0.034$). MAMC was associated with four domains of physical health and strongly correlated with PCS ($r = 0.821$, $p = 0.000$).

Conclusion: Kidney transplant recipients experience a better HRQOL than transplant candidates on dialysis, awaiting a transplant. Better nutritional status, indicated by prealbumin and MAMC was associated with better mental (MCS) and physical (PCS) HRQOL respectively.

Keywords: Keywords: Kidney transplant candidates, Kidney transplant recipients, Human immunodeficiency virus (HIV), Health-related quality of life, SF-36, mid arm muscle circumference

7.1 Introduction

Human immunodeficiency virus (HIV) infection was formerly a contraindication for kidney transplantation, until outcomes similar to transplant recipients in the general population were observed (1,2). Initially, HIV-negative donors were used (3), until 2008, when South Africa was the first country to successfully transplant HIV- positive patients with donor kidneys from HIV-positive individuals. By all objective clinical measures the transplant was successful, and HIV parameters showed no evidence of hastened HIV disease progression (4).

Traditional clinical markers of this medical breakthrough are important, and have paved the way for many more transplants in patients that would have otherwise demised. Recently though, it has also become increasingly important to evaluate the benefit-risk of a treatment from the perspective of the patient (5). Health related quality of life (HRQOL) refers to the way a patient perceives the functional impact of his illness and treatment, on multiple dimensions of his health and well-being (5,6). HRQOL in chronic disease and its treatment is very relevant because it becomes a part of an individual's life, intertwining in one's everyday personal and social context (7).

HRQOL studies in end stage renal disease (ESRD) describe the adverse effects of dialysis on HRQOL and improvements post-transplant (8). Studies also show that HRQOL relates to clinical outcomes in that the physical components of HRQOL which are predictive of graft and patient survival in transplant recipients (9). As it is affected by multiple factors in ESRD (10), nutritional status is one such factor that is also associated with HRQOL in the general population and various patient groups, including HIV (11-14). It is relevant in ESRD as a potentially modifiable component of HRQOL.

To date, there has not been a documented study exploring HQOL in ESRD patients, infected with HIV or the association with nutritional status. As these patients live with the burden of two debilitating diseases, incorporating HRQOL assessments in this group, will provide insight into psycho-social factors affecting health, and appraise their current health care, aiding decision-making to improve all aspects of the patient's life (15). Within this context, the aim of the current study was to evaluate the HRQOL of HIV-positive kidney transplant candidates and recipients from HIV-positive donors, and to determine the relationship between clinical, nutritional status and socio-demographic factors associated with HRQOL.

7.2 METHODS

7.2.1 Participants

For this longitudinal study, observational study, participants were recruited through the renal transplant programme for HIV-positive patients at Groote Schuur Hospital. HIV-positive kidney transplant recipients and those on the waiting list receiving dialysis, were contacted telephonically or in person at their outpatient clinic and invited to participate. Patients were excluded if they were severely ill, declined participation, were not contactable, uncooperative or missed several interview appointments (typically two or more without reason). Altogether 76 patients agreed to participate after the study details were explained to them. Data collection commenced in June 2015 and ended in June 2016, during which time participants were followed up across six provinces. All measurements were taken at baseline and repeated at six months. During the study period, 68 patients completed the SF-36 at baseline and six months.

Written informed consent was obtained from all patients. The study was approved by The University of KwaZulu-Natal's Biomedical Research Ethics Committee (Approval number BE 327/13), and where necessary from the provincial department of Health. Site permission was obtained from all institutions where patients were being followed up.

7.2.2 Socio-demographic and clinical information

Socio-demographic information was obtained during interviews using a questionnaire designed for the purpose of the study. The questionnaire was reviewed for content validity by the research supervisors and a research expert with experience in questionnaire design and experience within the context of HIV. Where possible, clinical information was obtained from medical records, or during patient interviews.

7.2.3 Health related quality of life

HRQOL was measured using mixed methods research to elucidate an in-depth understanding of the concept among study participants.

Quantitative measure of HRQOL

HRQOL was assessed using an interviewer-administered Short Form 36 (SF-36) version 2 (16). It is a generic instrument which takes into account quality of life experienced in the past month

and is the most commonly used generic measurement of quality of life in renal replacement therapy (17). The 36 items on the questionnaire are categorised into eight domains (also called dimensions or subscales) of a patient's health namely; physical function (PF), role physical (RP), bodily pain (BP), vitality (VT), social functioning (SF), role emotional (RE), mental health (MH), and general health (GH) (18). Table 7.1 provides a brief description of what each domain assesses (19,20). The SF-36 software uses a scoring algorithm to translate the raw data into scores for each domain that ranges from 0 (worst health) to 100 (best possible health) (21,22). Higher scores reflect better daily functioning and well-being (18). The eight domains are further merged into two composite scores, the physical component score (PCS) and mental component score (MCS). The average PCS and MCS for the general population is 50 (23). Therefore scores above or below 50 suggest better or worse perceived mental or physical health respectively, than the average person. A decrease in PCS shows more adverse effects in the domains of physical health namely worse body pain, vitality and fatigue as well as greater limitations in physical, social and self-care roles and activities. A decreasing MCS shows higher levels of mental stress and greater limitations in social activities and functional due to emotional stress (24).

The validity of the SF-36 has been shown in various groups across numerous nationalities and across different forms of renal replacement therapies (22,25). In the transplant population specifically, it has been found to be reliable i.e. internal consistency (22), valid (high correlation with general HRQOL assessments), discriminant (can distinguish changes in clinical status) and responsive (perceptive to variances in patients before and after transplantation) (26).

Table 7.1: Description of SF-36 domains

Component score		Domain/dimension/subscale	Description
Physical (PCS)		Physical Functioning (PF)	Limitations in daily physical activities such as walking and dressing
		Role Physical (RP)	Limitations with daily or work related activities caused by physical health
		Bodily Pain (BP)	Presence of pain and its limitations on daily activities
	Mental (MCS)	General Health (GH)	An evaluation of one's general health status, compared to others and future expectations
		Vitality (VT)	Loss of energy or presence of tiredness or fatigue
		Social Functioning (SF)	Limitations in the time available and type of social activities of e.g. meeting friends
		Role Emotional (RE)	Difficulties with daily or work related activities due to emotional problems
		Mental health (MH)	Evaluations of one's mood depressive feelings, happy, anxious or nervous

Qualitative measure of HRQOL

Face-to-face interviews were used to generate narratives on life experiences post-transplant or while awaiting one. Interviews were semi-structured, using a scope of inquiry developed for the purpose of the study with expert input from a clinical psychologist. Questions within the scope of inquiry were based on health experiences, support systems, challenges and concerns based on a theoretical framework of the literature. The interview guide, probing questions and introductory remarks were scripted to enhance reproducibility of the interview process between participants. However, questions posed were rephrased to include other constructs as they arose during the interview process, enabling the semi-structured interview to serve as a guide rather than an inflexible tool (27). The interview commenced with open-ended questions according to the scope of inquiry. However, participants were given the freedom to express their thoughts and feelings as they arose. As participants were not willing to have their interviews recorded, all narratives were manually recorded during the interview. Where necessary, areas of uncertainty expressed by participants were summarised by the researcher and repeated to allow for participant to amend, agree with or expand on content (27). The interviews were conducted in English, as interview participants understood the questions and were able to answer in English.

7.2.4 Anthropometry

Dietitians were recruited based on their training and experience with conducting anthropometric assessments. Furthermore, all dietitians received refresher training to further hone their skills, followed by a post-training test. All anthropometric measurements namely weight (WT), height (Ht), triceps skinfold thickness (TSF) mid upper arm circumference (MUAC) were taken using protocols described in the National Health and Nutrition Examination Survey (NHANES) anthropometry procedure manual (28). Height in centimetres (cm) and weight in kilograms (kg) were measured using available equipment at various outpatient and dialysis centres. Weight measurements of dialysis patients were taken post dialysis (dry weight). Arm measurements were taken on the non-access arm (29,30). All MUAC (cm) and TSF in millimetres (mm) were measured using the same callipers (Slim Guide, USA) and measuring tape (SECA 201, Germany). Measurements were taken to one decimal place and the mean of three readings were recorded. BMI was calculated as WT divided by Ht squared (kg/m^2) and classified according to the World Health Organization categories: Underweight (≤18.5), normal (18.5 – 24.9), overweight (25.0-29.9), obese class I (30.0-34.9), obese class II (35.0-39.9) and obese class III (≥40) (31). Mid arm muscle circumference (MAMC) was a proxy measure of muscle mass. TSF and mid upper arm circumference (MUAC) were used to calculate mid arm muscle circumference (MAMC) using the equation:

MAMC (cm) = MUAC (cm) – [3.1415 x TSF cm)] (32)

7.2.5 Biochemistry

Participants had their blood values analysed through the National Health Laboratory Services (NHLS), or through any one of three private laboratories across the six provinces. Laboratory choice was based on proximity to participant place of work or residence, whether a participant was a state or private patient or whether it was their usual laboratory service provider. Serum albumin was measured using the bromocresol green colour reaction method, with a cut-off of <38g/l set as a criterion for hypoalbuminaemia (33). Prealbumin was measured using the nephelometric assay technique as a biochemical marker of malnutrition, as good agreement, sensitivity and specificity was previously demonstrated, when compared to detailed nutritional assessments (34). Prealbumin with a cut-off of <30mg/l was set as a criterion for low prealbumin (33).

7.2.6 Pilot study

A pilot study was conducted on eight and four HIV-negative transplant candidates and recipients respectively. The socio-demographic and SF-36 questionnaires were tested for face validity (understanding and clarity of the questions), to evaluate for ambiguity (35,36) and for ease of administration. The semi-structured interview schedule was also piloted to determine participants understanding of the open-ended questions (37). Both questionnaires and interview schedule were acceptable for use in the main study as they proved understandable and easy to administer. As this data was obtained from HIV-negative patients, it was not included in the main study data.

7.2.7 Data analysis

Quantitative data

Quality Metric Health Outcomes™ Scoring Software 4.0 was used to generate the eight domain scores and the two component summary scores. The mean SF-36 scores were calculated per domain. Data was entered into and analysed using the Statistical Package for Social Sciences (SPSS®) version 25.0. Means and standard deviation were calculated for all continuous variables, and frequencies with percentages were analysed for categorical variables. Differences in the means of groups (gender and treatment) were compared at baseline and six months using the independent samples t-test. Paired samples t-test was used to calculate the change in HRQOL by calculating the difference in mean scores of each domain from baseline to six months. ANOVA (or independent samples t-test) was applied to test for significant differences in the measured SF-36 domains across demographic categories. Pearson's correlation was done to determine the relationship between HRQOL and nutritional status (MAMC values) and continuous variables. A p value of <0.05 was taken as statistically significant. The questionnaire items were tested for consistency and validity. Cronbach's alpha was used to test the scale reliability.

Interview analysis

Scripts were manually coded, and categorised to extract themes (27), by the primary researcher followed by an independent expert in the field. Categories were discussed and agreed upon and merged into themes that most succinctly captured the thoughts, feelings and attitudes of the participants (38). These were reported as per the framework of the SF-36 domains. Quotations from transplant candidates and recipients were tagged as TC and TR respectively, and numbered per individual.

7.3 Results

7.3.1 Participant characteristics

Sixty eight participants completed the SF-36 at both baseline and six months. Two participants who participated in the baseline screening had demised before the six month follow-up. The remaining participants completed the questionnaire at one time point only due to time constraints, or missed appointments. However, there were no differences in the socio-demographic or clinical characteristics of participants who completed the questionnaire at both time points versus those that did not.

Table 7.2 presents the socio-demographic and clinical characteristics of the study sample. All participants (N=68) were HIV-positive and suffered from end stage renal disease (ESRD). Of these, 21 were recipients of a kidney transplant from a HIV-positive donor. There were 44/47 on haemodialysis (HD) and 3/47 on peritoneal dialysis while awaiting a transplant. Six out of ten (61.8%, 42/68) were male, while the remaining 26/68 (38.2%) were female, with the majority being of black ethnicity 65/68 (95.6%). The mean age of patients was 43.5 ± 8.1 years, 31/68 (45.6%) were unemployed, and 36/68 (52.9%) had full-time or part-time employment or were self-employed. The mean duration of treatment for the entire group was 3.7 ± 3.0 years, although transplant candidates were on dialysis slightly longer than transplant recipients had their transplants (4.1 ± 3.2 versus 2.8 ± 2.3 years). The majority of patients were hypertensive 62/68 (91.2%). There were significantly more patients with diabetes 14/68 (20.6%) amongst transplant candidates compared to the one transplant recipient ($p = 0.049$). One participant in each group received treatment for hypercholesterolaemia. Better HIV parameters were observed for transplant recipients, as the majority 35/43 (81.4%) had viral loads lower than detectable limits, while 100.0% of transplant recipients had viral loads lower than detectable limits. The mean CD4 count was higher among transplant recipients compared to those on the waiting list (419.6 ± 261.1 versus 384.5 ± 166.4 cells/μL).

Table 7.2: Socio-demographic and clinical characteristics of the study sample (N= 68)

Patient Characteristics	Total sample	Transplant candidates (n=47)	Transplant recipients (n=21)
Age (years)	43.5 ± 8.1	44.6 ± 8.1	41.0 ± 7.7
Gender			
Male	42 (61.8)	28 (59.6)	14 (66.7)
Female	26 (38.2)	19 (40.4)	7 (33.3)
Ethnicity			
Black	65 (95.6)	46 (97.9)	19 90.5)
Coloured[a]	3 (4.4)	1 (2.1)	2 (9.5)
Employment			
Unemployed	31 (45.6%)	20 (42.6)	11 (52.4)
Employed part-time	1 (1.5%)	1 (2.1)	0 (0)
Employed full-time	31 (45.6%)	23 (48.9)	8 (38.1)
Self employed	4 (5.9%)	2 (4.3)	2 (9.5)
Retired	1 (1.5%)	1 (2.1)	0(0)
Type of treatment			
Transplant	21 (30.9)		
Haemodialysis	47 (69.1)	44 (64.7)	
Peritoneal dialysis		3 (4.4)	
Length of time on current treatment (years)	3.7 ± 3.0	4.1 ± 3.2	2.8 ± 2.3
Chronic illness			
Diabetes	14 (20.6)	13 (27.7)[a]	1 (4.8)[b]
Hypertension	62 (91.2)	44 (93.6)	18 (85.7)
Hypercholesteraemia	2 (2.9)	1 (2.1)	1 (4.8)
CD4 (cells/µL)[1]	394.9 ± 197.7	384.5 ± 166.4	419.6 ± 261.1
Viral load (copies /ml)[2]			
LDL	53 (86.9)	35 (81.4)	18 (100.0)
≤ 10 000	6 (9.8)	6 (14.0)	
> 10 000	2 (3.3)	2 (4.7)	

Data expressed as frequency with percentages or means and standard deviation

[a] In South Africa, refers to individuals of mixed race ancestry

[b] Significantly more than expected of the dialysis patients have diabetes (p = 0.049).

[1] transplant patients: n = 19, dialysis patients: n = 45

[2] transplant patients: n = 18, dialysis patients: n = 43

LDL: lower than detectable limit

7.3.2 Participant nutritional characteristics

The nutritional characteristics of the study group are shown in Table 7.3.

Transplant candidates

The mean serum prealbumin of transplant candidates on dialysis, was 357.1 ± 84.9mg/L and 369.1 ± 99.1 mg/L at baseline and six months respectively. The majority had normal prealbumin

levels at both time points (76.7% and 73.2%). Low prealbumin was present in 7/30 (23.3%) of the transplant candidates at baseline which increased slightly to 11/41 (26.8%) at six months. Transplant candidates had a mean serum albumin of 35.8 ± 4.7g/l and 37.2 ± 5.0g/l. When using < 38g/l as a reference for hypoalbuminaemia, more candidates were hypoalbuminaemic than those with normal albumin levels at baseline and at six months (63.4% and 51.1%).

There was a negligible change in mean BMI from baseline to six months (25.6 ± 4.1 and 25.2 ± 4.3). At both time points, one patient was classified as underweight, approximately 40.0% had a normal BMI, while slightly more were overweight (42.2% and 43.2% at baseline and six months respectively). Those in the obese class I category were 7/45 (15.6%) and 6/44 (13.6%) at both time points. MAMC, a surrogate measure of lean muscle mass decreased non-significantly from 24.6 ± 4.5cm to 23.3 ± 5.5cm.

Transplant recipients

The mean prealbumin levels of transplant recipients were 296.9 ± 69.0mg/L and 306.4 ± 68.0mg/L at baseline and six months respectively. These values were lower than that of transplant candidates, as 61.1% and 50.0% of recipients had low serum prealbumin at baseline and six months respectively. In addition, significantly more transplant recipients, 11/18 (61.1%) had low prealbumin levels compared to transplant candidates 7/30 (23.3%) (χ^2 (1) = 6.850, p = 0.009). Transplant recipients had mean serum albumin levels of 43.1 ± 4.2g/L (baseline) and 41.1 ± 4.1g/L (six months). When compared to transplant candidates, recipients had significantly higher serum albumin levels at baseline with more having normal serum albumin levels at this time point 7/19 (89.5%), compared to transplant candidates 15/41 (36.6%). χ^2 (1) = 14.592, p < 0.005).

Like transplant candidates, transplant recipients had BMI values that were similar at the two time points (24.5 ± 4.7 and 25.6 ± 5.9 kg/m^2), although more recipients had a normal BMI 14/20 (70.0%), compared to 18/45 (40.0%) of transplant candidates at baseline. However, more transplant candidates were overweight at this time point, Fisher's exact = 7.923, p= 0.031. At six months, 12/21 (57.1%) transplant recipients had a normal BMI, due to one patient with a lower BMI falling into the underweight category, and two more being classified as obese class I. The mean six month MAMC values indicated that transplant recipients' mean MAMC had improved slightly from 25.2 ± 4.3 cm to 26.6 ± 3.3cm.

Table 7.3: Nutritional characteristics of transplant candidates and recipients

Anthropometric Characteristics	**Transplant candidates**				**Transplant recipients**			
	n	Baseline	***n***	6 months	***n***	Baseline	***n***	6 months
Pre-albumin mg/L	30	357.1 ± 84.9	41	369.1 ± 99.1	18	296.9 ± 69.0	18	306.4 ± 68.0
Low pre- albumin (< 30mg/L)		7 (23.3)[a]		11 (26.8)		11 (61.1)[a]		9 (50.0)
Normal: pre-albumin (≥30mg/L)		23 (76.7)		30 (73.2)		7 (38.9)		9 (50.0)
Albumin (g/L)	41	35.8 ± 4.7	47	37.2 ± 5.0	19	43.1 ± 4.2	21	41.1 ± 4.1
Hypoalbuminaemia (<38g/L)		26 (63.4)		24 (51.1)		2 (10.5)		3 (14.3)
Normal: albumin (≥38g/L)		15 (36.6) [b]		23 (48.9)		17 (89.5)[b]		18 (85.7)
Weight (kg)	47	72.4 ± 12.1	46	71.1 ± 12.0	20	70.5 ± 17.6	21	73.0 ± 19.5
Height (m)	45	167.9 ± 8.3			21	168.6 ± 10.3	21	
BMI (kg/m^2)	45	25.6 ± 4.1	44	25.2 ± 4.3	20	24.5 ± 4.7	21	25.6 ± 5.9
Underweight		1 (2.2)		1 (2.3)		-		1 (4.8)
Normal		18 (40.0)		18 (40.9)		14 (70.0)		12 (57.1)
Overweight		19 (42.2)		19 (43.2)		2 (10)		2 (9.5)
Obese Class I		7 (15.6)		6 (13.6)		4 (20.0)		6 (28.6)
TSF (mm)	34	14.92 ± 9.17	45	14.30 ± 9.56	18	10.19 ± 5.1	18	14.1 ± 7.8
MUAC (cm)	34	29.1 ± 4.9	45	27.8 ± 6.0	17	28.4 ± 5.3	18	31.4 ± 4.7
MAMC (cm)	33	24.6 ± 4.5	44	23.3 ± 5.5	17	25.2 ± 4.3	18	26.6 ± 3.3

Data expressed as percentages or means with standard deviation or frequency with percentages
BMI: Body mass index, TSF: triceps skinfold, MUAC: mid upper arm circumference, MAMC: mid arm muscle circumference
[a] At baseline, a significant number of the transplant recipients had low pre-albumin (< 30mg/L), χ^2 (1) = 6.850, p = 0.009.
[b] At baseline, significantly more transplant recipients than candidates than had normal serum albumin , χ^2 (1) = 14.592, p < 0.0005.

7.3.3 Health related quality of life – Quantitative results

Before data analysis was conducted, reliability and validity tests were performed on the SF-36 questionnaire, showing suitability as measure of HRQOL. The results are presented in Table 7.4.

Reliability and validity

Table 7.4: Performance of the SF-36 against established validity and reliability criteria

Test	Validity and reliability criteria	SF-36 results
Item internal consistency	If the correlation between an item and its hypothesised scale score is > 0.4, internal consistency is established. Item internal consistency is considered satisfactory if at least 90% of the item-scale correlations are at least 0.4.	Of the items analysed, 92.8% had an item-scale correlation > 0.4, thereby indicating satisfactory item internal consistency.
Reliability of scales	Cronbach's alpha was used to determine scale reliability. An alpha of > 0.7 is considered to indicate a reliable scale.	The only scale with alpha < 0.7 was general health, baseline (alpha =.641). This value was considered as acceptable. As alpha is sensitive to the number of items and only five items represented the general health domain, it is likely that this number has influenced the alpha value.
Item discriminant validity	To check for item discriminant validity, correlations between items in a scale and the scale scores are calculated. If items correlate more highly with their own scale than with the other scales, discriminant validity is established. Item discriminant validity is considered to be satisfactory when at least 80% of items correlate higher with their own scale than with the other scales.	PF, RP, BP, GH, VT, SF, RE and MH items correlated higher with their own scale than with the other scales at baseline and six months. As 100% of the correlations between items and their scales were greater than between the items and the other scales, discriminant validity was established.

SF-36 HRQOL scores

SF-36 scores separated by treatment modality (candidates and recipients) and gender at both baseline and six months are displayed in Figures 7.1, 7.2, 7.3, and 7.4. These domain scores with significant differences, as well as the two composite scores (PCS and MCS) are reported in Table 7.5.

From Figure 7.1 and 7.2, it is evident that transplant candidates on dialysis experienced a lower HRQOL across all HRQOL domains when compared to transplant recipients. Lowest mean scores were VT domain for candidates on dialysis (57.1 ± 19.6 and 60.1 ± 19.7) at both time points. Candidates' subjective appraisal of their general health, as indicated by the GH score, was also low (59.5 ± 19.6 and 62.3 ± 22.2) at both time points. At six months, the GH domain had the largest significant difference in domain scores between candidates and recipients (d = 4.352, p = 0.000). For candidates, subjective perception of mental health had a score of 74.2 ± 19.3 at baseline, improving to 79.0 ± 14.1 at six months. The differences between MH scores for candidates versus recipients were not significant. Among recipients, HRQOL scores improved by the second assessment, especially in RP, BP, GH and SF. Similar to that of candidates, the low scores of recipients was for VT (73.3 ± 20.2 and 73.6 ± 21.5). GH was also low at baseline (71.3 ± 24.4) but improved considerably by six months (86.2 ± 17.5).

When the study sample was divided according to gender, females had lower scores than males (Figure 7.3 and 7.4). Differences between scores for the two groups were significant either at baseline, six months or both, for all domains (Table 7.5). The significant differences between scores for males and females were in the domain of RP (80.4 ± 35.6 and 49.0 ± 46.1, df = 2.961, p = 0.005), at baseline and at six months (84.5 ± 32.6 and 54.8 ± 48.0, df = 2.785, p = 0.08). The implication of this finding was that compared to males, females were most severely limited in their physical ability to perform daily activities.

For the physical and mental composite scores, the PCS for candidates was 47.4 ± 8.6 and 47.7 ± 9.5, while MCS was 47.6 ± 10.3 and 51.5 ± 8.7 at each time point. The PCS for transplant recipients was 53.8 ± 10 and 56.6 ± 6.5, while MCS was 51.3 ± 11.5 and 54.2 ± 8.5 at baseline and six months respectively. Differences between the two groups were significant for PCS only at baseline and six months (df = 2.708, p = 0.009 and df = 4.464, p = 0.000). There was no significant difference between candidates and recipients at either time point for MCS.

Over the six month period, SF-36 scores in each HRQOL domain increased, signalling improvements in HRQOL from baseline to six months for the study sample. Statistically significant differences between baseline and six months for all participants were GH: (t = -2.351, p = 0.022), SF: (t = -2.139, p = 0.036), RE: (t = -2.230, p = 0.029), MH: (t = -2.327, p = 0.023), MCS: (t = -3.213, p = 0.002).

Correlations of HRQOL with socio-demographic, nutritional status and clinical variables

Table 7.6 shows HRQOL correlations with clinical and nutritional variables. The association between HRQOL and albumin was demonstrated in both candidates and recipients in the overall PCS at the six month assessment, but not the MCS. For the candidates, there was a significant association with low albumin levels and low HRQOL scores in the physical domains of RP ($r = 0.304$, $p = 0.038$) and BP ($r= 0.358$, $p = 0.014$). This finding illustrated that candidates with lower albumin levels experienced more limitations in daily activities and were in more pain. Transplant recipients were also influenced by albumin at six months in the physical domains of PF ($r = 0.514$, $p = 0.017$) and RP ($r = 0.543$, $p = 0.011$), but were also limited in daily activities by emotions (RE) at lower levels of albumin ($r = 0.492$, $p = 0.024$). There was a lack of correlation with CD4+ count or significant differences in HRQOL between the VL categories. In transplant recipients only, MCS ($r = - 0.451$, $p = 0.040$) was negatively associated with treatment duration, with the implication being that mental health deteriorated in accordance with a greater time lapse since transplantation.

In candidates, indicators of nutritional status such as pre- albumin and BMI, correlated with GH at baseline (prealbumin: $r = 0.401$, $p = 0.031$ and BMI: $r = 0.338$, $p = 0.025$). Among transplant recipients on the other hand, indicators of nutritional status were significantly associated with more HRQOL domains at six months i.e. RP ($r = 0.493$, $p = 0.038$), RE ($r = 0.493$, p 0.038) and the MCS ($r = 0.495$, $p = 0.037$). Correlations of MAMC, a proxy of muscle mass, with HRQOL scores was evident in the transplant group, but not the dialysis group. There was a strong positive relationship between MAMC and the PCS ($r = 0.821$, $p = 0.000$) at baseline. MAMC also correlated with individual domains of physical; PF, RP, BP, and GH. There was a weak negative association with MAMC and MCS ($r = - 0.484$, $p = 0.042$).

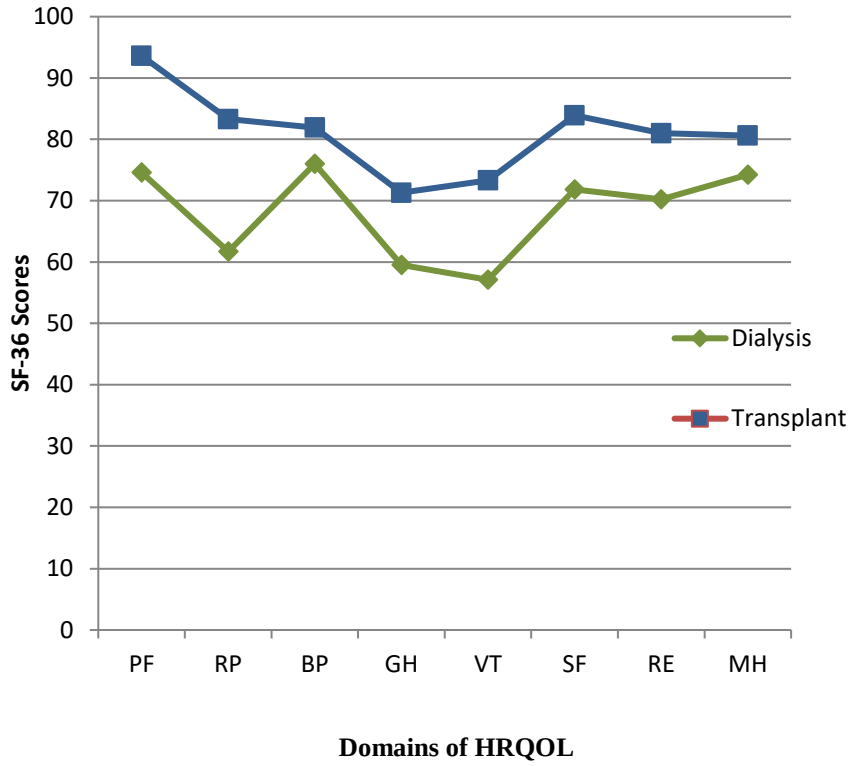

Figure 7.1: HRQOL domain scores for transplant candidates and recipients at baseline

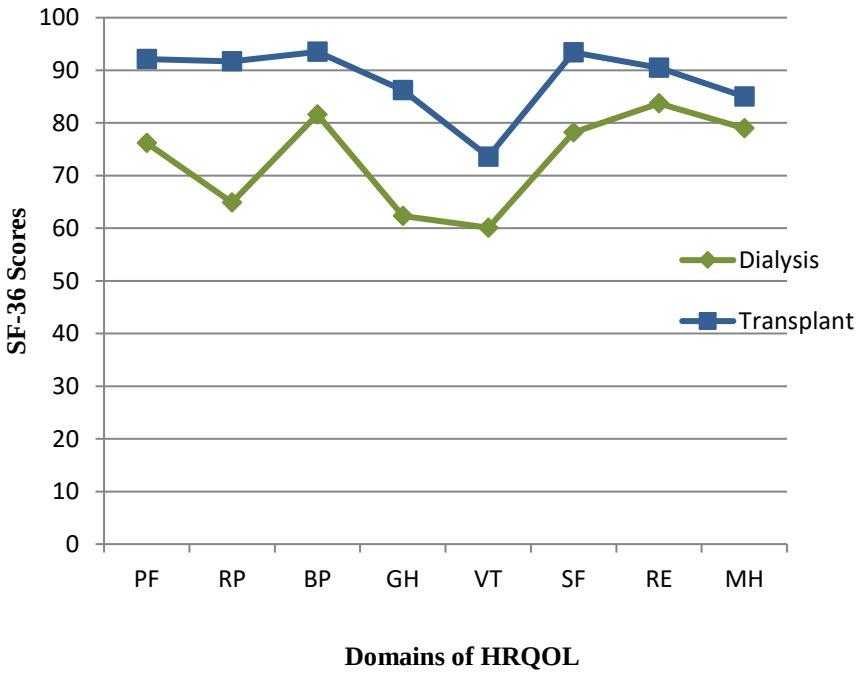

Figure 7.2: HRQOL domain scores for transplant candidates and recipients at six months

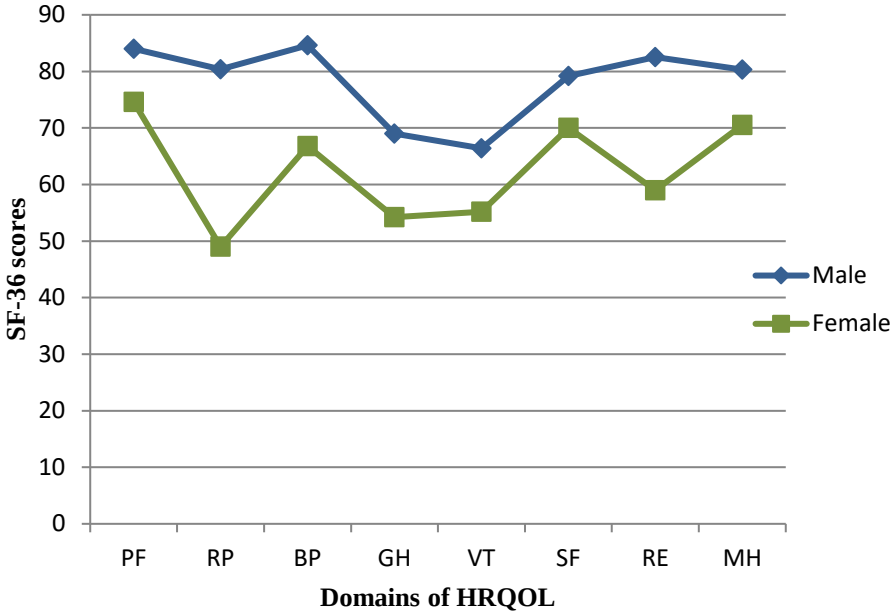

Figure 7.3: HRQOL domain scores for males and females at baseline

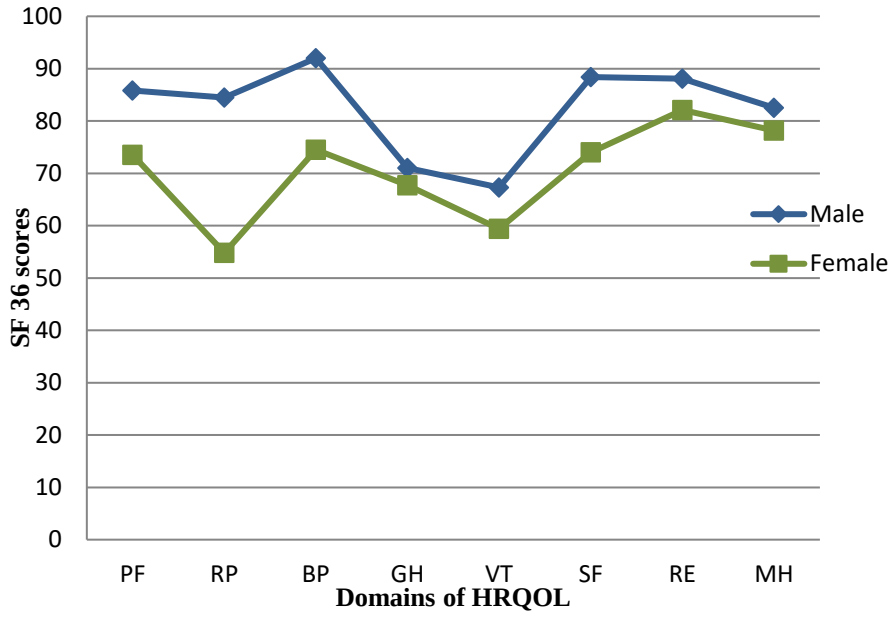

Figure 7.4: HRQOL domain scores for males and females at six month

Table 7.5: SF-36 scores with significant differences according to treatment group and gender expressed as means ± SD

Domains	All	Candidates	Recipients	d	P	Male	Female	d	p
PF (B)	80.4 ± 21.2	74.6 ± 19.7	93.6 ± 18.7	**3.726**	**0.000**	84.0 ± 20.1	74.6 ± 22.0	-	-
PF (6 M)	81.1 ± 21.3	76.2 ± 20.5	92.1 ± 19.0	**3.123**	**0.003**	85.8 ± 18.2	73.5 ± 23.8	**2.414**	**0.019**
RP (B)	68.4 ± 42.5	61.7 ± 43.9	83.3 ± 35.6	**2.147**	**0.037**	80.4 ± 35.6	49.0 ± 46.1	**2.961**	**0.005**
RP (6 M)	73.2 ± 41.5	64.9 ± 44.4	91.7 ± 26.6	**3.076**	**0.007**	84.5 ± 32.6	54.8 ± 48.0	**2.785**	**0.008**
BP (B)	77.8 ± 27.2	76.0 ± 28.2	81.9 ± 24.9	-	-	84.6 ± 23.3	66.8 ± 30.0	**2.747**	**0.008**
BP (6 M)	85.3 ± 24.5	81.6 ± 26.7	93.5 ± 16.3	**2.258**	**0.028**	92.0 ± 15.0	74.5 ± 32.4	**2.595**	**0.014**
GH (B)	63.2 ± 21.7†	59.5 ± 19.6	71.3 ± 24.4	**2.113**	**0.038**	69.0 ± 20.1	54.2 ± 21.5	**2.857**	**0.006**
GH (6 M)	69.8 ± 23.7†	62.3 ± 22.2	86.2 ± 17.5	**4.352**	**0.000**	71.0 ± 24.9	67.7 ± 21.5	-	-
VT (B)	62.1 ± 21.0	57.1 ± 19.5	73.3 ± 20.2	**3.135**	**0.003**	66.4 ± 20.8	55.2 ± 19.7	**2.210**	**0.031**
VT (6 M)	64.3 ± 21.1	60.1 ± 19.7	73.6 ± 21.5	**2.528**	**0.014**	67.3 ± 20.5	59.4 ± 21.6	-	-
SF (B)	75.6 ± 27.6†	71.8 ± 26.1	83.9 ± 29.6			79.2 ± 27.1	69.7 ±27.9	-	-
SF (6 M)	82.9 ± 24.6†	78.2 ± 25.5	93.5 ± 19.2	**2.725**	**0.009**	88.4 ± 20.0	74.0 ± 28.9	**2.223**	**0.032**
RE (B)	73.5 ± 42.5†	70.2 ± 43.5	81.0 ± 40.2	-	-	82.5 ± 36.2	59.0 ± 48.4	**2.140**	**0.038**
RE (6 M)	85.8 ± 31.2†	83.7 ± 31.8	90.5 ± 30.0	-	-	88.1 ± 28.3	82.1 ± 35.6	-	-
MH (B)	76.2 ± 20.2†	74.2 ± 19.3	80.6 ± 22.1	-	-	80.3 ± 18.4	70.0 ± 21.7	**2.188**	**0.032**
MH (6 M)	80.8 ± 14.3†	79.0 ± 14.1	85.0 ± 14.2	-	-	82.5 ± 13.8	78.2 ± 14.8	-	-
Composite									
PCS (B)	49.4 ± 9.5	47.4 ± 8.6	53.8 ± 10.0	**2.708**	**0.009**	51.8 ± 8.0	45.5 ± 10.5	**2.786**	**0.007**
PCS (6 M)	50.4 ± 9.6	47.7 ± 9.5	56.6 ± 6.5	**4.464**	**0.000**	53.1 ± 6.3	46.1 ± 12.2	**2.744**	**0.010**
MCS (B)	48.7 ± 10.8†	47.6 ± 10.3	51.3 ± 11.5	-	-	50.9 ± 9.9	45.4 ± 11.4	**2.095**	**0.040**
MCS (6 M)	52.3 ± 8.7†	51.5 ± 8.7	54.2 ± 8.5	-	-	53.0 ± 8.2	51.4 ± 9.4	-	-

B: baseline, 6 M: six months, PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social function, RE: role emotional, MH: mental health, d:difference, p (p value)
†Statistically significant difference between baseline and six month follow up for all participants, paired samples t-test:
GH: (t = -2.351, p = 0.022), SF: (t = -2.139, p = 0.036), RE: (t = -2.230, p = 0.029), MH: (t = -2.327, p = 0.023), MCS: (t = -3.213, p = 0.002).

Table 7.6: Correlations of SF- 36 scores with clinical and nutritional variables for transplant candidates and recipients

	Transplant candidates			Transplant recipients		
	Prealbumin r (p)	**Albumin r (p)**	**BMI r (p)**	**Prealbumin r (p)**	**Albumin r (p)**	**MAMC**
PF					**0.514* (0.017) [6M]**	**0.675**(0.003) [B]**
RP		**0.304* (0.038) [6M]**		**0.493* (0.038) [6M]**	**0.543* (0.011) [6M]**	**0.558* (0.020) [B]**
BP		**0.358* (0.014) [6M]**				**0.757** (0.000) [B]**
GH	**0.401* (0.031) [B]**		**0.338* (0.025) [B]**			**0.608** (0.010) [B]**
VT						
SF						
RE				**0.493* (0.038) [6M]**	**0.492* (0.024) [6M]**	
MH						
MCS				**0.495* (0.037) [6M]**		**-0.484*(0.042) [6M]**
PCS		**0.329* (0.024) [6M]**			**0.464* (0.034) [6M]**	**0.821**(0.000) [B]**

B: baseline, 6 M: six months

PF: Physical functioning, RP: Role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social function, RE: role emotional, MH: mental health, MCS: mental component score, PCS: physical component score

r (p): Correlations using Pearson's coefficient r (p value)

7.3.4 Health related quality of life – Qualitative results

Fifty six patients participated in the semi-structured interviews. Of these, 33 were male and 23 were female, with 38 on dialysis and 18 being transplant recipients. The narratives that participants provided were broadly aggregated into themes similar to those evaluated in the SF-36.

General impact of health on life

Transplant candidates: When expressing general feelings about their health and treatment, transplant candidates associated dialysis with a sense of loss and lifestyle limitations imposed by time constraints and a lack of energy.

"I cannot do the things I used to" (TC female 30)
"I used to be able to do everything. I felt free, but not anymore" (TC male 27)
"It has changed my life 100%" (TC male 2)
"I just feel like my kidney failure has taken over my life" (TC female 25)
"With HIV, it's up to you – but this dialysis!" (TC female 7)
"It takes up so much time in your day" (TC female 23)

Transplant recipients: Narratives of transplant recipients where indicative of how receipt of a donor kidney enhanced their quality of life and health.

"I feel alive and in good health after many years" (TR male 6)
"I have a second chance at life" (TR male 5)
"My life now is amazing. I was very sick on dialysis. I nearly died" (TR female 9)
"My health is excellent compared to how I used to be" (TR male 16)

Physical aspects of health

Transplant candidates: With the exception of one or two candidates, most reported how dialysis had a negative impact on physical health including fatigue, weakness and body pain. These side effects of dialysis had an impact on activities related to daily living, sport and leisure, employment and socialisation.

Narratives ranged from being cautious to feeling more severely impaired (the majority of candidates).

"I can do everything, but I have to be cautious of the fistula" (TC male 28)
"I can't take care of my child properly" (TC female 1)
"Work became too difficult. I lost my job" (TR male 20)
"Always I'm in pain" (TC female 9)
"I can't do strenuous activities; I have to take more breaks" (TC male 31)
"After dialysis I also feel very tired and weak, and sometimes get cramps" (TC female 22)

Mental aspects of health

Transplant candidates: Participants reported a number of concerns and fears and coping strategies that affected their mental well-being. Firstly, financial constraints related to travel expenses incurred to and from dialysis as well as medical expenses were often referred to as a source of stress, as was the loss of employment and the inability to work. This caused feelings of frustration due to an inability to support family members. Secondly, candidates also expressed various emotions associated with the wait for a donor namely anxiety, desperation, uncertainty and hope. Thirdly, they expressed their means of coping with mental and emotional stress.

"It is 66km (to dialysis). I leave at 7am and get there at 8am. I take public transport which costs me R100.00 a day. After dialysis, I leave at 4pm and get home at 6pm. I am very tired after dialysis" (TC female 15)
"My main problem is that I am not working. It doesn't feel good that my wife has to do everything" (TC male 4)
"Some towns don't have dialysis clinics so I can't sleep over (for work). It's a big inconvenience" (TC male 16)
"I was a man supporting my family, now they are supporting me" (TC male 20)

"Every time I wake up, I'm thinking about when I will get a transplant" (TC male 8)
"I wish for a kidney to come, I will take that kidney" (TC female 23)
"Most of the time I close my door and sit alone because I'm always thinking about one day I'm going to die. So I just wish I could get a donor" (TC female 7)
"I understand it better. I am now accepting it" (TC male 24)

"These thoughts (worries) don't affect my life, they just come and go" (TC male 2)
"I just go and pray and feel so much lighter" (TC female 21)
"After dialysis I feel very emotional. I prefer to be on my own sleeping" (TC female 30)
*"I have lots of support from my kid*s" (TC female 19)

Transplant recipients: With regards to the psychological health of transplant recipients, several expressed frustrations and stress regarding finances and unemployment. A few recipients had concerns regarding the donor kidney. However, the majority expressed gratitude.

"I do feel depressed. How can you be happy when you can't afford anything?" (TR male 14)
"I feel anxious, stressed and worried because of not having enough money" (TR female 7)

"My only worry is what will happen if my kidneys fail"(TR male 5)
"I was so worried when I got sick because I thought that I would maybe lose my kidney" (TR female 13)
"Osteoporosis revealed itself…I am afraid that the doctor won't be able to fix my bones" (TR female 8)

"I am very grateful for everything. I don't want to ask for more" (TR female 18)
"I got my kidney, it's my child, and she is my princess" (TR, female 2)
"I am very grateful to the person who donated this kidney to me and to the hospital staff" (TR male 17)

Social effects

Transplant candidates: A handful of candidates were still going out, however the majority of candidates stated that being on dialysis has a negative impact on their social life, and that they prefer to keep a smaller social circle where they gain supportive social interactions, rather than place themselves in awkward social situations. Social interaction that served as a source of emotional support included parents, a spouse, partner, children, church members, colleagues, employers, renal staff and other patients.

"They (family) can't involve me with their things, sometimes they say, 'you're sick!'" (TC female 7)

"I don't want to go out with friends or have a boyfriend; it makes me stressed to be with people because I can't have those drinks or food. So I'd rather just not be with them because I don't want the questions (TC female 23)

"I spend most of my time alone" (TC male 5)

"When I go to the renal unit, we are a family, nurses, doctors and patients" (TC female 19)

"I have great family support so I do not feel down at all" (TC male 29)

"I take it to God to sort it out for me" (TC female 21)

Transplant recipients: Without limitations, recipients felt free to participate in more activities. Like candidates, they rely on similar social support structures such as family, colleagues and the Church. They also felt strongly supported by the transplant team.

"There is a lady at work…we keep each other positive" (TR female 18)

"I was worried about my job, but the doctors and managers (work) had a meeting, and motivation from Sister P, she was the one who was outstanding" (TC male 5)

7.4 Discussion

There are currently no published data regarding the HRQOL of HIV-positive kidney transplant recipients who have received a kidney from a HIV-positive donor, or for HIV-positive candidates on the waiting list to receive a donor kidney. The current study was a longitudinal investigation of HRQOL in this unique group, employing a mixed methods study design. The quantitative generic SF-36 instrument demonstrated reliability and validity prior to analysis and, in agreement with numerous other studies (21,39,40,41), was considered a suitable measure of HRQOL. However, given the complexity of HRQOL, no single method can evaluate this concept with sufficient depth (42). Therefore, triangulation, using a mixed method approach was used. Triangulation not only corroborates the findings of either method, but also provides a greater depth of understanding regarding the HRQOL of this previously unexplored study sample. To this end, the study incorporated face-to-face semi-structured interviews into the research design (43) in conjunction with the calculation of participant SF-36 scores.

7.4.1 HRQOL of transplant recipients

In the present study, SF-36 scores were higher for transplant recipients, indicating a better QOL than transplant candidates at both time points. Previous HRQOL research also documented superior HRQOL in transplant recipients, when compared to transplant candidates on dialysis (44), or in prospective HRQOL assessments of transplant recipients conducted before and after their transplant (8), In a similar comparative study of transplant candidates and recipients, Kovacs et al reported that recipients had a significantly overall better QOL, although this was not consistent across all domains (45), thereby drawing attention to the concept that receipt of a transplant cannot categorically be viewed as an entirely positive event for all transplant recipients. Persisting issues that are not necessarily resolved by undergoing a transplant include side effects of treatment, unresolved psychological problems and difficulties in resuming employment, which may overshadow the expected gains from the transplant (45). In addition, psychological problems like depression occurs, with the prevalence thereof ranging from 11.8% to 75% (46-48). Mental health has been an important investigative area among transplant recipients due to the association of depressive symptomatology with negative outcomes such as sleep problems (49) and poor adherence to treatment (50). A meta-analysis by Dew et al found that depression increased the relative risk of mortality in organ transplant recipients with a 65% greater risk of mortality (8).

In the present study, the majority of transplant recipients did not display symptoms indicative of depression (51). This was supported by the high MH score. Moreover, the MCS, which encompasses multiple aspects of psychological health, was scored above the average for the general population (52). Transplant recipients recalled how terminally ill they were, and the devastating impact their ESRD diagnosis had on their lives. Hence, their current health experience could not be compared to that experienced while on dialysis. Although some anxieties and physical limitations persisted, these were mainly related to financial constraints, unemployment and a concern regarding graft rejection. However, these fears were outweighed by positive changes resulting from the transplant. The majority of participants associated their transplant with freedom, opportunities, and a second chance at a normal life, which was in stark contrast to the recollection of their lives while on dialysis. A similar observation by De Pascuale et al documented that the mental freedom attained once dialysis ceased, resulted in feelings of psychological well-being which remained undiminished by other problems recipients may have experienced (53).

In addition, all transplant recipients referred to social networks at church, family or friends which likely contributed to their social, emotional and mental well-being. In a Chinese study of renal transplant recipients, 59.2% of the sample had depressive symptoms, resulting in Lin et al to report that apart from financial and employment stressors, a lack of social support was a key factor contributing to depressive symptoms (48). In the present study, the SF score indicated good social interaction, which further improved by the second assessment. A possible reason for this finding is that patients are most likely to face their greatest limitations related to social and emotional aspects of life in the initial months post-transplant, which Espisito and colleagues speculate is due to numerous hospital procedures and protocols in the immediate post-transplant period (54). Thereafter, following the transition period, SF as well as other domains is likely to improve.

7.4.2 Transplant candidates

A distinction between HD and PD among candidates awaiting a transplant in the current study was not made, as it was previously shown that there are no significant differences in overall QOL between HD and PD patients (55-57).

The poorer HRQOL of candidates participating in the current study could be attributed to the effect of ESRD and dialysis, which is known to have a significant impact on physical and mental wellbeing (58). In the current study, the SF-36 score among recipients that differed most significantly from that of the general population , was the PCS representing aspects of physical health at six months ($d = 4.464$, $p = 0.000$). The PCS of 47.7 ± 9.5 was below the average of 50 in the general population (23). There are no South African studies for comparative purposes. However, US studies indicate that a PCS or MCS between 47 and 53 could be considered as within a normal range (5).

A decrease in PCS typically occurs in relation to a deterioration of kidney function of CKD patients (59,60) which when gathered from the present study's interviews, was partly due to bodily pain, but mainly due to fatigue and a lack of energy. This was also clearly evident from candidates' lowest scores being in the VT domain, as they felt greatly limited in their ability to continue with the activities of daily living and work when compared to before the onset of ESRD.

The MCS, although lower among candidates than recipients, did not differ significantly between the two groups. The SF or socialising, which falls within the MCS, includes participation in

social activities and the provision of emotional support. This is important as candidates are known to have higher rates of depression than recipients (61). Social interaction improves mood and reduces symptoms of depression and anxiety, and improves compliance with treatment (62). All candidates in this study indicated the presence of a support system ranging from a supportive partner to extensive church and work communities. However, they did express frustration that dialysis and post-dialysis recovery restricts time available for engaging in social and leisure activities. The support from the renal unit, including from staff as well as other patients on dialysis, appeared to be highly valued.

Although MCS improved by the second assessment, candidates expressed anxieties and concerns as causes of varying degrees of mental stress. Foremost among these, was the financial burdens due to a reduced income or unemployment.

7.4.3 Socio-demographic factors associated with HRQOL in transplant candidates and recipients

Income is a known socio-demographic factor having an impact on QOL. A lower income corresponds to a lower QOL in the general population (63), as do financial and employment concerns among HD and PD patients without HIV in Cape Town (55). Among transplant recipients, occupational status and financial burdens were associated with symptoms of depression (48).

In the present study, 31/68 (45.6%) of participants were unemployed. More candidates than recipients indicated that this was a source of considerable stress and depression, as the travel expenses incurred for HD, compounded by unemployment, limited available money that would normally be spent on food, socialising and education. The prevalence of unemployment amongst the current study sample, was higher than the 38.5% reported for HD and PD patients in Iran (64). Through doctors' correspondence with employers, some participants were able to continue working, albeit part-time. However, seeking employment was also impacted by the broader labour market in South Africa, where unemployment in the general population has increased over the last decade to 27.7% by the middle of 2017 (65). Candidates expressed their frustration about the time required for dialysis and loss of energy, making it challenging to retain employment.

Studies show that being employed has numerous benefits. It reduces stress through feelings of security (66) and reduces guilt regarding family responsibility (48), especially where individuals

used to be the main provider (66). The feeling of guilt was indeed voiced by some candidates. Employment also contributes to a higher self-esteem, as one is functioning as a contributing member of society (66). In a study of dialysed patients in Poland, QOL was most adversely affected by the inability to pursue work or study options (67). Again, in a sample of 34 Dutch transplant recipients, those that were not employed had significantly lower PF, RP, SF GH than those that were working as well as a poorer graft function (68).

In the present study other notable socio-demographic factors were gender and age, with a reduced PF being observed with increasing age. A Malaysian study of transplant recipients also reported a negative correlation between age with physical health (PCS) (22). The correlation in the present study was weak ($r = -0{,}277$, $p = 0.022$) (not shown), probably because the study sample was still young (mean age 43.5 ± 8.1). Male participants had significantly better HRQOL across all domains either at baseline, six months or both. These results are not unique to the transplant population, as similar results were documented among non-renal patients, in South African and elsewhere (5,6,21,44). Level of education was positively correlated with MCS in Chinese HD and PD patients (69). It is thought that more educated patients have a better QOL, as they possess a better understanding of their disease and management. This emphasises the value of patient education on all aspects of their disease and management as an important way to improve QOL. Participants in the current study consistently reported that their initial anxieties subsided after being spoken to by the nursing staff about their treatment, especially dialysis.

7.4.4 Comorbidity and HRQOL

The presence of comorbidity has been shown to affect HRQOL. Transplant recipients with hypertension and diabetes have lower PCS (66). In all probability, comorbid HIV will have a similar influence, as HIV independently affects multiple dimensions of health and wellbeing (70).

Despite the presence of HIV, the HRQOL scores and interviews did not reflect the burden of two diseases. In fact, transplant candidates on HD and PD scores were higher than that of other South African HD and PD patients without HIV (55). Similarly, transplant recipients also had higher HRQOL when compared to kidney transplant recipients that are not infected with HIV (Figure 7.5), measured using the SF-36 tool in Italy (54), Brazil (66), Norway (71) and Portugal (72). Moreover, the PCS and MCS for transplant recipients were above the average of the general population (23). A possible explanation offered by Burholt et al, is that ratings may vary

depending on how the questionnaire is administered. Interviewer- administered questionnaires, as was the case in the current study, yield higher scores than self-administered ones (21). However, based on the semi-structured interviews conducted in the current study, it would seem that the high scores documented, depicted the magnitude of change recipients perceived the transplant to have made to their lives. It could be assumed that recipients were most likely aware of the bleak outcome they would have faced without the option of a transplant.

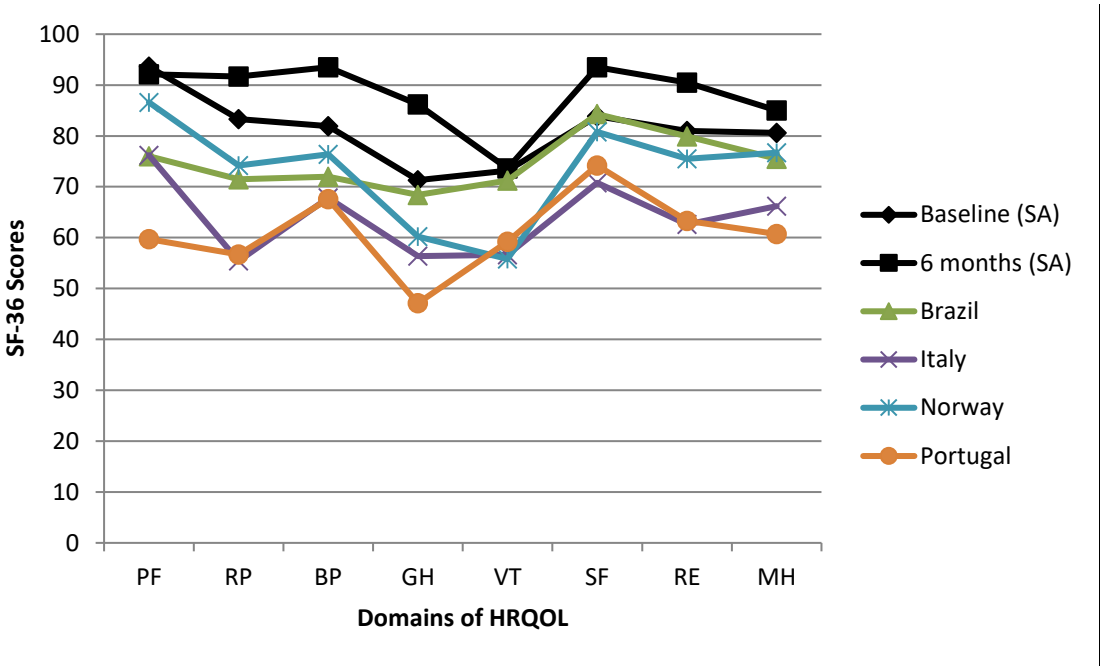

Figure 7.5: HRQOL domain scores for transplant recipients at baseline and at six months compared to other countries

7.4.5 Nutritional parameters associated with HRQOL

In the current study, BMI, MAMC and prealbumin were indicators of nutritional status. Although albumin was previously considered an indicator of nutritional status, it has been shown to be unrelated to dietary intake in CKD and poorly correlates with other nutritional markers in dialysed patients (73,74). Hence, it is of value as an indicator of illness and inflammation (33). Hypoalbuminaemia was present in more dialysis participants than recipients. Serum albumin showed significant association with PCS and physical health domains RP and BP, as well as PF and RP in candidates and recipients respectively. There was also a correlation

with RE, but only among recipients. As an indicator of disease activity or illness, understandably, sicker participants would have lower QOL.

As an alternative indicator of protein stores, The National Kidney Foundation Kidney Disease Quality Initiative (K/DOQI) recommends the use of prealbumin as a biochemical indicator of nutritional status (33). In the current study, the majority of candidates had prealbumin levels that were within the normal range. GH, a subjective perception of one's health status, and a domain of physical health, was better at higher prealbumin and BMI values. Other studies have also shown associations with several domains of physical aspects of health (75,76), However in transplant recipients, prealbumin correlated with more dimensions of health, i.e. not only with physical (RP), but also emotional (RE) and psychological (MCS) health.

In the present study, measures of lean muscle namely MAMC, strongly correlated with the PCS, albeit only amongst transplant recipients. Recipients with a higher muscle mass had better HRQOL in the PCS domains of PF, RP, BP and GH. In the general population, similar changes in muscle mass occur in the elderly, where a low muscle mass affects strength and impairs physical functional status and daily life (13). In turn, physical functional ability is also related to psychological distress and well-being and has bearing on subjective views of health (77). The finding that MAMC correlated inversely with MCS in transplant recipients, was unexpected. It is possible that MAMC increased over six months in relation to greater ambulation.

The validity of the study results were enhanced by its longitudinal design and use of mixed methods. The SF-36 used in the present study, has good psychometric properties and, as the most widely used generic HRQOL tool, allows comparisons between numerous populations. Despite the small sample size, the findings of this study are still generalisable, as the majority of patients on the transplant lists were included, thus being a fair representation of the group that was studied. Furthermore, the heterogeneity of the sample proved to be insightful as it was representative of the patient complement awaiting transplant and receiving a kidney from a HIV-positive donor, providing insight into the experiences of participants from varied backgrounds. For example, sample characteristics, which are subject to regional variability (21), were offset in this multicentre study. Similarly, the study included participants from areas with fewer resources compared to areas with better resources as well as including participants with varying levels of education and occupational background.

In conclusion, the current study findings, in agreement with other studies, showed that transplantation offers a better HRQO than being on dialysis. Furthermore, the results also

indicated that despite the presence of HIV, participant SF-36 scores were higher, indicating a good HRQOL when compared to other samples of HIV-negative transplant recipients. The experiences of candidates and recipients relayed through the semi-structured interviews, increased awareness of patients' subjective health experience and reinforce current healthcare practices or highlight opportunities for optimising patient management. For example, education from renal staff helping candidates and recipients to adjust to their disease and treatment is an important HRQOL strategy with implications for improving compliance and clinical health. The findings also suggest that clinicians should be aware of the significant impact of financial stress and unemployment on mental wellbeing. The provision of patient assistance to facilitate continued employment is of significant importance and should form part of the routine enquiry when assessing patient mental health. Referral to a social worker or psychologist may be beneficial. Finally, prealbumin and MAMC was associated with SE, MCS and PCS, and as such, nutritional status impacts on physical, mental and emotional health. Therefore regular assessment of these indicators and intervention through diet and physical activity may be effective behavioural approaches to improving HRQOL.

7.5 References

1. Frassetto LA, Tan-Tam C, Stock PG. Renal transpantation in patients with HIV. Nat Rev Nephrol. 2009; 5(10): 582-589.

2. Roland ME, Barin B, Carlson L, Frassetto LA, Terrault NA, Hirose R, Freise CE, Benet LZ, Ascher NL, Roberts JP, Murphy B, Keller MJ, Olthoff KM, Blumberg EA, Brayman KL, Bartlett ST, Davis CE, McCune JM, Bredt BM, Stablein DM, Stock PG. HIV-Infected liver and kidney transplant recipients: 1- and 3- year outcomes. Am J Transplant. 2008; 8(2): 355-365.

3. Trullas JC, Cofan F, Tuset M, Ricart MJ, Brunet M, Cervera C, Manzardo C, Lòpez-Dieguez M, Oppenheimer F, Moreno A, Campistol JM, Miro JM. Renal transplantation in HIV-infected patients. Kidney Int. 2011; 79(8): 825-842.

4. Muller E, Kahn D, Mendelson M. Renal transplantation between HIV-positive donors and recipients. N Engl J Med. 2010; 362(24): 2336-2337.

5. Kastien-Hilka T, Rosenkranz B, Sinanovic E , Bennett B, Schwenkglenks M. Health-related quality of life in South African patients with pulmonary tuberculosis. PLoS One. 2017; 12(4): e0174605. doi.org/10.1371/journal.pone.0174605

6. Uchmanowicz B, Panaszek B, Uchmanowicz I, Rosińczuk J. Sociodemographic factors affecting the quality of life of patients with asthma. Patient Prefer Adherence. 2016; 10:

345–354.

7. Higginson IJ, Carr AJ. Measuring quality of life: Using quality of life measures in the clinical setting. BMJ. 2001; 322(7297): 1297-1300.

8. Dew MA, Rosenberger EM, Myaskovsky L, DiMartini AF, DeVito Dabbs AJ, Posluszny DM, Steel J, Switzer GE, Shellmer DA, Greenhouse JB. Depression and anxiety as risk factors for morbidity and mortality after organ transplantation: A systematic review and meta-analysis. Transplantation. 2015; 100(5): 988–1003.

9. Griva K, Davenport A, Newman SP. Health-related quality of life and long-term survival and graft failure in kidney transplantation: A 12-year follow-up study. Transplantation. 2013; 95(5): 740-749.

10. Blake C, Plant WD. Measures to improve quality of life in end stage stage renal disease patients. In Wilcox CS. Therapy in nephrology and hypertension. Philadeliphia: Saunders Elsevier; 2008. p. 818-827.

11. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer – a systematic review of the epidemiological literature. Nutr J. 2012; 11: 7. doi: 10.1186/1475-2891-11-27.

12. Campbell KL, Ash S, Bauer JD. The impact of nutrition intervention on quality of life in pre-dialysis chronic kidney disease patients. Clin Nutr. 2008; 27(4): 537-544.

13. Amarantos E, Martinez A, Dwyer J. Nutrition and quality of life in older adults. Journal Gerontol. 2001; 56A(Special Issue 2): 54-64.

14. Thapa R, Amatya A, Pahari DP, Bam K, Newman MS. Nutritional status and its association with quality of life among people living with HIV attending public anti-retroviral therapy sites of Kathmandu Valley, Nepal. AIDS Res Ther. 2015; 12: 14. doi: 10.1186/s12981-015-0056-9.

15. Ortega F, Valdés C, Ortega T. Quality of life after solid organ transplanation. Transplant Rev. 2007; 21: 155-170.

16. Laucis NC, Hays RD, Bhattacharyya T. Scoring the SF-36 in orthopaedics: A brief guide. J Bone Joint Surg Am. 2015; 97(19): 1628-1634.

17. Liem YS, Bosch JL, Arends LR, Heijenbrok-Kal MH, Hunink MG. Quality of life assessed with the Medical Outcomes Study Short Form 36-Item health survey of patients on renal replacement therapy: a systematic review and meta-analysis. Value Health. 2007; 10(5): 390-397.

18. Ekberg H, Kyllönen L, Madsen S, Grave G, Solbu D, Holdaas H. Increased prevalence of gastrointestinal symptoms associated with impaired quality of life in renal transplant

recipients. Transplantation. 2007; 83(3): 282-289.

19. Posthouwer D, Plug I, van der Bom JG, Fischer K, Rosendaal FR, Mauser-Bunschoten EP. Hepatitis C and health-related quality of life among patients with hemophilia. Haematologica. 2005; 90(6): 846-850.

20. Home PD, Meneghini L, Wendisch U, Ratner RE, Johansen T, Christensen TE, Jendle J, Roberts AP, Birkeland KI. Improved health status with insulin degludec compared with insulin glargine in people with type 1 diabetes. Diabet Med. 2012; 29(6): 716-720.

21. Burholt V, Nash P. Short Form 36 (SF-36) health survey questionnaire: Normative data for Wales. J Public Health (Oxf). 2011; 33(4): 587–603.

22. Chiu SF, Wong HS, Morad Z, Loo LH. Quality of life in cadaver and living-related renal transplant recipients in Kuala Lumpur hospital. Transplant Proc. 2004; 36(7): 2030-2031.

23. Stewart M. The Medical Outcomes Study 36-item short-form health survey (SF-36). Aust J Physiother. 2007; 53(3): 208.

24. Piotrowicz K, Noyes K, Lyness JM, McNitt S, Andrews ML, Dick A, Hall WJ, Moss AJ, Zareba W. Physical functioning and mental well-being in association with health outcome in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial II. Eur Heart J. 2007; 28(5): 601-607.

25. Maglakelidze N, Pantsulaia T, Tchokhonelidze I, Managadze L, Chkotua A. Assessment of health-related quality of life in renal transplant recipients and dialysis patients. Transplant Proc. 2011; 43(1): 376-379.

26. Cleemput I, Kesteloot K, Moons P, Vanreterghem Y, Van Hooff JP, Squifflet JP, De Geest S. The construct and concurrent validity of the EQ-5D in a renal trasnplant population. Value Health. 2004; 7(4): 499-509.

27. Rodkjaer L, Sodemann M, Ostergaard L, Lomborg K. Disclosure decisions: HIV-positive persons coping with disease-related stressors. Qual Health Res. 2011; 21(9): 1249-1259.

28. Centers of Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) Anthropometry Procedures Manual. [Online]; 2009 [cited 22/02/2014]. Available from: https://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf.

29. Afshar M, Rebollo-Mesa I, Murphy E, Murtagh FEM, Mamode N. Symptom burden and associated factors in renal transplant patients in the UK. J Pain Symptom Manage. 2012; 44(2): 229-238.

30. Noori N, Kopple JD, Kovesdy CP, Feroze U, Sim, JJ, Murali SB, Luna A, Gomez M, Luna C, Bross R, Nissenson AR, Kalantar-Zadeh K. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. Clin J Am Soc Nephrol. 2010;

5(12): 2258–2268.

31. World Health Organization. Global database on body mass index. [Online]; 2006 [cited 19/03/2019]. Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.

32. Frisancho AR. Triceps skin fold and upper arm muscle size norms for assessment of nutritional status. J Clin Nutr. 1974; 27(10): 1052-1058.

33. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevinho-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney. Kidney Int. 2008; 73(4): 391-398.

34. Devoto G, Gallo F, Marchello C, Racchi O, Garbarini R, Bonassi S, Albalustri G, Haupt E. Prealbumin serum concentrations as a useful tool in the assessment of malnutrition in hospitalized patients. Clin Chem. 2006; 52(12): 2281-2285.

35. Venter E, Gericke GJ, Bekker PJ. Nutritional status, quality of life and CD4 cell count of adults living with HIV/AIDS in the Ga-Rankuwa re (South Africa). SA Afr J Clin Nutr. 2009; 22(3): 124-129.

36. Bertram C, Christiansen I. Understanding research. Pretoria: Van Schaik Publishers; 2014. p. 77.

37. Turner DW, III. Qualitative interview design: A practical guide for novice investigators. TQR. 2010; 15(3): 754-760.

38. Tong A, Tjaden L, Howard K, Wong G, Morton R, Craig JC. Quality of life of adolescent kidney transplant recipients. J Pediatr. 2011; 159(4): 670-675.

39. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: New outcome measure for primary care. BMJ. 1992; 305(6846): 160-164.

40. Ruta DA, Abdalla MI, Garratt AM, Coutts A, Russell IT. SF 36 health survey questionnaire: I. Reliability in two patient based studies. Qual Health Care. 1994; 3(4): 180-185.

41. Garratt AM, Ruta DA, Abdalla MI, Russell IT. SF 36 health survey questionnaire: II. Responsiveness to changes in health status in four common clinical conditions. Qual Health Care. 1994; 3(4): 186-192.

42. Tariq S, Woodman J. Using mixed methods in health research. JRSM Short Rep. 2013; 4(6): 2042533313479197. doi: 10.1177/2042533313479197.

43. Hussein A. The use of triangulation in social sciences research: Can qualitative and quantitative methods be combined? JCSW. [Online]; 2009; [cited 19/03/2019]. Available

from:http://www.bnemid.byethost14.com/NURSING%20RESEARCH%20METHODOLOGY%205.pdf?i=1

44. Rebollo P, Ortega F, Baltar JM, Badía X, Alvarez-Ude F, Díaz-Corte C, Naves M, Navascúes RA, Ureña A, Alvarez-Grande J. Health related quality of life (HRQOL) of kidney transplanted patients: variables that influence it. Clin Transplant. 2000; 14(3): 199-207.

45. Kovacs AZ, Molnar MZ, Szeifert L, Ambrus C, Molnar-Varga M, Andras Szentkiralyi A, Mucsi I, Novak M. Sleep disorders, depressive symptoms and health-related quality of life—a cross-sectional comparison between kidney transplant recipients and waitlisted patients on maintenance dialysis. Nephrol Dial Transplant. 2011; 26(3): 1058–1065.

46. Anvar-Abnavi M, Bazargani Z. Prevalence of anxiety and depression in Iranian kidney transplant recipients. Neurosciences (Riyadh). 2010; 15(4): 254-257.

47. Vásquez V, Novarro N, Valdés RA, Britton GB. Factors associated to depression in renal transplant recipients in Panama. Indian J Psychiatry. 2013; 55(3): 273-278.

48. Lin X, Lin J, Liu H, Teng S, Zhang W. Depressive symptoms and associated factors among renal-transplant recipients in China. IJNSS. 2016; 3(4): 347-353.

49. Ronai KZ, Szentkiralyi A, Lazar AS, Ujszaszi A, Turanyi C, Gombos F, Mucsi I, Bodizs R, Molnar M, Novak M. Depressive symptoms are associated with objectively measured sleep parameters in kidney transplant recipients. J Clin Sleep Med. 2017; 13(4): 557-564.

50. Jindal RM, Neff RT, Abbott KC, Hurst FP, Elster EA, Falta EM, Patel P, Cukor D. Association between depression and nonadherence in recipients of kidney transplants: analysis of the United States renal data system. Transplant Proc. 2009; 41(9): 3662-3666.

51. World Health Organization. Depression. [Online].; 2018 [cited 07/03/2019]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression.

52. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol. 1998; 51(11): 903-912.

53. De Pasquale C, Veroux M, Indelicato L, Sinagra N, Giaquinta A, Fornaro M, Veroux P, Pistorio ML. Psychopathological aspects of kidney transplantation: Efficacy of a multidisciplinary team. World J Transplant. 2014; 4(4): 267-275.

54. Esposito P, Furini F, Rampino T, Gregorini M, Petrucci L, Klersy C, Canton DA, Toffola ED. Assessment of physical performance and quality of life in kidney-transplanted patients: A cross-sectional study. Clin Kidney J. 2017; 10(1): 124-130.

55. Okpechi IG, Nthite T, Swanepoel CR. Health-related quality of life in patients on hemodialysis and peritoneal dialysis. Saudi J Kidney Dis Transpl. 2013; 24(3): 519-526.

56. Tannor EK, Archer E, Kapembwa K, van Schalkwyk SC, Davids MR. Quality of life in patients on chronic dialysis in South Africa: A comparative mixed methods study. BMC Nephrol (2017). 2017; 18(4). doi: 10.1186/s12882-016-0425-1.

57. Homaie Rad E, Mostafavi H, Delavari S, Mostafavi S. Health-related quality of life in patients on hemodialysis and peritoneal dialysis: a meta-analysis of Iranian studies. Iran J Kidney Dis. 2015; 9(5): 386-393.

58. Fukuhara S, Lopes AA, Bragg-Gresham JL, Kurokawa K, Mapes DL, Akizawa T, Bommer J, Canaud BJ, Port FK, Held PJ; Worldwide dialysis outcomes and practice Patterns Study. Health-related quality of life among dialysis patients on three continents: the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 2003; 64(5): 1903-1910.

59. Gorodetskaya I, Zenios S, McCulloch CE, Bostrom A, Hsu CY, Bindman AB, Go AS, Chertow GM. Health-related quality of life and estimates of utility in chronic kidney disease. Kidney Int. 2005; 68(6): 2801-2808.

60. McClellan WM, Abramson J, Newsome B Temple E, Wadley VG, Audhya P, McClure LA, Howard VJ, Warnock DG, Kimmel P. Physical and psychological burden of chronic kidney disease among older dults. Am J Nephrol. 2010; 31(4): 309–317.

61. Szeifert L, Molnar MZ, Ambrus C, Koczy AB, Kovacs AZ, Vamos EP, Keszei A, Mucsi I, Novak M. Symptoms of depression in kidney transplant recipients: A cross-sectional study. Am J Kidney Dis. 2010; 55(1): 132-140.

62. Gerogianni SK, Babatsikou FP. Social aspects of chronic renal failure in patients undergoing haemodialysis. IJCS. 2014; 7(3): 740-745.

63. Lubetkin EI, Jia H, Franks P, Gold MR. Relationship among sociodemographic factors, clinical conditions, and health-related quality of life: Examining the EQ-5D in the U.S. general population. Qual Life Res. 2005; 14(10): 2187-2196.

64. Parvan K, Ahangar R, Hosseini FA1, Abdollahzadeh F, Ghojazadeh M, Jasemi M. Coping methods to stress among patients on hemodialysis and peritoneal dialysis. Saudi J Kidney Dis Transpl. 2015; 26(2): 255-262.

65. Sulla V, Zikhali P. Overcoming poverty and inequality in South Africa : an assessment of drivers, constraints and opportunities (English). Washington: World Bank Group. [Online]; 2018 [cited 24/01/209]. Available from: http://documents.worldbank.org/curated/en/530481521735906534/Overcoming-Poverty-and-Inequality-in-South-Africa-An-Assessment-of-Drivers-Constraints-and-Opportunities

66. Bohlke M, Marini SS, Rocha M, Terhorst L, Gomes RH, Barcellos FC, Irigoyen MC, Sesso R. Factors associated with health-related quality of life after successful kidney transplantation: A population-based study. Qual Life Res. 2009; 18(9): 1185-1193.

67. Dąbrowska-Bender M, Dykowska G, Żuk W, Milewska M, Staniszewska A. The impact on quality of life of dialysis patients with renal insufficiency. Patient Prefer Adherence. 2018; 12: 577-583.

68. van der Mei SF, Kuiper D, Groothoff JW, van den Heuvel WJ, van Son WJ, Brouwer S. Long-term health and work outcomes of renal transplantation and patterns of work status during the end-stage renal disease trajectory. J Occup Rehabil. 2011; 21(3): 325-334.

69. Wu F, Cui L, Gao X, Zhou H, Yang M, Pan J, Jiang Y, Zhu G, Xiang L, Zou Y, Liu H, Di J, Zong Y, Li M, Sun Y, Tao Q, Wang B. Quality of life in peritoneal and hemodialysis patients in China. Ren Fail. 2013; 35(4): 456-459.

70. Basavaraj KH, Navya MA, Rashmi R. Quality of life in HIV/AIDS. Indian J Sex Transm Dis AIDS. 2010; 31(2): 75–80.

71. Aasebø W, Homb-Vesteraas NA, Hartmann A, Stavem K. Life situation and quality of life in young adult kidney transplant recipients. Nephrol Dial Transplant. 2009; 24(1): 304–308.

72. Fructuoso M, Castro R, Oliveira L, Prata C, Morgado T. Quality of life in chronic kidney disease. Nefrologia. 2011; 31(1): 91-96.

73. Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. JASN. 2010; 21(2): 223-230.

74. Gama-Axelsson T, Heimbürger O, Stenvinkel P, Bárány P, Lindholm B, Qureshi AR. Serum albumin as predictor of nutritional status in patients with ESRD. Clin J Am Soc Nephrol. 2012; 7(9): 1446-1453.

75. Wu LW, Lin YY, Kao TW, Lin CM, Liaw FY, Wang CC, Peng TC, Chen WL. Mid-arm muscle circumference as a significant predictor of all-cause mortality in male individuals. PLoS One. 2017; 12(2): e0171707. doi: 10.1371/journal.pone.0171707

76. Rambod M, Kovesdy CP, Bross R, Kopple JD, Kalantar-Zadeh K. Association of serum prealbumin and its changes over time with clinical outcomes and survival in patients receiving hemodialysis. Am J Clin Nutr. 2008; 88(6): 1485-1494.

77. Schulz T, Niesing J, Stewart RE, Westerhuis R, Hagedoorn M, Ploeg RJ, Homan van der Heide JJ, Ranchor AV. The role of personal characteristics in the relationship between health and psychological distress among kidney transplant recipients. Soc Sci Med. 2012; 75(8): 1547-1554.

CHAPTER 8

CONCLUSION AND RECOMMENDATIONS

Kidney transplantation only became an available treatment modality for end stage renal disease (ESRD) among HIV-positive individuals in recent years with outcomes having surpassed all expectations (1). Nutritional comorbidities are common among the kidney transplant population and impact on patient and graft survival (2). Those who are also infected with HIV, live with the burden of two debilitating diseases. Fortunately, nutrition is a modifiable factor and improvements in nutritional status can contribute to meaningful changes in health and quality of life. However, there is an absence of data regarding the state of nutritional health in this group, despite the fact that it can be used to optimise nutrition therapy. Hence, this research set out to explore the nutritional status and quality of life of HIV-positive kidney transplant candidates and recipients from HIV-positive donors, by conducting assessments to determine numerous measures of nutritional health at baseline and at six month follow-up.

8.1 Objectives and methods

Guided by the "ABCD" (anthropometry, biochemical, clinical and dietary) assessment method (3), a number of nutritional status indicators were selected to describe the existence and extent of nutrition-related problems typically found in transplant candidates and recipients. These included the following variables:

- Clinical symptoms of gastrointestinal health were determined using a validated questionnaire, namely the gastrointestinal symptoms rating scale.

- Anthropometry was used to determine body composition and changes thereof over a six month period. In addition, body composition and bone mineral density was also measured by dual energy X-ray absorptiometry (DEXA) in a subset of participants.

- Biochemical parameters indicative of protein status, serum 25(OH)D, fasting glucose and lipid profile were selected for investigation.

- Dietary intake was evaluated using the retrospective 24-hour recall method.

The assessment of health related quality of life (HRQOL) was conducted using mixed methods.

- The SF-36 questionnaire quantitatively determined HRQOL

- A qualitative evaluation using semi-structured interviews provided a more comprehensive understanding of HRQOL

8.2 Summary of findings and implications for practice

This research provides for the first time, a view of the nutritional health of kidney transplant candidates and recipients who are also infected with HIV. Overall, the cumulative findings are broadly aligned with that observed in the uninfected kidney transplantation population. In chapter three, the investigation regarding **the frequency and prevalence of gastrointestinal symptoms,** confirmed a high frequency of gastrointestinal symptoms in both groups, with a greater severity of symptoms in transplant candidates. Since ongoing gastrointestinal symptoms have previously been shown to place patients at nutritional risk (4), and affect quality of life (5), it is recommended that firstly, periodic regular enquiry about gastrointestinal symptoms should be included in patient consultations. This could be by means of open-ended questions or using a validated tool such as the gastrointestinal rating scale (GSRS), which performed well in this study. Secondly, consideration should be given to feasible intervention strategies. Identification of unhealthy dietary practices and implementing changes via dietetic counselling is often a first-line approach. Failing this, the use of pharmaceuticals or probiotics is an option, albeit an ambivalent one, as polypharmacy and drug interactions have previously posed challenges for this group (6). **Bone mineral density and the prevalence of osteoporosis** were investigated in a cross-sectional study. The results indicated a higher prevalence of osteopenia and osteoporosis in transplant candidates and recipients respectively. Surprisingly, when compared to several other studies in chapter four, more participants had a normal bone density than transplant recipients elsewhere. As dietary calcium intake was associated with bone density, ensuring adequate dietary calcium intake should be an important take-home message forming part of nutrition education. Bone mineral density assessments are costly and therefore not a viable option for most patients. However, based on available evidence and the current study's results, that a lower lean muscle mass is associated with a lower bone density, individuals can optimise bone density through a lifestyle that promotes general physical activity and exercise to preserve muscle mass. The most suitable anthropometric methods for measuring and monitoring muscle mass as well as adiposity, were investigated in the chapter five entitled: **correlation of anthropometry with dual energy X-ray absorptiometry**. This investigation confirmed that

body mass index, waist circumference and mid arm muscle circumference were suitable proxy measures of overall and regional adiposity (including visceral adipose tissue) as well as musculature based on correlations with body composition derived from DEXA as a reference standard. Thus, the suitability of these measures for bedside and field investigation was established. In the study that followed, BMI and waist circumference evaluated **overall and regional adiposity**. Differences in body composition and its changes were observed in candidates and recipients. The majority of candidates were found to be overweight and obese. However, a significant mean weight loss was observed after six months. Although weight and weight change was not linked to diet, a comparison to daily recommendations revealed that the daily dietary intake was inadequate in terms of total protein and energy. Dietitians and clinicians are therefore encouraged to evaluate patients for weight loss as it increases mortality risk. Relying solely on BMI may be misleading if patients are overweight, as the single index might still be within an acceptable BMI range. It is also recommended that dietary inadequacy and weight loss should be promptly addressed through intervention via education and/or supplementation, even before changes in other nutritional indicators become visible. Among recipients, waist circumference increased significantly after six months, without significant changes in BMI. A correlation between waist circumference and animal protein intake was detected at the six month follow-up. Steps that could be implemented to improve nutritional status, include ongoing education to encourage a healthy diet. In addition to education, it is proposed that like BMI, waist circumference should be a mandatory measurement. Furthermore, taking of this measurement could potentially be taught to patients as a self-monitoring tool. The final chapter reported on participants' **health related quality of life.** Consistent with the literature (7), patients on dialysis had a lower HRQOL than transplant recipients. The semi-structured interviews and variables that correlated with HRQOL scores highlighted modifiable factors that if addressed, can improve HRQOL. Most notably from the interviews, stressors related to a lack of income and unemployment were perceived as major stressors impacting on mental health. The current support provided by clinicians by through corresponding with employers, is highly valued and must be continued as a major HRQOL intervention. Correlation analysis with SF-36 scores showed that muscle mass was significantly associated to several domains of physical function, reinforcing the importance of diet and exercise in maintaining muscle mass.

8.3 Strengths and Limitations

The strengths and limitations for each study were alluded to as part of the discussion in chapters three to seven. However, strengths and limitations as they apply to the overall research project include the following. Firstly, the major strength of the research was that it is the first study to investigate nutritional health in kidney transplant candidates and recipients who are also infected with HIV. Secondly, the accuracy of data was enhanced by using trained and experienced health professionals in the form of dietitians for fieldwork. Thirdly, the use of validated tools such as the SF-36 and the GSRS enabled comparison with uninfected patient groups elsewhere. It should be emphasised that the scope of this research focused on the major nutritional abnormalities that usually threaten graft and patient morbidity and mortality. Dietary analysis was purposely limited to the investigation of macronutrients and selected micronutrients. However, although multiple micronutrients play a role in optimising nutritional status, it was beyond the scope of this research. It is also acknowledged that it was the intention to obtain three non-consecutive 24-hour recalls. Indeed three were obtained during the pilot study in Cape Town. However, when the main study was conducted over multiple locations, logistical reasons rendered it impossible for many patients to complete three 24-hour recalls. The study sample was 93.4% black. Hence, these results are generalizable to the South African population as it is reflects the racial distribution of HIV infection. However, the applicability of the results to other ethnicities and other countries was not investigated.

8.4 Recommendations for future research

8.4.1 Logistical and design considerations

Problems encountered that were related to patient retention, missed patient appointments, fieldworker dropout and poor compliance of staff with research requests, are not uncommon in field research. However, despite careful planning and a pilot study, other problems encountered that should be taken into consideration when executing a multi-centre study in South Africa are related to the following.

a) Access to data

Prior to the commencement of data collection, all relevant stakeholders were contacted. Hence problems related to data access were not anticipated. However, in the course of data collection, the recently introduced The Protection of Personal Information (POPI) act (8) was being

incorporated into clinic and hospital policies. At the time, the act was fairly new, and in the absence of set protocols being put in place, many facilities (especially private clinics) became reluctant to release patient information. In addition, the sensitive nature of the research due to the HIV status of participants, further complicated access to patient information. However, the majority of patient data was eventually obtained, but resulted in major time delays that could not be foreseen in the planning of time lines for the research.

b) Unequal distribution of resources between the provinces

A lack of motivation to remain in the study, fieldworker drop out, lost data, geographical access and technological difficulties had financial implications and extended the data collection phase. It was of interest to note that the majority of these setbacks primarily occurred in regions with a known lack of healthcare resources and infrastructure, pointing to social inequality across South Africa. When conducting future research, it should be borne in mind that these areas may require additional financial and fieldworker resources during the data collection phase of multi-centre studies (9).

c) Longer follow-up period

As is the nature of chronic conditions, the clinical course of the disease and treatment is seldom static and hence problematic to predict. In addition, symptom burden, nutritional status and quality of life are dynamic, changing in nature and magnitude. With the available resources, the study prospectively spanned over six months with significant changes being observed. However, given a longer follow-up period, it is highly probable that further changes would be observed. Hence it would be highly desirable for future research to source the necessary resources to facilitate a longer follow-up period. Furthermore, it would be advisable to capture baseline data from the time of acceptance onto the waiting list as a candidate, and from the time of transplantation for recipients.

8.4.2 Suggestions for future research

This research was the first nutritional study conducted among this group of study participants. Undoubtedly, more research is needed as the programme expands. Suggestions for future studies include:

- An assessment of the type and amount of physical activity study participants engage in.

- Evaluating the feasibility of using tools and practices recommended by the current study.
- Conducting intervention studies to improve muscle mass, metabolic syndrome and prevent weight loss.

8.5 Conclusion

Nutrition has always formed a vital part of patient care in both pre- and post-kidney transplant patients as well as in those with HIV. Nutrition therapy is aimed at minimizing the effects of the disease, its complications, side effects of medication and optimising quality of life. As diet is a modifiable factor, prevention of post-transplant complications and HIV-related morbidity can be achieved through nutrition and lifestyle support. However, timeous identification of nutritional abnormalities is the first step in nutrition therapy. The current study has shown the extent to which nutritional status is altered in HIV-positive patients with ESRD undergoing dialysis and transplantation. Given the associated morbidity and mortality risks, early and ongoing assessment, followed by prompt intervention is crucial in optimising long-term health and quality of life outcomes.

8.6 References

1. Muller E, Barday Z, Mendelson M, Kahn D. HIV-positive–to–HIV-positive kidney transplantation - results at 3 to 5 Years. N Engl J Med. 2015; 372(21): 2070-2071.

2. Phillips S, Heuberger. Metabolic Disorders Following Kidney Transplantation. J Ren Nutri. 2012; 22(5): 451-460.

3. The American Dietetic Association. Position of the American Dietetic Association: Nutrition Intervention and Human Immunodeficiency Virus Infection. J Am Diet Assoc. 2010; 110(7): 1105-1119.

4. Hammond KA. Dietary and Clinical Assessment. In: Mahan KL, Escott-Stump S, editors. Krause's Food Nutrition & Diet Therapy. Philadelphia: Saunders Elsevier; 2004. p. 411.

5. Ekberg H, Kyllönen L, Madsen S, Grave G, Solbu D, Holdaas H. Increased prevalence of gastrointestinal symptoms associated with impaired quality of life in renal transplant recipients. Transplantation. 2007; 83(3): 282-289.

6. Frassetto LA, Tan-Tam C, Stock PG. Renal transplantation in patients with HIV. Nat Rev Nephrol. 2009; 5(10): 582-589.

7. Liem, YS, Bosch JL, Arens LR, Heijenbrok MH, Hunink MGM. Quality of life asessed with the Medical Outcomes Study Short Form 36-Item Health Survey of patients on renal replacement therapy: A systematic review and meta-analysis. Value Health. 2007; 10(5): 390-397.

8. Buys M. Protecting personal information: Implications of the Protection of Personal Information (POPI) Act for healthcare professionals. S Afr Med J 2017;107(11):954-956. 2017; 107(11): 954-956.

9. Stuckler D, Basu S, McKee M. Health care capacity and allocations among South Africa's provinces: infrastructure–inequality traps after the end of apartheid. Am J Public Health. 2011; 101(1): 165-172.

APPENDIX A: Ethical Approval from Biomedical Research Ethics Committee (BREC) of UKZN

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

05 December 2013

Mrs Claire Juliet Martin
27 Ruby Crescent
Newholmes
Pietermaritzburg
3201
Clairejm32@gmail.com

PROTOCOL: Nutritional Status and Quality of Life in HIV positive Pre and Post-Renal transplant recipients from HIV positive Donors. BE327/13

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 27 August 2013.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 04 December 2013 to queries raised on 04 October 2013 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 05 December 2013.

This approval is valid for one year from **05 December 2013.** 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 (2004), 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 **RATIFIED** by a full Committee at its next meeting taking place on **11 February 2014.**

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

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

ADDENDIX B: Participant information and informed consent

Date…….

Dear Patient,

My name is Claire Martin. I am a dietitian and a student at the University of KwaZulu-Natal (UKZN). The department I am studying with, their contact details as well as my personal details are listed below.

You are invited to consider participating in a research project, which is being conducted by myself, through the University of KwaZulu Natal (UKZN) in conjunction with the Renal Unit at Groote Schuur Hospital. All HIV positive patients that have had a kidney transplant from a positive donor, and those that are on the waiting list to receive one will be approached to participate.

STUDY INFORMATION

***Study aim*:** The study will focus on finding out about the nutritional well-being of all HIV positive patients after they have had a kidney transplant, as well as those that are receiving dialysis and are on the waiting list to receive one.

.

Procedures: The study would involve collecting information about your medical history from your files, interviews about your health and food intake, and a series of body measurements and blood tests. This will give us an indication of your nutritional status and its impact on your health.

a) Dietary intake assessment: During this interview, a dietitian will ask you questions about the food you eat.

b) Body measurements: These measurements are non-invasive and will include height, weight, waist, hip and arm measurements using a tape measure and calipers.

c) Quality of life assessment: During this interview you will be asked questions about how you feel about your current health and its effect on your daily life.

d) Laboratory tests: Your routine blood test results will be used together with an additional two blood tests. These blood samples will be drawn at the same time as your routine blood tests.

e) Bone Density: This is a test that uses a machine to take an X-ray of your body. It provides an indication of how strong your bones are, and your fracture risk. The amount of radiation is very low, less than you get in daily life.

Duration and cost: The study will run for two years. In that time, your participation will be required every six months i.e. 4 times in total. All assessments will take between half an hour to one hour each. Only the dietary interviews will require that you be interviewed on three different days, to find out what you had eaten the day before. Every effort will be made to conduct all other assessments on the days of your usual hospital visit. For additional assessments, we could come to you or you could come back to the hospital, as is convenient to

you. You will be reimbursed for any additional transport costs that you may incur. Funding will be sought from the University.

Risks: The bone density test is safer than an X-ray of the bones as there is no exposure to radiation. The study will not expose you to any additional health risks. In the event of further questions or concerns, you could contact me or the UKZN Biomedical Research Ethics Committee. Contact details are as follows:

CONTACT DETAILS:

Researcher: Claire Martin Department of Dietetics and Human Nutrition Discipline of Dietetics and Human Nutrition College of Agriculture, Engineering & Science University of KwaZulu - Natal Pietermaritzburg Cell: 0723862358 Email: clairejm32@gmail.com	**Biomedical Research Ethics Administration** Research Office, Westville Campus Govan Mbeki Building Private Bag X 54001 Durban 4000 KwaZulu-Natal Tel: 031-2604769 Fax: 031 2604609 Email: BREC@ukzn.ac.za

Benefits: Results from this study will be available to all patients, which they could use to seek assistance in improving their nutritional and overall health.

Voluntary Participation: Participation in the study is voluntary and you have the option to refuse to participate at any stage; and if you do, it will not affect your usual care/treatment in any way.

Confidentiality: All personal and medical information will be stored and utilized confidentially. No names will be used in analysis or reporting of any results.

Findings: The study results will be used for the researcher's a thesis write-up for the researcher and will be published without any breach of confidentiality.

This study has been ethically reviewed and approved by the UKZN Biomedical Research Ethics Committee (Approval number_____)

If you are willing to participate in this study, please can you provide consent by signing below.

CONSENT FORM

I, _____ declare that the details of the study have been explained to me by_____.
I understand the aim and assessments required of me in the study and I have been given the opportunity to ask questions. I understand that my participation is entirely voluntary, and that I can choose to exit at any time without effect to my healthcare.

I am aware that I can contact the researcher at any time for any queries related to the study. Should I have any concerns about my rights as a participant, I can contact the Biomedical Research Ethics Administration (Both contact details listed above).

I HEREBY CONSENT TO VOLUNTARY PARTICIPATION IN THE ABOVE MENTIONED PROJECT.

Participant Name……..

Participant Signature……. Date……

Witness Name……

Witness signature…….Date……..

Researcher Name……..

Researcher……... Date……

Thank you

APPENDIX C: SOCIODEMOGRAPHIC QUESTIONNAIRE

(All information in this questionnaire is confidential)

NAME:	INTERVIEW DATE:
ADDRESS: Street & no: Suburb: Province:	
DOB (D/M/Y)	AGE:
TEL: (H)	TEL:(C)

Please tick appropriate block

1. Patient group

PATIENT GOUP	Tick
H+KTR(+D)	
H+WL(+D)	
H-KTR	
H-WL	

2. Home language

1	2	3	4
English	Afrikaans	Xhosa	Other (Specify)

3. Marital status

1	2	3	4	5	6	7	8
Unmarried	Married	Divorced	Separated	Widowed	Living together	Traditional marriage	Other (specify)

4. Educational Status

1	2	3	4
None	Primary school	High school	Tertiary education
	Specify last grade completed	Specify last grade completed	Qualification obtained

5. Type of house

1	2	3	4	5
Brick/concrete	Tin/iron	Mud/clay	Plank/wood	Other (specify)

6. Who does the house belong to?

1	2	3	4	5
My own	Sibling	Parents	Rented	Other (specify)

7. Number of bedrooms if separate from the rest of the house

1	2	3	4	5	6
There is no separate bedroom	1 bedroom	2 bedrooms	3 bedrooms	4 bedrooms	More than 4 bedrooms

8. Employment Status

1	2	3	4	5	6	7
Unemployed	Housewife	Self-employed	Employed part-time	Employed full-time	retired	Other (Specify)
Describe current employment						
If no longer working, describe previous employment						

9. Household occupancy

Names of people that live at home	M/F	Age (yrs)	Relationship to you

10. How many people are there living at home that are working, and contribute to the monthly household income?

1	2	3	4	6
1 person	2 people	3 people	4 people	5 people or more

11. How many people living at home are receiving State Grants?

1	2	3	4	6
1 person	2 people	3 people	4 people	5 people or more
Specify who, the type of grant and the amount:				
a.		b.		
c.		d.		
e.		f.		

12. What is the total household income per month? (Including wages, rent, salaries and grants)

Amount
R

13. How much of this money is spent on food each month?

Amount
R

14. Living circumstances

	Y	N
Do you have electricity?		
Do you have a refrigerator?		

15. Where do you get drinking water?

1	2	3	4	5
Own tap	Outside tap	Communal tap	River/dam	Other (specify)

16. Which of these do you have at home and use to cook with?

1	2	3	4	5	6	7	8
Hot plate	Microwave	Electric stove	Primus stove	Wood/ coal	Gas	Open fire	Other (specify)

17. Food provision

	Relationship to participant
Who does the food preparation and cooking?	
Who decides what food to buy?	
Who buys the food?	

18. How many visits do you make to the hospital

	Number of visits	Reason
per week		
Per month		
Per year		

19. How do you get to the hospital?

1	2	3	4	5
Car (own)	Taxi	Bus	bicycle	walking

20. Distance from home to hospital

Minutes/ hours to get to the hospital	Distance to the hospital (estimated km)

Appendix D : SCOPE OF INQUIRY: SEMI – STRUCTURED INTTERVIEW GUIDE

Introduction:

Thank you for agreeing to talk to me. I would like to find out more about your experiences so far, as you await a donor/ after your transplant. By talking about your life, its difficulties, improvements and other changes, we hope that we (clinical staff and other health professionals) can be more understanding about what you are going through. Knowing how your health has affected your life may improve our management of patients on dialysis/ after transplantation. All that you say is completely confidential.

I will ask you a few a questions about your daily living experiences dealing with HIV and dialysis/ transplantation, but feel free to say anything at all. I want to record all that you say completely and accurately but I cannot write it all down quickly and accurately. Would you mind if I record this talk between us? Once again, no one will know that it is you on the recorder. Can I go ahead and put it on?

Questions: Health and daily living

1. **How do you feel about your health?**
2. **What are your health concerns?**
   (Probe: What worries do you have about your health now?)
3. **How has your life changed since you started dialysis/or since the transplantation**
4. **How has it affected your everyday life?**
   (Probe: Are you still able to do all the things you used to?
   Are there things you no longer can do?)
5. **How has your family been affected?**
6. **What else do you feel worried or anxious about?**
   (Probe: What are you afraid of?
   What is worrying you the most?)
7. **What are you most grateful for?**
8. **Who has been your greatest support and how have they helped you?**
9. **What is a positive aspect of your life?**
10. **Did you have a bad experience that you want to talk about?**
11. **Did you have a good experience that you want to talk about?**

Concluding

Thank you very much for agreeing to talk to me. If at any stage you would like to add anything or feel you want to say something more, please call me on this number. I would like to get an update from you on how you are doing in 6 months again. I will contact you again.

SF-36 QUALITY OF LIFE HEALTH SURVEY

Please answer every question.

Patient Name:

_____

Date: _____

Interviewer_____

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the block that best represents your response.

1. In general, would you say your health is:

- ❑ Excellent
- ❑ Very good
- ❑ Good
- ❑ Fair
- ❑ Poor

2. Compared to one year ago, how would you rate your health in general now?

- ❑ Much better now than a year ago
- ❑ Somewhat better now than a year ago
- ❑ About the same as one year ago
- ❑ Somewhat worse now than one year ago
- ❑ Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?

- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

c. Lifting or carrying groceries.

- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

d. Climbing several flights of stairs.

- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

e. Climbing one flight of stairs.

- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

f. Bending, kneeling or stooping.

❑ Yes, limited a lot.
❑ Yes, limited a little.
❑ No, not limited at all.

SF-36 2

g. Walking more than one mile.
❑ Yes, limited a lot.
❑ Yes, limited a little.
❑ No, not limited at all.

h. Walking several blocks.
❑ Yes, limited a lot.
❑ Yes, limited a little.
❑ No, not limited at all.

i. Walking one block.
❑ Yes, limited a lot.
❑ Yes, limited a little.
❑ No, not limited at all.

j. Bathing or dressing yourself.
❑ Yes, limited a lot.
❑ Yes, limited a little.
❑ No, not limited at all.

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Cut down the amount of time you spent on work or other activities?
☐ Yes ☐ No

b. Accomplished less than you would like?
☐ Yes ☐ No

c. Were limited in the kind of work or other activities
☐ Yes ☐ No

d. Had difficulty performing the work or other activities (for example, it took extra time)
☐ Yes ☐ No

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Cut down the amount of time you spent on work or other activities?
☐ Yes ☐ No

b. Accomplished less than you would like
☐ Yes ☐ No

c. Didn't do work or other activities as carefully as usual
☐ Yes ☐ No

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

❑ Not at all
❑ Slightly
❑ Moderately
❑ Quite a bit
❑ Extremely

7. How much bodily pain have you had during the past 4 weeks?

❑ Not at all
❑ Slightly
❑ Moderately
❑ Quite a bit
❑ Extremely

SF-36 3

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- ❑ Not at all
- ❑ Slightly
- ❑ Moderately
- ❑ Quite a bit
- ❑ Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

a. did you feel full of pep?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

b. have you been a very nervous person?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

c. have you felt so down in the dumps nothing could cheer you up?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

d. have you felt calm and peaceful?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

e. did you have a lot of energy?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

f. have you felt downhearted and blue?

- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time

❑ None of the time

SF-36 4

g. did you feel worn out?

❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

h. have you been a happy person?

❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

i. did you feel tired?

❑ All of the time
❑ Most of the time
❑ A good bit of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

❑ All of the time
❑ Most of the time
❑ Some of the time
❑ A little of the time
❑ None of the time

11. How TRUE or FALSE is each of the following statements for you?

a. I seem to get sick a little easier than other people

❑ Definitely true
❑ Mostly true
❑ Don't know
❑ Mostly false
❑ Definitely false

b. I am as healthy as anybody I know

❑ Definitely true
❑ Mostly true
❑ Don't know
❑ Mostly false
❑ Definitely false

c. I expect my health to get worse

❑ Definitely true
❑ Mostly true
❑ Don't know
❑ Mostly false
❑ Definitely false

d. My health is excellent

❑ Definitely true
❑ Mostly true

- ❑ Don't know
- ❑ Mostly false
- ❑ Definitely false

APPENDIX F: GASTROINTESTINAL SYMPTOM RATING SCALE

Instructions:

a) Answer all questions
b) Think about whether these symptoms have worried you in the **<u>past week</u>**?
c) Mark a tick in the block that most describes your symptoms

1. Have you been bothered by stomach ache or pain?

No discomfort at all	Slight discomfort	Mild discomfort	Moderate Discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort
1	2	3	4	5	6	7

(*Stomach ache refers to all kind of aches or pains in your stomach or belly)*

2. Have you been bothered by hearturn?

No discomfort at all	Slight discomfort	Mild discomfort	Moderate Discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort
1	2	3	4	5	6	7

(Heartburn refers to a burning pain or discomfort behind the breastbone in your chest)

3. Have you been bothered by acid reflux?

No discomfort at all	Slight discomfort	Mild discomfort	Moderate Discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort
1	2	3	4	5	6	7

(Acid reflux refers to regurgitation or flow of bitter fluid into your mouth)

4. Have you been bothered by hunger pains in the stomach or belly?

No discomfort at all	Slight discomfort	Mild discomfort	Moderate Discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort
1	2	3	4	5	6	7

(This hollow feeling in the stomach is associated with the need to eat between meals)

5. Have you been bothered by nausea?

No discomfort at all	Slight discomfort	Mild discomfort	Moderate Discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort
1	2	3	4	5	6	7

(By nausea we mean a feeling of wanting to be sick)

6. Have you been bothered by a rumbling in your tummy or belly?

No	Slight	Mild	Moderate	Moderately	Severe	Very severe

discomfort at all	**discomfort**	**discomfort**	**Discomfort**	**severe discomfort**	**discomfort**	**discomfort**
1	**2**	**3**	**4**	**5**	**6**	**7**

(Rumbling refers to vibration or noise in the stomach)

7. Has your stomach felt bloated?

No discomfort at all	**Slight discomfort**	**Mild discomfort**	**Moderate Discomfort**	**Moderately severe discomfort**	**Severe discomfort**	**Very severe discomfort**
1	**2**	**3**	**4**	**5**	**6**	**7**

(Feeling bloated refers to swelling in the stomach or belly)

8. Have you been bothered by burping?

No discomfort at all	**Slight discomfort**	**Mild discomfort**	**Moderate Discomfort**	**Moderately severe discomfort**	**Severe discomfort**	**Very severe discomfort**
1	**2**	**3**	**4**	**5**	**6**	**7**

(Burping refers to bringing up gas or air through the mouth)

9. Have you been bothered by passing gas or flatus?

No discomfort at all	**Slight discomfort**	**Mild discomfort**	**Moderate Discomfort**	**Moderately severe discomfort**	**Severe discomfort**	**Very severe discomfort**
1	**2**	**3**	**4**	**5**	**6**	**7**

(Passing gas or flatus refers to the release of air or gas from the bowel)

10. Have you been bothered by constipation?

No discomfort at all	**Slight discomfort**	**Mild discomfort**	**Moderate Discomfort**	**Moderately severe discomfort**	**Severe discomfort**	**Very severe discomfort**
1	**2**	**3**	**4**	**5**	**6**	**7**

(Constipation refers to a reduced ability to empty the bowels)

11. Have you been bothered by diarrhoea?

No discomfort at all	**Slight discomfort**	**Mild discomfort**	**Moderate Discomfort**	**Moderately severe discomfort**	**Severe discomfort**	**Very severe discomfort**
1	**2**	**3**	**4**	**5**	**6**	**7**

(Diarrhoea refers to frequent loose or watery stools)

12. Have you been bothered by loose stools?

No discomfort at all	**Slight discomfort**	**Mild discomfort**	**Moderate Discomfort**	**Moderately severe discomfort**	**Severe discomfort**	**Very severe discomfort**
1	**2**	**3**	**4**	**5**	**6**	**7**

(If your stools have been alternately hard and loose, this question only refers to the extent you have been bothered by the stools being loose)

13. Have you been bothered by hard stools?

No discomfort at all	Slight discomfort	Mild discomfort	Moderate Discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort
1	2	3	4	5	6	7

(if your stools have been alternately hard and loose, this question only refers to the extent you have been bothered by the stools being hard)

14. Have you been bothered by an urgent need to have a bowel movement?

No discomfort at all	Slight discomfort	Mild discomfort	Moderate Discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort
1	2	3	4	5	6	7

(This urgent need to open your bowels makes you rush to the toilet)

15. When going to the toilet during the past week, have you had the feeling of not completely emptying your bowels?

No discomfort at all	Slight discomfort	Mild discomfort	Moderate Discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort
1	2	3	4	5	6	7

(The feeling that after finishing a bowel movement, there is still more stool that needs to be passed)

Additional: Have you been bothered by vomiting?

No discomfort at all	Slight discomfort	Mild discomfort	Moderate Discomfort	Moderately severe discomfort	Severe discomfort	Very severe discomfort
1	2	3	4	5	6	7

(vomiting refers to food that has been spewed out)