

**A COMPARISON BETWEEN THE EXCESS FLUID
TO BE REMOVED IN CHRONIC HAEMODIALYSIS PATIENTS,
ESTIMATED BY HD UNIT STAFF VERSUS THE MULTIPLE
FREQUENCY BIA MEASUREMENT.**

**Submitted in fulfilment of the academic requirements for the degree of
MASTER OF SCIENCE IN DIETETICS**

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ABSTRACT

A COMPARISON OF EXCESS FLUID TO BE REMOVED IN HAEMODIALYSIS PATIENTS, AS ESTIMATED BY HD STAFF VERSUS MULTIPLE FREQUENCY BIA.

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Background: Currently, in most haemodialysis (HD) units in South Africa, the excess fluid to be removed in HD, is estimated by comparing the previous post-HD versus the subsequent pre-HD body weight (wt). Bioelectrical impedance analysis (BIA) may potentially yield more accurate estimates that protect the HD patients from the risks associated with under and over-hydration.

Objective: To compare excess fluid to be removed in HD as estimated by the staff and multiple frequency BIA.

Methods: A prospective, non-randomized observational study was conducted. Repeated measures of 24 BIA pre- and post-HD measurements were conducted over 3 months on 20 chronic HD subjects (50% male; ages 21 - 63 years) at the King Edward VIII Hospital HD unit.

Results: There was a significant difference when comparing the excess fluid estimation by staff and the BIA method, even when volumes over different days of measurements were combined (RM ANOVA; $p=0.000$). In clinical practice, the difference between the excess fluid measured per BIA and the HD staff estimate (1.29 L difference) is profound. This difference was more profound in patients with a body fat percentage $\geq 30\%$ and a BMI ≥ 28 kg/m² when compared to their leaner counterparts ($p=0.000^*$). Also, within each of these groups, there is a significant difference between the staff estimation and the BIA measurements ($p=0.000$ for those with a BF $\geq 30\%$ and a BMI ≥ 28 kg/m², and $p=0.002$ for their leaner counterparts). Patients with a body fat percentage of $\geq 30\%$ and a BMI ≥ 28 kg/m² had a negative 3rd water space, compared

to those with lower body fat percentage and BMI's. There was a significant difference between the two groups were statistically significant ($p=0.000$).

Conclusion: Excess fluid measured per BIA compared with staff estimates significantly differed. The findings (negative 3rd water space in patients with a body fat percentage $\geq 30\%$ and a BMI $\geq 28\text{ kg/m}^2$, and positive 3rd water space in their leaner counterparts) of this study suggest that there is a potential benefit of a higher body fat and BMI in End Stage Renal Disease (ESRD) patients on HD, versus the conventional perception of a healthy BMI and body fat, namely a BMI between 19 and 25 kg/m^2 , and body fat percentage between 15 and 20%. Previous studies have shown HD patients with a higher BF and BMI have a lower mortality risk. It is of utmost importance, that further studies in a larger population with ESRD on HD be conducted, to confirm this finding. If confirmed, it may be pivotal in changing the dietary management of ESRD patients on HD. It is possible that current practice of aiming for a "healthy" body fat and BMI, maybe deleterious and is possibly negatively impacting on this patient populations risk for mortality, and long-term survival.

PUBLICATIONS

Abstract of poster presentation presented at the congress of the Critical Care Society of Southern Africa, held in July 2015.

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ABSTRACT (*Accepted for oral presentation at the International Congress of Renal Nutrition and Metabolism, to be held in Japan, in April 2016*).

NEW INSIGHTS IN THE OBESITY SURVIVAL PARADOX IN CHRONIC CARE HAEMODIALYSIS PATIENTS.

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Background: It has been shown that chronic care haemodialysis (HD) patients with a high body mass index (BMI) have a survival advantage, which has consistently been shown to have a strong predictive correlation to decreased all-cause mortality. This is in stark contrast to the general population, in whom obesity is a significant risk factor for the development of cardiovascular disease. The paradoxical observation, named the obesity survival paradox was first reported in the 1970's. The mechanism of this benefit has eluded scientists for over three decades.

Objective: To assess whether there is a significant difference in the 3rd water space between the subjects with a higher body fat percentage and BMI when compared to their leaner counterparts.

Methods: A prospective, non-randomized observational study was conducted. Repeated measures of 24 bioelectrical impedance analysis pre- and post-HD

measurements were conducted over three months on 20 chronic HD subjects (50% male; ages 21 - 63 years) at the King Edward VIII Hospital HD unit.

Results: Patients with a body fat percentage of $\geq 30\%$ and a BMI $\geq 28 \text{ kg/m}^2$ had a negative 3rd water space, compared to those with lower body fat percentage and BMI. The difference between the two groups was statistically significant ($p=0.000^*$).

Conclusion: Persistent excess fluid in the 3rd water space has been shown in previous studies to cause progressive soft tissue damage, and contributes to cardiac failure and brain cell damage in chronic HD patients. The findings of this study suggest that there is a potential benefit of a higher body fat and BMI in patients on chronic HD, in contrast to the conventional perception of a healthy BMI and body fat, namely, a BMI between 19 and 25 kg/m^2 , and body fat percentage between 15 and 20%. Previous studies have shown HD patients with a higher body fat percentage and BMI have a lower mortality risk. It is of utmost importance, that further studies in a larger population with on chronic HD be conducted, to confirm this finding. The results of such a study may be pivotal in changing the dietary management of chronic HD patients. It is possible that current practice of aiming for a “healthy” body fat and BMI maybe deleterious, as it has a direct impact on the risk for mortality, and long-term survival in chronic HD patients.

DECLARATION OF ORIGINALITY

I, *Jane Downs*, hereby declare that:

- i. The research reported in this thesis, except where otherwise indicated is my original research.
- ii. This thesis has not been submitted for any degree or examination at any other university
- iii. This thesis does not contain other person's data, pictures, graphs or other information unless specifically acknowledged as being sourced from those persons.
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 - a) their words have been re-written but the general information attributed to them has been referenced;
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Signed

Dated

I, *Frederick J. Veldman*, supervisor, approve the release of this thesis for examination.

Signed

Dated

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DEDICATION

I wish to dedicate this thesis to one of my most inspiring colleagues, and a great friend for nearly twenty years, whose positivity, excellent wit and sense of humour, and strong work ethic was unprecedented, and who sadly passed prematurely in the peak of his career, the surgeon, the late Mr (Dr) Haroon Docrat.

LIST OF ABBREVIATIONS

BIA	=	Bioelectrical impedance
BIS	=	Bioelectrical spectroscopy
BMI	=	Body mass index
BP	=	Blood pressure
CKD	=	Chronic kidney disease
CPG	=	Clinical practice guidelines
CV	=	Cardiovascular
ECW	=	Extracellular water
eGFR	=	Estimated glomerular filtration rate
ESRD	=	End stage renal disease
HD	=	Haemodialysis
Hg	=	Mercury
HR	=	Hazard ratio
HPT	=	Hypertension
ICW	=	Intracellular water
K/DOQI	=	Kidney Diseases Outcomes Quality Initiative
MRI	=	Magnetic resonance imaging
SLE	=	Systemic lupus erythematosus
TBW	=	Total body water

TABLE OF CONTENTS

ABSTRACT	II
PUBLICATIONS	IV
DECLARATION OF ORIGINALITY	VI
ACKNOWLEDGEMENTS.....	VII
DEDICATION.....	VIII
LIST OF ABBREVIATIONS.....	IX
TABLE OF CONTENTS	X
LIST OF FIGURES	XIV
LIST OF TABLES.....	XV
Chapter 1: The Problem and It’s Setting	1
1.1 The Importance and Purpose of the Research.....	1
1.2 Aim and Objectives of the Study.....	3
1.3 Study Hypothesis.....	4
1.4 Description of the Study Site.....	4
1.5 Definition of Terms	4
1.6 Principal Investigator and Supervisors.....	6
1.7 Study Methodology.....	6
1.7.1 Study Design.....	6
1.7.2 Study Population and Sampling	6
1.8 Data Collection Procedures and Data Collection Sheets	7
1.9 Duration.....	7
1.10 Statistical Analysis.....	7
1.11 Ethical Considerations.....	7
1.11.1 Subject Consent	8
1.11.2 Potential Risk to the Subjects	8

1.11.3 Risk Minimization.....	9
1.11.4 Subjects Incentives and Reimbursement.....	9
1.12 Funding and Resources	9
1.13 Disclosure of Conflict of Interest	10
1.14 Consultation.....	10
1.15 Structure of the dissertation.....	10
Chapter 2: Literature Review.....	11
2.1 Introduction.....	11
2.2 Fluid Overload and the Consequences Thereof.....	12
2.2.1 Impact of Fluid Overload on Hypertension.....	13
2.2.2 Impact of Salt (Sodium) Intake on Fluid Intake and Fluid Overload	14
2.2.3 Gastrointestinal Oedema	17
2.2.4 Uremic Cardiomyopathy	18
2.3 Hypertension.....	18
2.4 Dry Weight.....	19
2.5 The Association between Body Mass and Mortality.....	19
2.6 Bioelectrical Impedance Analysis.....	20
2.6.1 Phase Angle.....	23
2.6.2 Prediction Marker	24
2.7 Conclusion and Recommendations.....	24
Chapter 3: Methodology	26
3.1 Introduction.....	26
3.2 Research Design	26
3.3 Study Population and Sampling	26
3.3.1 Inclusion Criteria	26
3.3.2 Exclusion Criteria.....	27
3.4 Data Collection Procedures and Sheets	27
3.4.1 Anthropometry Measurements	27

3.5	Duration.....	28
3.6	Statistical Analysis	28
3.7	Ethical Considerations.....	29
3.7.1	Subject Consent	29
3.7.2	Potential Risks to the Subjects.....	29
3.7.3	Risk Minimization.....	30
3.7.4	Incentives and Reimbursement	30
3.8	Reduction of Bias.....	30
3.9	Funding and Resources	31
3.10	Disclosure of Conflict of Interest.....	31
3.11	Consultation.....	31
3.12	Summary.....	31
	Chapter 4: Results	33
4.1	Introduction.....	33
4.2	Study Population Demographics.....	33
4.2.1	Baseline Serum Albumin	34
4.2.2	Pre-Dialysis Systolic Blood Pressure.....	35
4.2.3	Phase Angle.....	36
4.3	Comparison of the Excess Fluid Estimation by Staff and the BIA Measurement.....	37
4.4	Difference in Third Water Space	39
4.5	Intracellular Fluid	41
4.6	Pre- versus Post-Dialysis Prediction Marker	41
4.7	Summary.....	42
	Chapter 5: Discussion.....	43
5.1	Introduction.....	43
5.2	Significant Findings.....	43
5.2.1	Staff Estimated versus the BIA Measurement of Excess Fluid to be removed	43
5.2.2	Intracellular Fluid	44

5.2.3 Prediction Marker: Pre- versus Post-Dialysis	45
5.2.4 Phase Angle	45
5.2.5 Survival Benefit of a Higher Body Fat and BMI in Dialysis Patients	46
5.3 Study Limitations	46
Chapter 6: Conclusion and Recommendations	47
6.1 Conclusion.....	47
6.2 Recommendations	48
Chapter 7: References	49
Chapter 8: Addenda	57
8.1 Addendum 1: Procedure for Subject Consent Counselling, and Data Collection	57
8.2 Addendum 2: Procedure for the Measurement of Standing Height	59
8.3 Addendum 3: Procedure for the Measurement of Body Weight	60
8.4 Addendum 4: Calibration of Equipment	61
8.5 Addendum 5: Data Sheet – Allocation of Research Codes to Subjects.....	63
8.6 Addendum 6: Subjects Demographics	64
8.7 Addendum 7: Daily & Monthly Data Collection Spreadsheets	65
8.8 Addendum 8: Subject Consent Forms – English and Zulu Version and UKZN and DOH Ethics Approval to Conduct the Study.....	66

LIST OF FIGURES

	Page
Figure 1: Baseline serum albumin (g/L) levels of the patients tested.	34
Figure 2: Pre-haemodialysis blood pressure readings of the patients over the number of days versus the ideal range as indicated by the two arrows.	35
Figure 3: Pre-HD phase angle of the patients repeated measure over days.	36
Figure 4: The difference in pre-HD phase angle between the patients with a body fat percentage of $\geq 30\%$ and a BMI of $\geq 28 \text{ kg/m}^2$, versus the leaner patients.	37
Figure 5: The pre-haemodialysis BIA measurement of the excess fluid (total fluid minus the maximum normal range); the patients with a BMI $\geq 28 \text{ kg/m}^2$ and a body fat percentage of $\geq 30\%$ versus the leaner patients, shown over the number of days.	38
Figure 6: The fluid to be removed as calculated by the HD staff as per usual practice of taking into account the patients pre- HD and last post-HD body weight.	39
Figure 7: The difference in pre-HD third water space between the patients with a body fat percentage of $\geq 30\%$ and a BMI of $\geq 28 \text{ kg/m}^2$, versus the leaner patients.	40
Figure 8: Pre-HD intracellular fluid versus the normal range, illustrating the patients' intracellular fluid was consistently below the normal range, irrespective of the total fluid being over- or dehydrated.	41

Figure 9: Pre-HD versus post-HD prediction marker of the patients shown over days. The post prediction marker consistently improved post dialysis.

42

LIST OF TABLES

	Page
Table 1: Demographic profile of study sample.	33

Chapter 1: The Problem and It's Setting

1.1 *The Importance and Purpose of the Research*

Currently, in the majority of renal haemodialysis (HD) units in South Africa, the excess extracellular fluid to be removed in HD, is estimated by the HD unit staff, who compare the patient's previous dry weight (post dialysis of the last dialysis session) to the current wet weight (pre-dialysis of the subsequent session), to determine the volume of fluid to be removed during HD. Optimal fluid management plays a critical role in the management of HD patients. Celik *et al.* (2011) have demonstrated that bioelectrical impedance analysis (BIA) has clinical value in the estimation of dry weight and other haemodynamic parameters of dialysis, and hence could potentially protect HD patients from the risks associated with under- and over-hydration.

Optimal fluid management requires accurate measurement of excess extracellular fluid to be removed during dialysis, and simultaneous minimization of potential intra- and post-dialytic adverse events (Onofriescu *et al.*, 2011). If too much excess fluid is removed during HD, this may result in excessive lowering of the dry weight and total blood volume, which may in turn result in intra-dialytic and post-dialytic complications, for example hypotension and muscle cramps, nausea and vomiting (Hecking *et al.*, 2012).

Chronic fluid overload in HD patients is associated with poor survival. It has been well documented, that excessive fluid in the extracellular fluid compartment, may significantly increase risk of cardiac failure and consequently increase the mortality risk in HD patients. The risk of cardiovascular (CV) mortality in dialysis patients is several times higher than the general population. The CV mortality risk of a 25 to 34 year old dialysis patient is approximately the same as an otherwise healthy 85 year old in the general population (Panichi & Tetta, 2011). Inadequate fluid removal during dialysis may also lead to chronic fluid overload, which in turn could result in

hypertension, left ventricular hypertrophy and heart failure (Ion Titapiccolo *et al.*, 2010). One in four dialysis patients will die suddenly. The latter is thought to be associated with factors related to end stage renal failure namely: inflammation, vascular stiffness, left ventricular hyperatropy, coronary heart disease, electrolyte or fluid abnormalities or autonomic dysfunction (Green & Roberts, 2010). Optimal fluid management is hence critical.

Bioelectrical impedance analysis (BIA) in the assessment of hydration status in dialysis patients has recently been demonstrated to be a cost-effective tool in fluid management of HD patients (Haapio *et al.*, 2012). Ideally, BIA should be utilized in conjunction with a clinical assessment, rather than in isolation (Woodrow & Ronco, 2012). BIA has been validated as a reliable and simple bedside tool in the fluid management of HD patients (Voroneanu *et al.*, 2010). Zhou *et al.* (2010) demonstrated that the use of a calf BIA ratio not only significantly improved dry weight assessment in 117 HD patients, but also facilitated improved blood pressure control, and resulted in reductions in anti-hypertensive medication doses. Fluid overload in renal failure is not only associated with increased mortality risk, but also increased hospital treatment costs. Arneson *et al.* (2010) reported that the treatment of fluid overload in the Medicare haemodialysis population in the United States, cost \$6372 per episode (41699 care episodes), resulting in a total cost of \$266 million over a two-year period.

For over thirty years, scientists have failed to demonstrate why chronic HD patients with a higher BMI and body fat, have a better long-term prognosis (Beberashvili *et al.*, 2009; Leinig *et al.*, 2008). One possibility is that the key/s to this puzzle may be found in the level of over- and under-hydration in the total body water and third water space. The intention of this study was to elucidate whether the BIA multiple frequency machine would be useful to estimate over- and under-hydration in clinical practice in the South African context, and whether it would aid in solving a puzzle that has eluded scientists for decades.

1.2 Aim and Objectives of the Study

The aim of the study was to compare the excess fluid volume to be removed in haemodialysis patients as estimated by the HD unit staff and the volume measured by a multiple frequency BIA machine. The outcome of which, would be used to inform future clinical practice for HD patients.

The principle objective of this study was to determine whether there was a significant difference in the excess fluid volume to be removed in HD, estimated by the HD unit staff member(s) and the volume measured by the a multiple frequency BIA machine (Body stat Quadscan 4000®). A difference would indicate that it is pertinent to review current clinical practice not only at King Edward VIII Hospital, but at all HD renal units in South Africa, to improve the quality of life and life expectancy for all HD patients.

A secondary objective was to assess whether there was a significant difference in the 3rd water space between the subjects with a higher body fat and BMI when compared to their leaner counterparts.

An additional secondary objective was to evaluate whether the prediction marker (also referred to as the Illness marker), which is an indirect value measured by the Bodystat Quadscan 4000®, improves post dialysis. A value of 1 is the highest value and reflects fluid overload. The integrity of cells is characterized by the ratio between the measured impedance values at 5 kHz and 50 kHz. A healthy ratio (prediction marker) is 0.85. Unhealthy or ill patients have a prediction marker closer to 1, whilst more athletic and muscular individuals (especially highly trained athletes) tend to have a prediction marker of less than 0.85. The measurement of the prediction marker pre- and post-dialysis will serve as an indicator of the potential health impact for HD patients, through the use of a more sensitive/ accurate fluid measurement tool in estimating the total volume of fluid to be removed during HD (Sobotka, 2011).

1.3 Study Hypothesis

It was hypothesized that the excess fluid estimated by the HD staff members versus the amount determined by a multiple frequency BIA machine, the Bodystat Quadscan 4000® differ. It was predicted that the BIA values are better indicators.

1.4 Description of the Study Site

The research was conducted at the King Edward VIII hospital, Congella, Durban, Haemodialysis Renal Unit.

1.5 Definition of Terms

- **End stage renal disease:** All individuals with GFR <15 mL/min/1.73 m² for ≥ 3 months are classified as having end stage renal disease, irrespective of the presence or absence of kidney damage (National Kidney Foundation K/DOQI Working Group, 2000).
- **Haemodialysis:** “the filtering of circulating blood through a semipermeable membrane in an apparatus (haemodialyser or artificial kidney) to remove waste products: performed in cases of kidney failure” (Collins Dictionary, 2015).
- **Intracellular fluid volume:** “a fluid within cell membranes throughout most of the body, containing dissolved solutes that are essential to electrolytic balance and to healthy metabolism. Also called intracellular water.” (Mosby's Medical Dictionary, 2009).
- **Extracellular fluid volume:** “the fraction of body water not in cells, about 20% of body weight; it consists of plasma water (about 4% of body weight), water between cells (interstitial water-lymph, about 15% of body weight), and water in dense bone and connective tissue (about 1% of body weight).” (Farlex online Medical Dictionary, 2015).
- **Total fluid volume:** “About two thirds of the human body's water is held in its cells and the remainder is found in the extracellular compartment. The extracellular fluids may be divided into three types: interstitial fluid in the

"interstitial compartment" (surrounding tissue cells and bathing them in a solution of nutrients and other chemicals), blood plasma in the "intravascular compartment" (the blood vessels), and small amounts of transcellular fluid such as ocular and cerebrospinal fluids in the "transcellular compartment". The interstitial and intravascular compartments readily exchange water and solutes but the third extracellular compartment, the transcellular, is thought of as separate from the other two and not in dynamic equilibrium with them." (Jacob *et al.*, 2009).

- **Third water space:** "It the abnormal accumulation of water outside of the extracellular and intracellular fluid spaces that is in the interstitial space, for example between the skin and fascia, which is not normally perfused with fluids" (Farlex online Medical Dictionary, 2015).
- **Phase Angle:** The phase angle is a measure of the quantity of metabolically active cells and the lean body cell mass, which contains large amounts of water and electrolytes. Low phase angles have been associated with an increased risk of mortality in haemodialysis patients (Manlucu *et al.*, 2010).
- **Prediction Marker:** The Prediction Marker or Impedance Ratio is the ratio between the impedance measurement at 200 kHz and 5 kHz. At 200 kHz the current is strong enough to penetrate the cell membrane and therefore total body water (TBW) can be measured. However, at 5 kHz the membrane cannot be penetrated and only extracellular water (ECW) can be measured. Intracellular water (ICW) is derived by $TBW - ECW$. The greater the variance between the two impedance values at 5 kHz and 200 kHz, the healthier the body cells. To allow easy monitoring of change, these figures are expressed as a ratio. A ratio closer to 1.00 indicates poor cellular health or extreme fluid overload (Sobotka, 2011).

1.6 *Principal Investigator and Supervisors*

The principal investigator of the study was Jane Downs, Registered Dietitian, employed full time at King Edward VIII Hospital.

The principal supervisors of the study were Professor Frederick J Veldman (HOD, Dietetics & Human Nutrition, UKZN) and Dr Suna Kassier (Lecturer & Academic Coordinator: Post-Graduate Diploma, Dietetics & Human Nutrition, UKZN).

1.7 *Study Methodology*

1.7.1 Study Design

This study followed a prospective, non-randomized observational (multiple series of data per subject) design.

1.7.2 Study Population and Sampling

BIA measurements were conducted on 20 chronic care haemodialysis (HD) patients. All the patients that were on the chronic HD programme at the time the study was conducted, that is, non-randomized selection, were included in the study. Both male and female patients with an age range of 18 to 65 years at the King Edward VIII Hospital Renal Unit were selected.

1.7.2.1 Inclusion Criteria

KEH VIII chronic care HD patients, with a urine output of less than 800 ml per day.

1.7.2.2 Exclusion Criteria

Pregnant patients, patients with acute renal failure, patients with advanced cardiac failure (specifically those with a pacemaker), and those with orthopaedic implants.

1.8 Data Collection Procedures and Data Collection Sheets

Standardized data collection and documentation procedures were followed; refer to addenda 1, 2, 3, 4, 5, 6, and 7.

1.9 Duration

The study was conducted over a 7 month period during 2014 to 2015. BIA measurements were conducted twice a week, that is, per dialysis session per week for a period of three months.

1.10 Statistical Analysis

The data were analysed using descriptive statistics and the generalised linear model of repeated measures and the analysis of variance (ANOVA) to account for the repeated measures on the same patients with time, using Statistica Version 7.1, StatSoft, Tulsa, OK, USA, and IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 23. A statistician was consulted to assist with the statistical analyses.

1.11 Ethical Considerations

UKZN Medical School (BREC) ethics was obtained (reference number: **BE041/14**), and concurrent written approval from the KZN Department of Health was also sought. A subject code was allocated to each subject, to protect the subject's identity, as well as, for each HD unit staff member who estimated the fluid volume to be removed, to protect their identity.

1.11.1 Subject Consent

Each subject was individually counselled in their preferred language, regarding the purpose and scope of the study. Subsequently each subject was provided with an information sheet stipulating the purpose and scope of the study. Following this, written informed consent was obtained in their language of choice (see addendum 8 for the English and Zulu version of the consent form).

1.11.2 Potential Risk to the Subjects

There was no potential risk to the patient. The study was essentially an observational study, and the BIA measurements were non-invasive. The measurement of BIA is contra-indicated in pregnant women, patients with pace makers, and those with orthopaedic implants; hence such patients were excluded from the study.

Usual renal unit protocols as per the study site were strictly adhered to, regarding patient monitoring during dialysis. The BIA measurements did not influence usual practice and patient care interventions.

The following risks were taken into account during the study:

- i. **Biological risks** - Nil
- ii. **Psychological risks** - Nil
- iii. **Social Risks** - Nil
- iv. **Legal risks** - Nil
- v. **Financial risks** - Nil
- vi. **Other risks** – None known

1.11.3 Risk Minimization

The following steps were taken to minimize risk:

- i. **Biological risks:** Usual renal HD unit monitoring during dialysis was strictly followed.
- ii. **Psychological risks:** Each subject was individually counselled in their language of preference before the study was commenced. In addition, subjects were made aware of the fact that they are able to exercise their right to exit the study at any time, without any discrimination or dire consequences to their treatment or care.
- iii. **Social Risks:** There was no social risk, nor stigma associated with participation in this study. The data were collected on the subjects' usual clinic visits.
- iv. **Legal risks:** The test was non-invasive and all subjects signed a consent form, with a disclaimer, at the onset of the study.
- v. **Financial risks:** The study costs were limited (Bodystat tabs); no special/ additional blood tests nor any other biological tests were required for this study, other than those routinely used in the management of the HD patients.
- vi. **Other risks:** Nil known.

1.11.4 Subjects Incentives and Reimbursement

The study subjects did not receive any incentives, nor re-imburement, as the research was conducted during their usual clinic visits at the regular clinic times.

1.12 Funding and Resources

The funding required for the study was for the cost of 8 electrodes for duplicate measurements in 25 patients over a period of 12 weeks (= 2400 Bodystat electrodes at an estimated cost of R10 560).

The Bodystat Quadscan 4000® multiple frequency BIA machine, was loaned to the researcher by LifeMax (South African distributor) or Bodystat (UK manufacturer).

1.13 Disclosure of Conflict of Interest

The principal researcher has not received any funding/ sponsorship from neither LifeMax nor Bodystat.

1.14 Consultation

During the process of compiling the study protocol (prior to the onset of the study), the principal investigator consulted both Prof A. Assounga (Head of Nephrology, Medicinal School, UKZN) and the KEH VIII HD renal unit staff. These individuals strongly supported the study objectives and the potential benefit the results held for HD patient care.

1.15 Structure of the dissertation

The structure of the dissertation is as follows:

Chapter 2 is a literature survey, in which the most critical information needed to understand and interpret the hypothesis and the results of this study, is examined. Chapter 3 explains and gives the motivation behind experimental methods and the research tools. The results of the study are provided in Chapter 4, followed by a discussion of the results of the study in Chapter 5. Finally, in Chapter 6, the conclusions and recommendations are made based on the findings of the study.

Chapter 2: Literature Review

2.1 Introduction

Once 90% or more of kidney function is lost, either kidney transplantation or dialysis is required to sustain life. Approximately 400 000 persons in the United States (USA) and over 2 million persons worldwide are dependent on dialysis. About 90% of American patients and approximately 70% of Canadian patients with end stage renal disease (ESRD) are on haemodialysis (HD) (The FHN Trial Group, 2010). In South Africa from 1999 to 2006, there was a 67% increase in deaths due to chronic kidney disease (CKD) (Moosa *et al.*, 2015). In 2010, Naicker reported that there were 2070 South Africans on haemodialysis (Naicker, 2010). Typically ESRD patients on haemodialysis receive HD three times a week. The rationale for the latter is based on a combination of physiological experiments, assessments of patient acceptance, feasibility, logistics and costs. Mortality amongst ESRD patients on HD remains high (18 to 20%) despite improvements in the dialysis technology, new pharmaceutical agents, and experience accumulated in the past 40 years since the inception of HD (The FHN Trial Group, 2010).

More than 50% of ESRD patients die from cardiovascular disease, a risk 10 to 20 times greater than the general population. Greater than 80% of ESRD patients have hypertension (HPT), a potentially modifiable cardiovascular risk factor, however, an estimated 70% are poorly controlled. An expanded extracellular fluid volume, an increase in peripheral vascular resistance due to haemodynamic and trophic effects of sympathetic nerve activity and inflammation are key contributing factors to hypertension in ESRD (Zimmerman *et al.*, 2014).

Fluid management is central to the management of ESRD. Persistent fluid overload damages the cardiovascular system and leads to hypertension, left ventricular hypertrophy, congestive heart failure, pulmonary oedema, peripheral oedema and other adverse cardiovascular consequences (Moissl *et al.*, 2013;

Tsai *et al.*, 2014). Mortality risk increases with a pre-dialysis fluid overload of 2.5 litres (Moissl *et al.*, 2013). Conversely, dehydration, excessive fluid removal or ultrafiltration, may result in intradialytic symptoms of hypotension such as acute ischaemic events with recurrent episodes, potentially causing functional impairment and organ damage (Vasko *et al.*, 2013). Controlling fluid status in an optimal range is crucial to improve cardiovascular tolerance, quality of life and survival (Moissl *et al.*, 2013).

New non-invasive bedside tools, such as bioelectrical impedance spectroscopy (BIS) are useful in accurately and objectively assessing fluid status, versus the usual clinical practice of measuring pre- and post-body weight, to determine how much fluid to remove during haemodialysis (Moissl *et al.*, 2013).

2.2 Fluid Overload and the Consequences Thereof

Severe fluid overload is defined as 15% above normal total fluid, and is associated independently with mortality in long-term HD patients (Wizemann *et al.*, 2009). Strict volume control has been shown to increase survival in ESRD patients on HD. In addition to many traditional risk factors, such as diabetes mellitus, hypertension, hyperlipidaemia and advanced age, fluid overload is an important element in the progression of adverse clinical outcomes in dialysis patients. Decreased kidney function contributes to decreased water excretion and excessive fluid overload. An enlarged left atrium diameter, an indicator of volume overload, and impaired diastolic function, has been associated with a more rapid decline in estimated glomerular filtration rate (eGFR) (Tsai *et al.*, 2014).

Fluid accumulation as assessed by weight change between dialyses or by relative plasma volume monitoring during dialysis predicts death and cardiovascular events independently of other risk factors in the HD population. (Zoccali *et al.*, 2013). Hence, hyper-hydration is a modifiable risk factor, and has been linked to more than a 2 fold increased mortality risk (Chazot *et al.*, 2012). It is critically important that HD patients be guided on the path between fluid overload and dehydration, although it is difficult to achieve in practice. Machek

et al. (2010) have shown that pre-dialysis blood pressure can be decreased by 12.5 mmHg per 1 litre reduction of fluid overload over a year without an increase in intra-dialytic adverse events.

Increased arterial stiffness might result in greater transmission of elevated systemic blood pressure to the glomerular capillaries, and hence aggravating glomerular hypertension, a key determinant of progressive kidney damage. The interaction between fluid overload and arterial stiffness may be one of the major causes of kidney disease progression in patients with CKD (Tsai *et al.*, 2014).

2.2.1 Impact of Fluid Overload on Hypertension

It has been shown in the USA, that as many as 72 % of HD patients suffer from hypertension despite being on anti-hypertensive medication. Normohydration has been described as a 1.1 litre above or below the normal range. Blood pressure responds positively to volume removal when hypertension is fluid related. However, progressive slow reduction of fluid overload is imperative, as even with modest reductions of extracellular water (500ml) in volume sensitive patients can be responsible for the difference between hypertension and vascular shock. It has been observed that ESRD patients receiving HD in the USA population tend to have the highest inter-dialytic weight gains, as well as, higher mortality rates than their European counterparts (Wabel *et al.*, 2008).

Slow removal of excess salt and water during dialysis has been shown to treat hypertension in 90% of HD patients. Anti-hypertensive medications (including diuretics) have been shown to exacerbate fluid retention in HD patients. The addition of each medication is associated with approximately 1 litre excess ECW. The slow reduction of estimated dry weight, results in the successful reduction of the number of anti-hypertensive medications, and a decrease in blood pressure (Tapolyai *et al.*, 2011). Poorly controlled hypertensive patients undergoing haemodialysis are more likely to have large inter-dialytic weight gain (Vujičić *et al.*, 2013). In a prospective study conducted by Vujičić *et al.*

(2013), the group of patients with poor compliance, usually had more than four kilograms inter-dialytic weight gain.

It is extremely important to take cognizance of the fact that oedema may only become clinically evident when there is an extracellular fluid overload of up to 10% of body weight (Tomson, 2001). It is concerning that fluid overload leads to increased mortality risk, although the clinical signs may not be evident in all HD patients (Chazot *et al.*, 2012). An HD patient may also remain hyper-hydrated despite the low inter-dialytic weight gain (Wizemann *et al.*, 2009).

2.2.2 Impact of Salt (Sodium) Intake on Fluid Intake and Fluid Overload

The distribution of sodium in the body is not homogenous. Approximately 90% of the exchangeable sodium is found in the extracellular volume, and about 10% is found in the intracellular volume. The sodium concentration directly determines the size of the extracellular volume. The depletion of sodium results in extracellular volume reduction, whilst sodium overload results in extracellular overload. Hence, the extracellular volume may be exposed to wide and rapid variation due to salt ingestion variability (Charra, 2007).

In normal individuals, low sodium sensitivity allows for wide variations in extracellular volume, but not consequent significant changes in blood pressure. An increase in sodium intake results in increased thirst and consequent increased fluid ingestion, which in turn results in an increase in extracellular volume (Charra, 2007). According to Tomson (2001), sodium intake drives thirst, and it is physiologically impossible for a conscious patient to ignore thirst. Attempts to limit fluid intake without limiting salt intake, may be described as an act of futility. Hence, if a dialysis patient's sodium intake exceeds the recommended restricted intake, the individual will not be able to resist the stimulus to drink fluids, in order to maintain serum osmolality in the normal range (Tomson, 2001).

Haemodialysis patients may experience challenges in adapting to sodium restrictions, due to their longstanding dietary habits and taste preferences. There is a need to develop culturally diverse education tools and interventions to decrease dietary sodium intake in HD patients. Further quality improvement studies which assess patient and patient family interventions to decrease dietary sodium intake, are necessary (Weiner *et al.*, 2014).

Serum osmolality which is primarily determined by sodium levels, stimulates thirst. Elevated sodium levels not only drive thirst, but draw intracellular fluid into the extracellular space, and when that is saturated, results in an increase in third water space, presents clinically as oedema (Tomson, 2001; Levin *et al.*, 2010).

Small amounts of water are lost in the form of perspiration, but these losses are usually limited to 500ml per day, and possibly less in cooler climates. Small amounts of water are also lost in the stool, in individuals with normal bowel function. The average healthy individual (70kg) contains approximately 40 litres of water. Approximately two thirds of the water is found in the intracellular volume, and one third in the extracellular volume, most of which comprises of the interstitial fluid. The circulating volume is about 4 litres, of which the plasma water comprises approximately 50% (2 litres); the latter is dependent on the haematocrit (Tomson, 2001).

Fluid weight gained between dialysis sessions, tends to remain in the extracellular space. A high extracellular fluid sodium concentration will tend to result in a flux of water from the cells, resulting in intracellular dehydration, which in turn may result in rebound hypernatraemia post-dialysis. The latter results in an increased thirst post-dialysis, with increased inter-dialysis fluid weight gain. Hence, in the absence of adequate sodium intake restriction, the vicious cycle is perpetuated (Tomson, 2001).

Excessive fluid intake, may result in hyponatraemia and a consequent increased intracellular volume, which may result in cerebral oedema (Tomson, 2001). Recently, persistent cerebral oedema has been shown to cause

progressive irreversible brain damage in ESRD patients on dialysis. Kong *et al.* (2014) recently reported that HD patients had diffuse interstitial brain oedema and moderate white matter integrity disruption, which correlated with cognitive dysfunction. Similarly, Zhang *et al.* (2015) have observed that brain oedema and white matter demyelination resulted in structural damage of the radiation and associative fibre tracts. It was further suggested that the cognitive deficits in ESRD patients may be caused by the fibre tract damage.

Concern has been expressed that avoiding added salt in cooking and at the table, is insufficient to restrict sodium intake in ESRD patients, due to the wide availability of processed foods with a high salt content (>600 mg sodium per 100 g), including in commonly eaten foods, for example, bread, cereals, and in fast foods (He & MacGregor, 2010). Haemodialysis patients are often reliant on food provided/ eaten by the family, in which the use of stock cubes and flavourants such those containing monosodium glutamate are common place. There is a need to not only educate the patient but also the family on how to flavour food without salt, using herbs (not high in potassium) and salt free natural spices (*pers obs*). The intake of salt in healthy individuals should ideally be limited to 6 g per day (Charra, 2007); whilst ESRD patients on HD need to limit their sodium intake to under 2000mg sodium per day (which is equivalent to 5 g sodium chloride) (Akbari *et al.*, 2015).

Sodium intake not only drives fluid intake but effects blood pressure levels. Approximately 90% of ESRD patients have hypertension at the time of HD initiation. Excess sodium has been described as a dominant factor in hypertension in ESRD (Charra, 2007).

It has been shown that a moderately sodium restricted diet usually results in an inter-dialytic weight gain of less than 2 kg, whilst an unrestricted diet (approximately 10 to 15 g salt per day) results in a weight gain of up to 4 kg or more between dialysis sessions. Excessive inter-dialytic weight gain and the prevalence of hypertension have been shown to be strongly related (Charra, 2007).

Not only dietary sodium, but also dialysate sodium concentration is correlated with inter-dialytic weight gain and blood pressure control (Beduschi *et al.*, 2013; Hecking *et al.*, 2012). The importance of reducing sodium overload in order to reduce or prevent fluid overload, has been strongly emphasized, and more recently sodium individualization (in terms of dialysate sodium content) has been encouraged in practice. The latter needs to be implemented with caution, as a lower sodium prescription can potentially cause osmotic disequilibrium, and consequently be hazardous (Hecking *et al.*, 2012). Manlucu *et al.* (2010) have suggested that increased sodium removal during dialysis, and through reduced salt intake, may lead to decrease water consumption.

It has been suggested that individualized sodium prescriptions may improve clinical outcomes, through the benefits of reduced extracellular fluid volume, and the improvement of cellular health. Cellular health can be measured indirectly per BIA; the prediction marker (ratio of impedance) reflects the health of cells (Manlucu *et al.*, 2010).

It has been recently reported that excess sodium without osmotic activity is stored in the skin in concentrations of 180 to 190 mEq/L in the skin. This sodium is bound to glucosaminoglycans, and the sodium stored in the skin could potentially function as a buffer to exogenous sodium loading. It is also possible that when these sodium stores are released into the circulation, may cause hypervolemia and oxidative stress. The latter may be aggravated by a progressive decrease in connective tissue mass which occurs in ageing and catabolism, hence reducing the skins capacity to act as a sodium reservoir (Levin *et al.*, 2010). This possibly plays a role in increased risk for mortality in older HD patients (*pers obs*).

2.2.3 Gastrointestinal Oedema

In ESRD patients with chronic congestive cardiac failure with fluid overload, bowel wall oedema may contribute to increased gut permeability and bacterial endotoxin translocation. Inflammation suppresses water channel aquaporin1,

a molecular counterpart of the ultra-small pore responsible for transcellular water permeability (Tsai *et al.*, 2014).

2.2.4 Uremic Cardiomyopathy

Uremic cardiomyopathy is considered to be the irreversible end result of the prolonged damaging effect of factors associated with end stage renal failure. Despite an ESRD patient previously being severely hypertensive, the blood pressure is often normal or low when the diagnosis of cardiomyopathy is made. Severe cardiac enlargement and systolic dysfunction (low ejection fraction) are usually used to describe uremic cardiomyopathy, and are indicative of a particularly a poor prognosis. Management of poor volume control due to excess inter-dialytic fluid weight gain, is critical in preventing uremic cardiomyopathy (Töz *et al.*, 2007).

2.3 Hypertension

Owing to the high prevalence of 60 to 90% of ESRD patients having HPT, the 2005 National Kidney Foundation Kidney Diseases Outcomes Quality Initiative (K/DOQI) clinical practice guidelines (CPG) recommended pre-and post-dialysis blood pressure (BP) of less than 140/90 and 130/80 mm Hg. These guidelines are based in part on data collected in the non-dialysis population. Conversely, it has been consistently observed in observational studies, ESRD patients have elevated mortality with persistently low blood pressures. It has been speculated that ESRD patients with a low BP, have co-existing illness such as poor ventricular function which lowers BP and poor general health (Robinson *et al.*, 2012).

End stage renal disease patients with a pre-dialysis systolic BP of greater than 160 mm Hg have increased mortality, as do ESRD patients with a pre-dialysis systolic BP of less than 130 mm Hg. Hence, it is important ESRD management guideline to maintain pre-dialysis systolic BP between 130 and 159 mm Hg. Treatment with anti-hypertensive medication has been associated with longer survival and fewer CV complications. However, modulation of BP in ESRD

patients' needs to be done with caution, as too aggressive modulation may contribute to myocardial stunning, associated with intra-dialytic hypotension, which is likely to be harmful (Robinson *et al.*, 2012).

There are various potential causes for blood pressure variability in HD patients, namely: baroreceptor dysfunction, aortic stiffness and variations in intravascular volume. The variability in BP can result in increased risk for cerebral small blood vessel disease, cerebral haemorrhage and sudden cardiac death in HD patients, compared to the general population (Selvarajah *et al.*, 2014).

According to Curatola *et al.* (2011), either more frequent or longer in duration HD, and improved efforts to increase low salt diet compliance, are required to decrease the high prevalence of hypertension in the HD population.

2.4 Dry Weight

Dry weight has been conventionally defined as the lowest body weight that can be tolerated without developing intra-dialytic and inter-dialytic symptoms of hypovolemia or symptoms of dehydration, and in the absence of overt fluid overload (Vasko *et al.*, 2013; Onofriescu *et al.*, 2012; Vujičić *et al.*, 2013).

2.5 The Association between Body Mass and Mortality

It has been shown that chronic care HD patients with a high body mass index (BMI) have a survival advantage. This patient group has consistently been shown to have a strong predictive correlation to decreased all-cause mortality. The latter is in contrast to the general population, where the opposite is true, where obesity has been shown to be a risk factor in the development of cardiovascular disease (Beberashvili *et al.*, 2009). The paradoxical observation, named the obesity survival paradox or reverse epidemiology regarding a decrease in mortality with a high BMI was first reported in the 1970's (Yen *et al.*, 2010). The mechanism of this benefit has eluded scientists for over three decades.

Beberashvili *et al.* (2009) have reported that HD patients with a higher BMI had a higher lean body mass, a higher phase angle and a lower extracellular mass (ECM) to body cell mass (BCM) ratio. Conversely, a low BMI and loss of muscle mass have been associated with morbidity and mortality in chronic kidney disease (Leinig *et al.*, 2008). Interestingly, in a study conducted by Leinig *et al.* (2008), a stronger correlation between BMI and fat mass (FM) versus BMI and lean body mass (LBM), in survival advantage in patients with chronic kidney disease was observed. Increased visceral fat mass has been shown to predict poor outcome in male but not female HD patients (Ikizler, 2008). Tapolyai *et al.* (2011) reported that the percentage body fat has a reverse relationship with over hydration, and with every 10% increase in body fat, there is a 1.2 L decrease in over hydration, and suggested that patients with a greater body fat and higher BMI have less fluid retention.

Chronic care HD patients tend to experience anorexia and catabolic effects of dialysis, and have inappropriately increased basal energy expenditure, which results in a significant negative energy balance. This in turn results in loss of weight and subcutaneous adipose tissue over time, in HD patients who survive over a decade. This patient group often experience a decrease in nutrient supply or intake, altered metabolism, and increased nutrient requirements (Ikizler, 2008). Segall *et al.* (2009) have shown that not only advancing age, diabetes and heart failure, but also a body fat percentage of less than 15 % and a phase angle of less than 6 degrees were associated with a significantly increased risk of death in HD patients.

2.6 Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) estimates body composition, including hydration status, by measuring the body's resistance and reactance to electrical current (Onofriescu *et al.*, 2012). Bioelectrical impedance analysis is a relatively inexpensive, safe, and portable tool, and easy to perform without extensive training, to assess both body fluid and nutritional status. It provides an indirect measure of body composition, and the accuracy of BIA is largely determined by mathematical models and their assumptions, which have essentially been

validated in Caucasian populations without renal disease (Oei & Fan, 2015). BIA spectroscopy has been found to be both highly reproducible and have a high specificity (Garagarza *et al.*, 2013). The use of BIA to measure muscle and fat mass has been validated by magnetic resonance imaging (MRI) and maybe used routinely. After years of BIA research in HD patients, it is now increasingly used clinically (Kotanko *et al.*, 2008).

The nutritional assessment of HD patients is an important aspect of the management of these patients, but clinically may be quantitatively challenging. Body composition alterations which are associated with malnutrition over time in HD patients, are strong predictors of mortality. Hence BIA is not only important for fluid management but also nutritional management of HD patients (Kaysen *et al.*, 2005).

Clinical signs such as oedema, HPT and pulmonary congestion do not correlate well with the degree of fluid over load, whilst traditional reference methods based on dilution techniques using deuterium or sodium bromide, are invasive, expensive, labour intensive and have not been adopted in clinical practice (Oei & Fan, 2015). Fluid assessment using BIA measurement has been used in HD patients for more than 4 decades (Anand *et al.*, 2012).

BIA is based on the principle of bioelectrical impedance (the vector sum of resistance and reactance) (Caravaca *et al.*, 2011). Single or mono frequency BIA utilizes a frequency of 50 Hz, which passes through both intra- and extracellular fluid. Equations to estimate total body water are based on the volume conductor model and multiple regression analysis (Oei & Fan, 2015). Whilst multiple-frequency BIA spectroscopy is more developed and has complex theoretical bases, which allow for more accurate determination of total body water (TBW), and measure the distribution of water between the intracellular and extracellular spaces, and in the recent decade been extensively used in HD patients (Caravaca *et al.*, 2011). The measurement of extracellular water (ECW) is especially important in HD patients, as most of the excess fluid removed in HD is from the ECW (Chen *et al.*, 2014). Multiple frequency BIA measures frequencies from 5 to 1000 Hz, that is, a wide range of frequencies (Moon *et al.*, 2010).

BIA has been successfully used to guide HD patients toward normohydration and better blood pressure control (Onofriescu *et al.*, 2014). In a randomized controlled parallel-group study conducted Onofriescu *et al.* (2014), a significant difference in survival, BP and fluid overload between the bioelectrical impedance group and the clinical methods (control) group was demonstrated after a 2.5 year intervention period. The extracellular water to total body water ratio (as a marker of over hydration) was shown to be an independent predictor of mortality, with a hazard ratio (HR) of 2.1, second only to that related to diabetes (HR = 2.7). BIA was shown to be a useful tool in achieving a true dry weight, with consequent improvements in BP control, arterial stiffness, left ventricular hypertrophy, with an overall reduction in mortality.

Similarly, Hur *et al.* (2013) in a prospective randomized controlled study, after 12 months, found fluid status in the intervention group (BIA monitored) was significantly lower, with improvements in cardiovascular parameters, namely, a decrease in pre-dialysis and ambulatory BP, decrease in arterial stiffness and a decrease left ventricular mass index.

Anand *et al.* (2012) found that compared to using body weight changes pre- and post HD, BIA is a more sensitive measure in measuring changes in body fluid, with a larger dynamic range. BIA was recommended as a cost effective simple non-invasive method for monitoring fluid especially for HD patients with a recent acute decompensatory heart failure event, providing an early diagnostic opportunity, and allowing for early intervention to avoid hospitalization and reduce the corresponding risk of mortality.

Vujičić *et al.* (2013) found BIA allows for more effective management of fluid status and BP control in patients on maintenance HD. The BIA measurements of over hydration were used as a tool to intervene in fluid overloaded patients, to achieve better dry weights and improved BP. In a study conducted by Caravaca *et al.* (2011), the findings suggested that BIA aids in identifying changes in hydration status in CKD patients, which may not be fully appreciated through clinical and biochemical assessment.

2.6.1 Phase Angle

Phase angle is a bioelectrical parameter associated with nutrition, and has a prognostic value in patients with renal failure (Teruel-Briones *et al.*, 2012). The phase angle is a measure of the quantity of metabolically active cells and the lean body cell mass, which contains large amounts of water and electrolytes. Low phase angles have been associated with an increased risk of mortality in haemodialysis patients (Manlucu *et al.*, 2010). Caravaca *et al.* (2011) observed that HD patients with a phase angle above the mean value of 5.3 degrees, had a better survival than those with a low angle. The predictive strength of mortality risk of the phase angle was also demonstrated with an increase in age in the subjects in this study. Whilst the Spanish researchers Abad *et al.* (2011) found an improved survival benefit associated with a phase angle of 8 degrees, however, there was a high mortality rate in this study, 61 % (n = 100) of the subjects had demised at the 6 year follow-up.

In healthy individuals, the cell membrane consists of a layer of non-conductive lipid material sandwiched between two layers of conductive protein molecules. The structure of cell membrane allows for capacitive element function, and hence when exposed to alternating currents, function as capacitors. Theoretically, reactance is a measure of the volume of cell membrane capacitance and an indirect measure of the intracellular volume or body cell mass. Body fat, total body water and extra cellular water provide electric resistance to an electrical current. Cell membranes and tissue interfaces provide capacitive reactance (Kumar *et al.*, 2012).

The phase angle is a linear method of measuring the relationship between electric resistance and reactance in a series or parallel circuits. The phase angle is derived from the tangent value of the ratio of reactance versus electric resistance (Kumar *et al.*, 2012). The latter is indicative of alterations in the integrity of cell membranes and intercellular space. The phase angle for healthy individuals will range from 3 to 10 degrees, depending on gender. Lower phase angles appear to be consistent with low reactance, cell death, or loss of the selective permeability of cell membrane (Costa de Oliveira *et al.*,

2010). There is a significant difference in phase angle between healthy and disease states. The phase angle increases with improving clinical status (Kumar *et al.*, 2012).

2.6.2 Prediction Marker

The Prediction Marker or Impedance Ratio (which was previously referred to as the illness marker) is the ratio between the impedance measurement at 200 kHz and 5 kHz. At 200 kHz the current is strong enough to penetrate the cell membrane and therefore total body water (TBW) can be measured. However, at 5 kHz the membrane cannot be penetrated and only extracellular water (ECW) can be measured. Intracellular water (ICW) is derived by $TBW - ECW$. The greater the variance between the two impedance values at 5 kHz and 200 kHz, the healthier the body cells. To allow easy monitoring of change, these figures are expressed as a ratio. A ratio closer to 1.00 indicates poor cellular health or extreme fluid overload (Sobotka, 2011).

2.7 Conclusion and Recommendations

Fluid management is of utmost importance in the management of ESRD. Persistent fluid overload damages the cardiovascular system, and leads to hypertension, left ventricular hypertrophy, congestive heart failure, pulmonary oedema, peripheral oedema and other adverse cardiovascular consequences (Moissl *et al.*, 2013; Tsai *et al.*, 2014). Current practice in most South African haemodialysis units is to use the pre- and post-dialysis body weights to determine the volume of fluid to be removed during dialysis.

Recent studies have shown that BIA is a useful, cost effective and reliable tool in guiding both HD staff and patients, so that the patients achieve an optimal dry weight, without compromising lean and fat weight. In order to evaluate whether BIA needs to be implemented as standard practice in South African HD units, it is extremely relevant that the difference between standard practice and BIA measurements in the estimation of excess fluid be investigated. The effective reduction of third water space could potentially not only prevent or delay the

onset of cardiac failure, but also reduce the prevalence of hypertension and consequently significantly reduce the mortality risk in this group of patients.

Differences in the BIA pre-and post-illness marker may demonstrate the positive effects of regular HD. Whilst investigating the differences in excess fluid, third water space, intracellular and extracellular fluid in the HD patients with a higher BMI and body fat percentage versus their leaner counterparts, may shed some illuminating light on the mystery that has eluded scientists for the past 30 years, namely, the reason the HD patients with a higher body fat percentage and BMI have a lower mortality risk.

Chapter 3: Methodology

3.1 Introduction

In this chapter, an overview is given of the study design, the sampling procedure, as well as, the methods and measuring instruments that were used for data collection in the current study. The sections on study population and sample selection and the inclusion and exclusion criteria, provides an overview of eligibility for participation and the criteria that were used to select subjects. This is followed by the methods and materials which includes a detailed description of how the data was collected. This was followed by how the data was statistically analysed. Lastly, the reliability and validity of the data was discussed in addition to ethical considerations.

3.2 Research Design

This study followed that of a prospective, non-randomized observational (multiple series of data per subject) design over a period of 7 to 8 months, recruited haemodialysis patients attending the King Edward VIII Hospital Renal Unit. Pre- and post-bioelectrical impedance analysis (BIA) measurements using a multiple frequency BIA machine were conducted on the patients.

3.3 Study Population and Sampling

All the patients who were on the chronic programme during the study period, that is, non-randomized selection, both males and females with an age range of 19 to 63 years at the KEH VIII Renal Unit were requested to volunteer for the study. Two subjects demised during the study, and one subject dropped out of the study. The data of the latter patients were not included in the data analyses. The data of 20 subjects were analysed.

3.3.1 Inclusion Criteria

KEH VIII chronic care HD patients, with a urine output of less than 800 ml per day were included in the study.

3.3.2 Exclusion Criteria

Pregnant patients, patients with advanced cardiac failure (specifically those with a pacemaker) and those with orthopaedic implants were excluded from the study.

3.4 Data Collection Procedures and Sheets

Standardized data collection procedures were followed, and standardized data records were utilized. Refer to addenda 1, 2, 3, 4, 5, 6, and 7 for the data collection procedures and records.

3.4.1 Anthropometry Measurements

3.4.1.1 Measurement of Height and Weight

Standardized procedures were followed in the measurement of the patients' height and weight. Refer to addenda 2 and 3 for the detailed procedure followed. The Frankfort Horizontal Plane method was used for measuring the height. The electronic scale was calibrated on a weekly basis, as described in addendum 4.

3.4.1.2 Measurement of Bioelectrical Impedance

The bioelectrical impedance was performed with a multiple frequency BIA machine (Bodystat Quadscan 4000 ®, United Kingdom). Prior to the BIA measurement, the patients were requested to remove all jewellery. The patients laid in a supine position for approximately 10 minutes on a non-conductive surface. During both the inclusion process and prior to the first BIA measurement, a medical history was taken to ascertain whether the patient had a pace maker, any orthopaedic implants, or was pregnant.

The patients' legs were separated at a 30 to 40 degree angle. The procedure made use of the right arm and leg, unless the presence of a fistula in the right arm. The left side of the body was then used for all tests.

Electrodes were placed at the dorsum of the hand and foot on the metacarpal and metatarsals, respectively. The reading electrodes were placed between the medial and lateral malleolus of the same side of the body. Patients were requested not to move nor talk during the test. All the tests (both pre- and post-) were conducted by the principal investigator. A single measurement was taken both prior to HD, and 15 minutes post dialysis.

The HD unit staff were blinded; the BIA results were not discussed during the study period with the HD staff. The results were only explained to the patients, once the patients were on HD, to prevent the patients from influencing the HD staff's usual practice in calculating fluid to be removed during HD.

3.5 Duration

The study was conducted over a 7 month period during 2014 to 2015, in which the consecutive pre- and post- HD BIA measurements were performed on each subject twice or three times per week (depending on the subjects frequency of dialysis), that is, per dialysis session per week for a period of three months (12 weeks).

3.6 Statistical Analysis

The data were analysed using descriptive statistics and the generalised linear model of repeated measures analysis of variance (RM ANOVA) using Statistica Version 7.1, StatSoft, Tulsa, OK, USA, and IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 23, to account for the repeated measures on the same patients over time.

3.7 Ethical Considerations

UKZN Medical School Biomedical Research Ethics Committee (BREC) ethics approval was obtained (Reference number: BE041/14), and concurrent written approval from the KZN Department of Health was sought, and issued. A subject code was allocated to each subject, to protect the subject's identity, as well as, for each HD unit staff member who estimated the fluid volume to be removed, to protect their identity.

3.7.1 Subject Consent

Each subject was individually counselled in their preferred language, regarding the purpose and scope of the study. Subsequently, each subject was provided with a written information sheet which explained the purpose and scope of the study. Thereafter, written informed consent was obtained in the subject's language of choice. Refer to addendum 8 for a copy of the English consent form, and the Zulu version of the consent form.

3.7.2 Potential Risks to the Subjects

There was no obvious potential risk to the patient. The study was of an observational nature, and the BIA measurements were non-invasive. The measurement of BIA is contra-indicated in pregnant women, patients with pace makers and in those with orthopaedic implants; hence such patients were excluded from the study.

Usual renal unit protocols practiced at the study site were strictly adhered to, regarding patient monitoring during dialysis. The BIA measurements did not interfere with usual practice and patient care interventions.

- I. **Biological risks** – Nil
- II. **Psychological risks** – Nil
- III. **Social Risks** – Nil
- IV. **Legal risks** – Nil

- V. **Financial risks** – Nil
- VI. **Other risks** – None known

3.7.3 Risk Minimization

The following steps were taken to minimize risk:

- I. **Biological risks:** Usual renal HD unit monitoring during dialysis was strictly followed.
- II. **Psychological risks:** Each subject was individually counselled in their language of preference before the study commences. In addition, subjects were made aware of the fact that they are able to exercise their right to exit the study at any time, without any discrimination or dire consequences to their treatment or care.
- III. **Social Risks:** There was no social risk, nor stigma associated with participation in this study. The data were collected on the subjects' usual clinic visits.
- IV. **Legal risks:** The test was non-invasive and all subjects signed a consent form, with a disclaimer, at the onset of the study.
- V. **Financial risks:** The study costs were limited (Bodystat tabs); no special/ additional blood tests nor any other biological tests were required for this study, other than those routinely used in the management of the HD patients.
- VI. **Other risks:** Nil known

3.7.4 Incentives and Reimbursement

The study subjects did not receive any incentives, nor re-imburement, as the research was conducted on their usual clinic visits at the usual clinic times.

3.8 *Reduction of Bias*

The researcher did not discuss the BIA measurement results with the HD staff during the duration of the study, to reduce potential bias. The HD staff followed the standard operating procedures in calculating the amount of fluid

to be removed during dialysis.

3.9 Funding and Resources

The funding required for the study was the cost of 4 tabs x 2 measurements per subject x 25 patients x 12 weeks = 2400 Bodystat tabs (Actual cost = R10560).

The Bodystat Quadscan 4000® multiple frequency BIA machine, was loaned to the researcher by LifeMax (South African distributor) from Bodystat (United Kingdom manufacturer), and was returned upon completion of the data collection.

3.10 Disclosure of Conflict of Interest

The principal researcher has not received any funding/ sponsorship from neither LifeMax nor Bodystat.

3.11 Consultation

During the process of compiling the study protocol (prior to the onset of the study), the principal investigator consulted both Prof A. Assounga (Head of Nephrology, Medicinal School, UKZN) and the KEH VIII HD renal unit staff. These individuals strongly supported the study objectives and the potential benefit the results held for HD patient care.

3.12 Summary

This study Prospective, non-randomized observational (multiple series of data per subject) study. UKZN Medical School Biomedical Research Ethics Committee (BREC) ethics approval was obtained (Reference number: BE041/14), and concurrent written approval from the KZN Department of Health was sought, and issued. Pre- and post- BIA repeated consecutive measurements using a multiple frequency BIA machine (Bodystat Quadscan

4000 ®) were conducted over a 12 week period, on 23 chronic care HD patients (all the patients who were on the chronic programme during the study period, that is, non-randomized selection) both males and females with an age range of 19 to 63 years at the KEH VIII Renal Unit. Two patients demised and one dropped out before the completion of the data collection; the data for 20 subjects (48 BIA measurements per subject) were analysed. A total of 960 BIA tests were conducted during the study period. The HD unit staff were blinded; the BIA results were not discussed during the study period with the HD staff. The usual practice of determining fluid to be removed was recorded for each pre-HD test. The latter was compared to the pre-HD measurement of excess fluid to be removed.

Chapter 4: Results

4.1 Introduction

This chapter presents the results of the study, of which the primary aim was to compare the excess fluid volume to be removed in haemodialysis patients as estimated by the HD unit staff and the volume measured by a multiple frequency BIA machine, and to determine whether there were statistically significant differences between the two methods of assessing the excess fluid to be removed.

4.2 Study Population Demographics

Pre- and post-bioelectrical impedance analysis (BIA) measurements were conducted on 23 chronic care haemodialysis (HD) patients with an age range of 19 to 63 years at the King Edward VIII Hospital (KEH VIII) Renal Unit. Two patients demised during the study, and one subject dropped out of the study. The data of the latter patients were not included in the data analyses. An equal number of men and women (n = 10 for each gender, respectively) were recruited to participate in the study.

All the patients had pre-existing hypertension prior to requiring HD. Two subjects were human immunodeficiency virus (HIV) positive and were on anti-retroviral treatment. One patient was diagnosed with systemic lupus erythematosus (SLE), one with diabetes (Type II), and one was diagnosed with a congenital cardiac disease.

Table 1: Demographic profile of the study sample

Variable	Mean \pm SD*	Range	
		Minimum	Maximum
Age (years)	46.45 (\pm 10.75)	20	63
Weight (kg)	68.13 (\pm 9.98)	52.2	88.6
Height (cm)	160.86 (\pm 7.43)	144	180
BMI (kg/m ²)	26.5 (\pm 4.33)	20.1	33.7

* Standard Deviation

4.2.1 Baseline Serum Albumin

Hypoalbuminaemia has been described as an indicator of malnutrition and inflammation and a risk factor for kidney disease progression in chronic kidney disease (Tsai *et al.*, 2014). The lower limit of the normal blood serum albumin concentration is considered to be 35 g/L. A serum albumin of ≥ 38 g/L however, is associated with a better survival in the maintenance of the HD population (Sridhar & Josyula, 2013). Seventy five percent ($n = 15$) of the sample population had a baseline serum albumin concentration of below the lower limit of the normal reference range of 35 g/L. However, all of these patients fell within the range of 20 to 35 g/L, which is defined as moderately depleted, (refer to Figure 1).

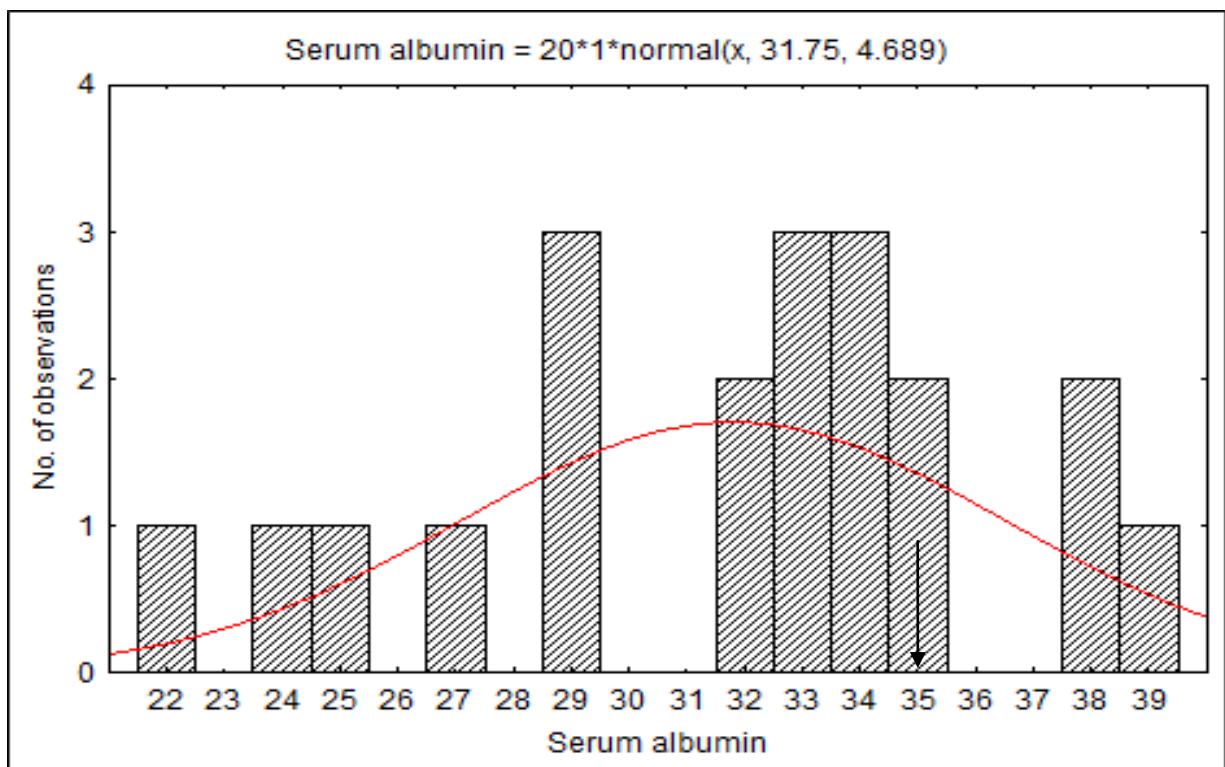


Figure 1: Baseline serum albumin (g/L) levels of the patients tested; number of observations versus the lower normal range as indicated by the arrow.

4.2.2 Pre-Dialysis Systolic Blood Pressure

Both end stage renal disease patients with a pre-dialysis systolic blood pressure (BP) of greater than 160 mmHg and end stage renal disease (ESRD) patients with a pre-dialysis systolic BP of less than 130 mmHg have been reported to carry a risk of increased mortality. Hence, it is an important ESRD management guideline to maintain pre-dialysis systolic BP between 130 and 159 mmHg (Robinson *et al.*, 2012). Pre-HD systolic BP is generally utilized to make clinical decisions regarding the management of blood pressure; although home BP monitoring has been shown to be of greater prognostic value, in terms of mortality, as well as serving as a marker for the presence of left ventricular hypertrophy associated with cardiac failure (Shafi *et al.*, 2014; Alborzi *et al.*, 2007). The pre-HD systolic blood pressure measurements collected over a number of days and ideal range are illustrated in Figure 2. The majority of the patients in this study had a mean pre-HD systolic BP that fell within the normal range. However, some outliers (both over and above the normal reference range) were present in the study.

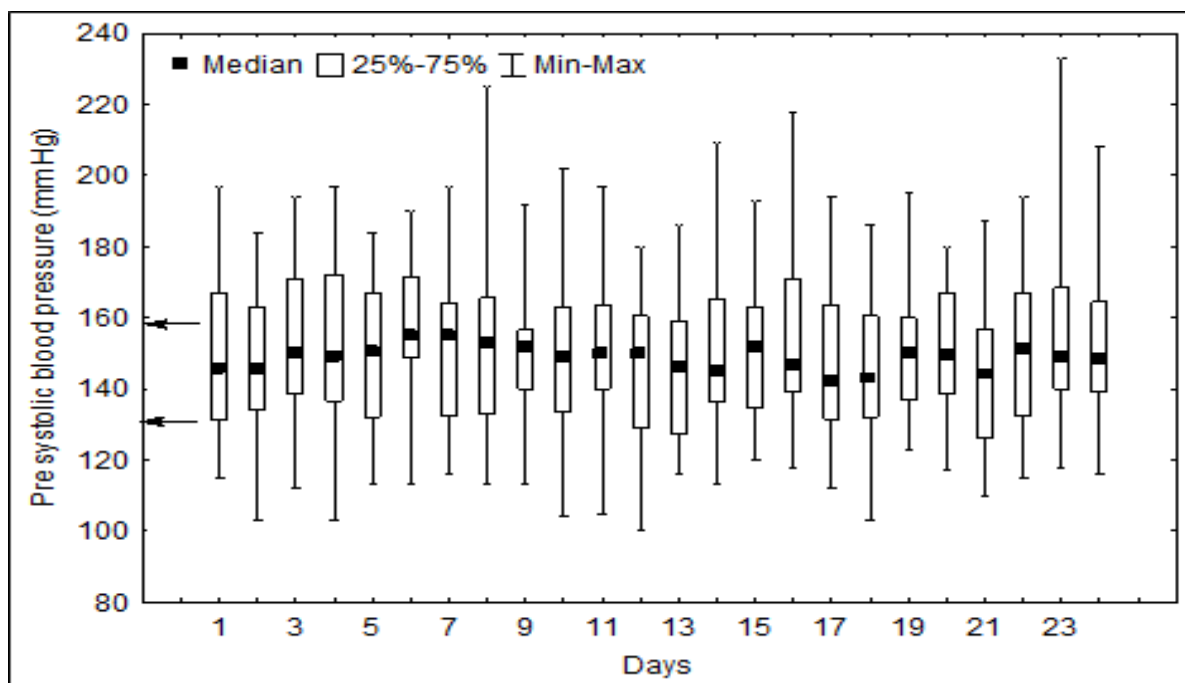


Figure 2: Pre-haemodialysis blood pressure readings of the patients over the number of days versus the ideal range for chronic HD patients as indicated by the two arrows.

4.2.3 Phase Angle

The phase angle for healthy individuals ranges from 3 to 10 degrees, depending on gender. Lower phase angles appear to be consistent with low reactance, cell death, or loss of the selective permeability of the tissue cell membranes. (Costa de Oliveira *et al.*, 2010). Low phase angles have been associated with an increased risk of mortality in haemodialysis patients (Manlucu *et al.*, 2010). The pre-haemodialysis median phase angle measured over 24 days is reported in Figure 3. Although the median fell in the range of that described for healthy individuals, it was less than 5.3. Caravaca *et al.* (2011) observed that HD patients with a phase angle above the mean value of 5.3 degrees, had a better survival when compared to those with a lower phase angle.

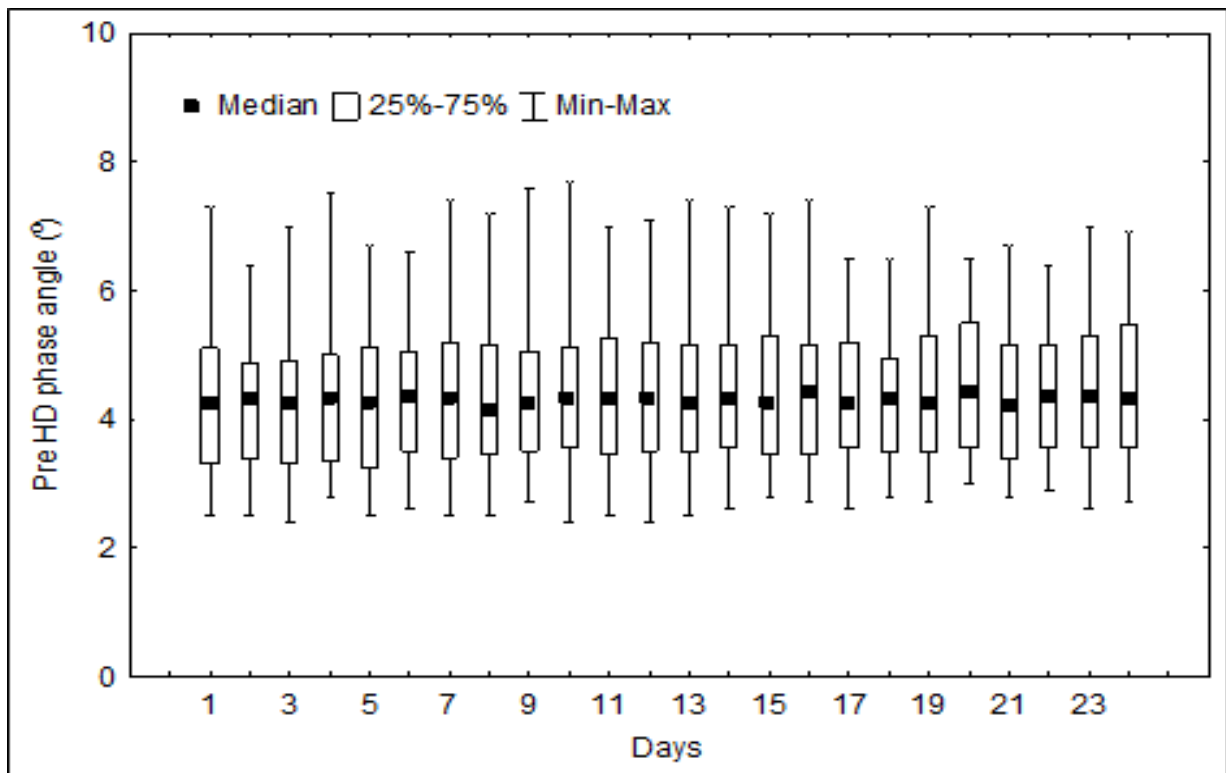


Figure 3: Pre-HD phase angle of the patients repeated measure over days.

Patients with a higher body fat (BF) percentage ($\geq 30\%$) and a BMI of $\geq 28 \text{ kg/m}^2$ had a slightly higher mean phase angle when compared to that of the leaner patients ($p=0.539$; t-test for equality of means), suggesting a

tendency towards a healthier cell mass in the group with a higher body fat and BMI (refer to Figure 4).

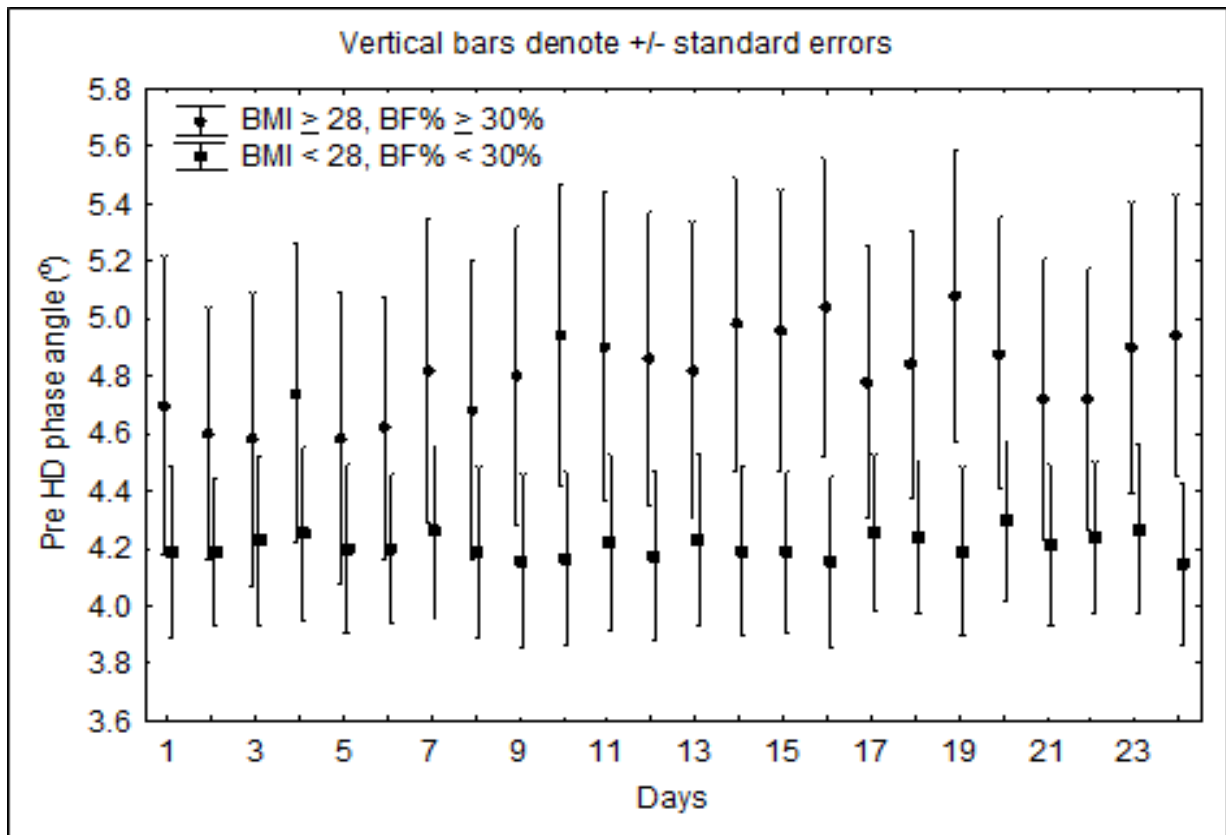


Figure 4: The difference in pre-HD phase angle between the patients with a body fat percentage of $\geq 30\%$ and a BMI of $\geq 28\text{ kg/m}^2$, versus the leaner patients. The trend shown demonstrates the median phase angle of higher body fat and BMI patients was consistently higher than that of the leaner patients, suggesting a healthier cell mass in the group with a higher body fat and BMI, over time.

4.3 Comparison of the Excess Fluid Estimation by Staff and the BIA Measurement

There was a significant difference when comparing the excess fluid estimation by staff and the BIA method, even when volumes over different days of measurements were combined (RM ANOVA; $p= 0.000$). In clinical practice, the difference between the excess fluid measured per BIA and the HD staff estimate (1.29 L difference) is profound. This difference was more profound in patients with a body fat percentage $\geq 30\%$ and a BMI $\geq 28\text{ kg/m}^2$ compared to

their leaner counterparts ($p=0.000^*$; Fig. 5 & 6). Also, within each of these groups, there is a significant difference between the staff estimation and the BIA measurements ($p=0.000$ for those with a BF $\geq 30\%$ and a BMI ≥ 28 kg/m², and $p=0.002$ for their leaner counterparts).

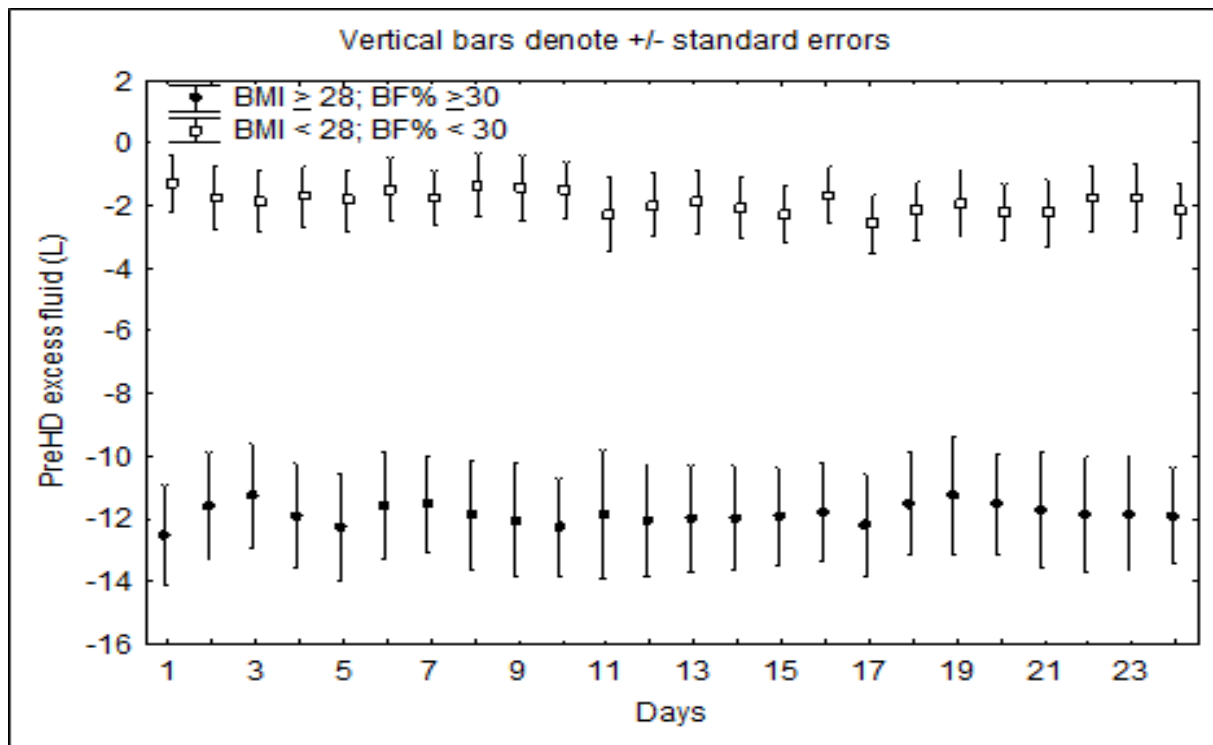


Figure 5: The pre-haemodialysis BIA measurement of the excess fluid (total fluid minus the maximum normal range); the patients with a BMI ≥ 28 kg/m² and a body fat percentage of $\geq 30\%$ versus the leaner patients, shown over the number of days.

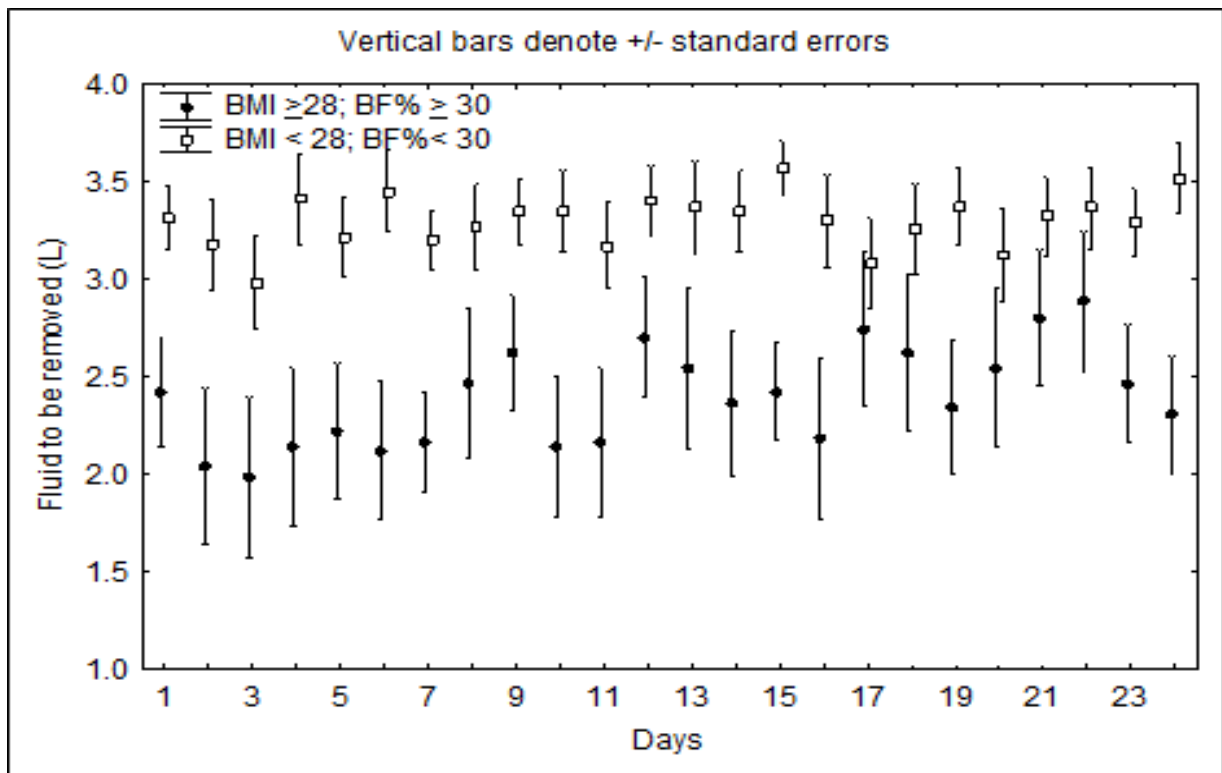


Figure 6: The fluid to be removed as calculated by the HD staff as per usual practice of taking into account the patients' pre-HD and last post-HD body weight. The patients with a BMI of $\geq 28 \text{ kg/m}^2$ and a body fat percentage of $\geq 30\%$ consistently required less fluid to be removed, when compared to their leaner counterparts.

4.4 Difference in Third Water Space

Patients with a body fat percentage of $\geq 30\%$ and a BMI $\geq 28 \text{ kg/m}^2$ had a negative 3rd water space, compared to those with lower body fat percentage and BMI's. There was a significant difference between the two groups were statistically significant ($p=0.000^*$; Figure 7).

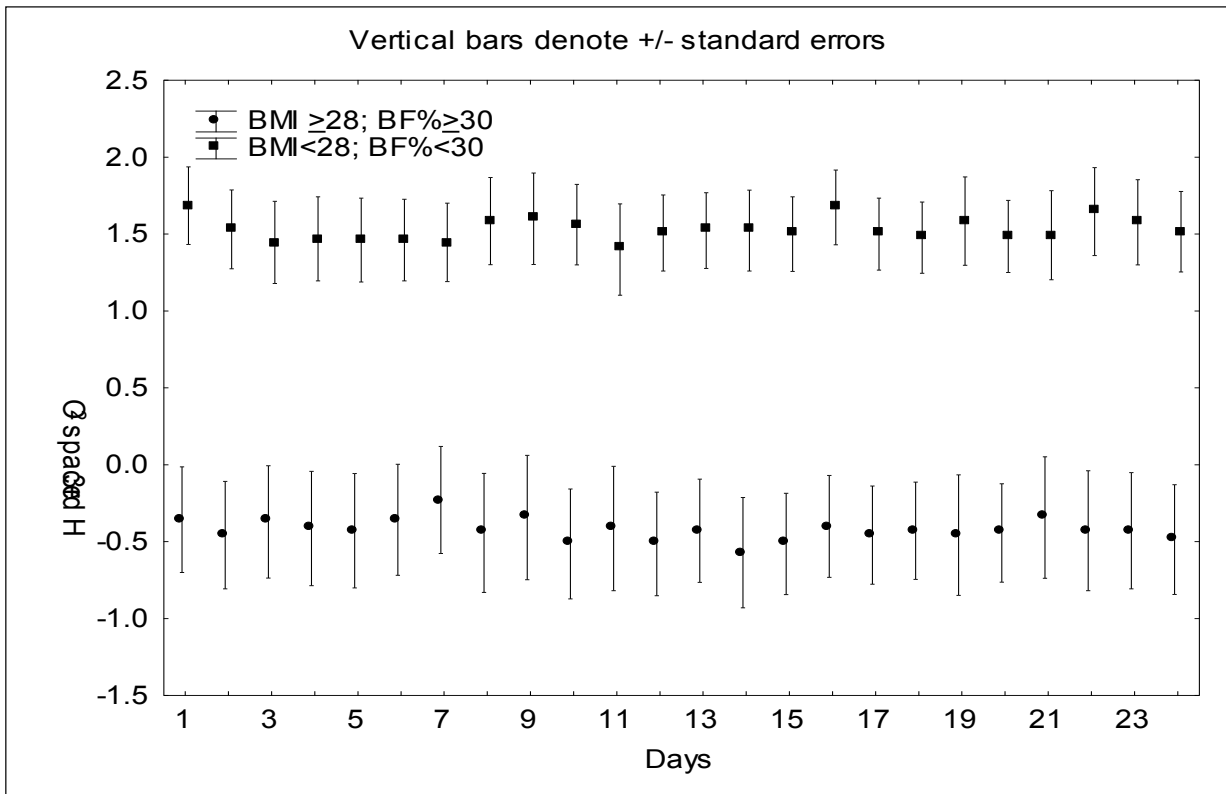


Figure 7: The difference in pre-HD third water space between the patients with a body fat percentage of $\geq 30\%$ and a BMI of $\geq 28\text{ kg/m}^2$, versus the leaner patients. The trend shown demonstrates the mean of higher body fat and BMI patients' 3rd water space is negative, whilst the leaner patients had a positive 3rd water space, which is associated with deleterious side-effects in the long-term.

4.5 Intracellular Fluid

All patients' intracellular fluid was below the normal range despite their hydration status. There was no significant difference when combined effects including days were considered but there was a significant difference between pre-dialysis value and normal intracellular fluid level ($p=0.003^*$), as illustrated in Figure 8.

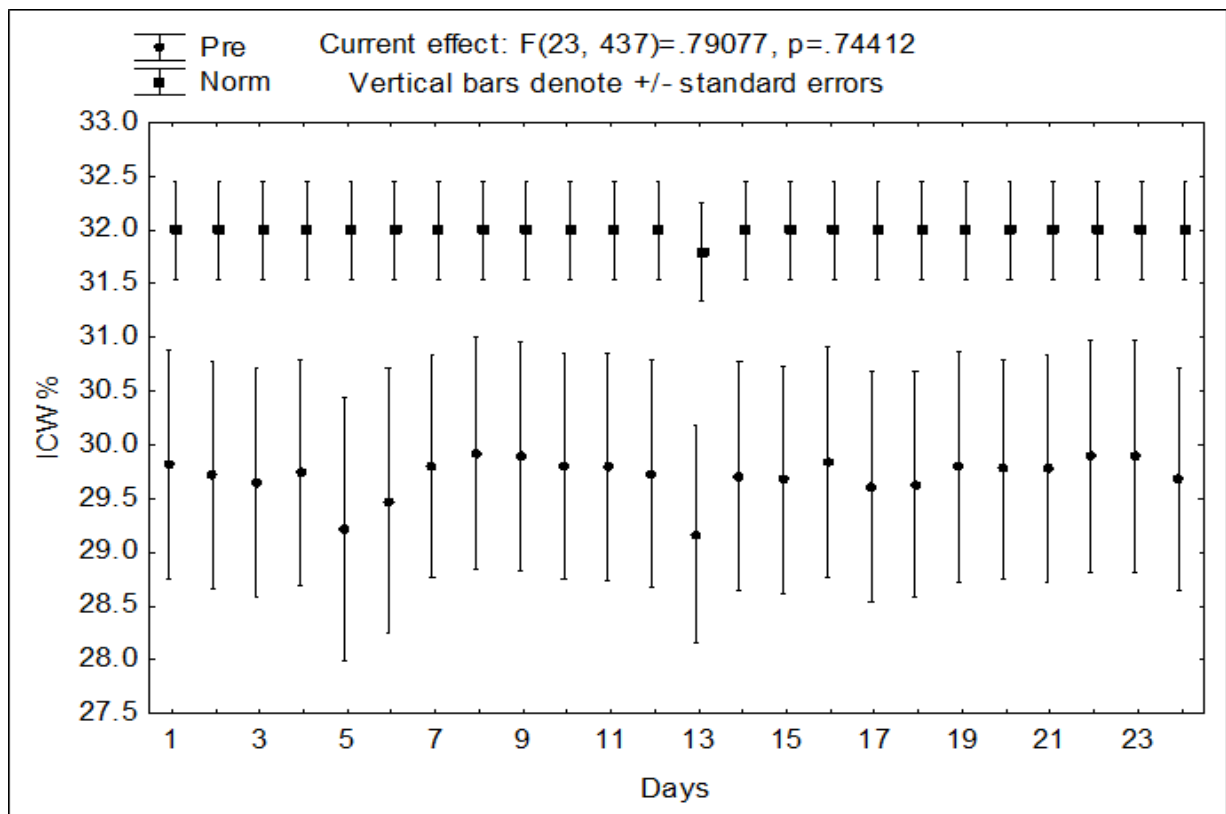


Figure 8: Pre-HD intracellular fluid versus the normal range, illustrating the patients' intracellular fluid was consistently below the normal range, irrespective of the total fluid being over- or dehydrated.

4.6 Pre- versus Post-Dialysis Prediction Marker

The prediction (illness) marker as measured by the Bodystat Quadscan 4000 ® (BIA), showed a post-dialysis improved trend, as illustrated in Figure 9. A ratio closer to 1.00 indicates poor cellular health or extreme fluid overload. During the study a total of 960 measurements were recorded, and there was only one incident when a value of 1 was recorded, on which day the patient's serum potassium level was over 7 mmol/L (the patient admitted to eating a baked bean

curry the night before). The latter suggests the level of sensitivity of the prediction marker.

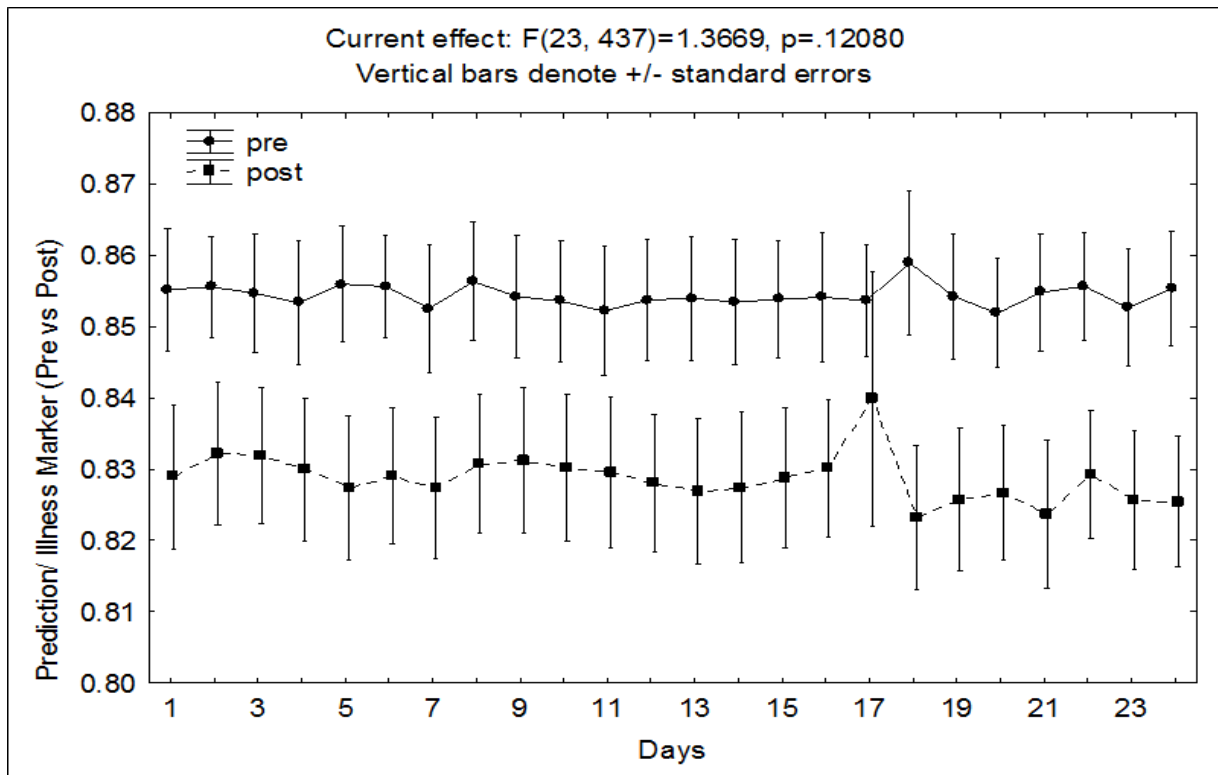


Figure 9: Pre-HD versus post-HD prediction marker of the patients shown over days. The post-HD prediction marker consistently improved post dialysis.

4.7 Summary

There was a statistically and clinically significant difference between the excess fluid measured per BIA and the staff estimate. This difference was more pronounced in patients with a body fat percentage $\geq 30\%$ and a BMI $\geq 28 \text{ kg/m}^2$ compared to their leaner counterparts. Subjects with a body fat $\geq 35\%$ and a BMI $\geq 28 \text{ kg/m}^2$, had a negative 3rd water space versus those with lower BF and BMI's ($p=0.000^*$). The pre-HD versus post-HD prediction marker of the patients over days, showed a consistently improved post-HD prediction marker trend.

Chapter 5: Discussion

5.1 Introduction

Fluid management is central to the management of end stage renal disease (ESRD). Persistent fluid overload damages the cardiovascular system, and leads to hypertension and left ventricular hypertrophy, congestive heart failure, pulmonary oedema, peripheral oedema and other adverse cardiovascular consequences (Moissl *et al.*, 2013; Tsai *et al.*, 2014). Mortality risk increases with a pre-dialysis fluid overload of 2.5 litres (Moissl *et al.*, 2013). Conversely, dehydration, excessive fluid removal or ultrafiltration, may result in intradialytic symptoms of hypotension such as acute ischaemic events with recurrent episodes, potentially causing functional impairment and organ damage (Vasko *et al.*, 2013). Controlling fluid status in an optimal range is crucial to improve cardiovascular tolerance, quality of life and survival of haemodialysis (HD) patients (Moissl *et al.*, 2013).

The use of bioelectrical impedance analysis (BIA) in clinical practice for the management of HD patients on maintenance HD is becoming increasingly more prevalent, and the benefits thereof have been demonstrated in recently published prospective randomized controlled studies (Onofriescu *et al.*, 2014; Hur *et al.*, 2013). The implementation of BIA in clinical practice does have cost implications (cost of the machine and disposable tabs), so it was important to evaluate whether there was a clinical benefit in the South African context.

5.2 Significant Findings

5.2.1 Staff Estimated versus the BIA Measurement of Excess Fluid to be removed

In this study, there was a significant difference (1.29 L) between the excess fluid measured per BIA versus the HD staff estimate. This difference was

more pronounced in patients with a body fat (BF) percentage of $\geq 30\%$ and a BMI ≥ 28 kg/m² versus their leaner counterparts. It is suggested in future studies, more focus be placed on the difference of these two groups.

5.2.2 Intracellular Fluid

Of concern, was that all the patients irrespective of whether they were overhydrated or dehydrated, had an intracellular fluid % below the normal range. We postulate that this patient group has an excessive sodium intake, resulting in fluid shifts from the intra- to the extracellular space. Sodium levels not only physiologically drive thirst, but draw intracellular fluid into the extracellular space, and when that is saturated, results in an increase in third water space, which ultimately clinically presents as oedema (Charra, 2007; Tomson, 2001). Persistent excess fluid in the third water space has been associated with progressive organ damage (including the brain) in individuals with ESRD (Kong *et al.*, 2014; Zhang *et al.*, 2015). A sub-group of the patients consistently gained up to 4 litres fluid between dialysis sessions, which suggests both the sodium and fluid intake were not being optimally managed.

Sodium has been found to directly increase oxidative stress, and has been associated with the secretion of endogenous ouabain-like substances, for example marinobufagenin, and endogenous ouabain. The latter compounds inhibit sodium/ potassium ATPase, and may result in myocardial cell atrophy *in vitro*. In HD patients, the concentration of endogenous ouabain has been found to correlate with left ventricular mass, independent of arterial pressure (Levin *et al.*, 2010).

In a recently published Cochrane review, it was reported that salt/ sodium reduction in persons with chronic kidney disease (CKD) considerably decreased blood pressure, and consistently decreased proteinuria. Hence, further under pinning the need to address excessive sodium intake in the HD population (McMahon *et al.*, 2015).

There is a dire need for further research to be conducted in the South African, especially the KwaZulu-Natal HD units to establish whether the HD patients' on maintenance HD, sodium and fluid intake are adequately controlled. If compliance is found to be poor, then to evaluate what steps and tools can be implemented to achieve optimal fluid and sodium intake between dialysis sessions.

5.2.3 Prediction Marker: Pre- versus Post-Dialysis

The prediction (illness) marker as measured by the Bodystat Quadscan 4000[®] (BIA), showed a post-dialysis improved trend, as illustrated in Figure 7. A ratio closer to 1.00 is indicative of poor cellular health or extreme fluid overload. This may prove to be a useful tool for both HD staff and patients, in long-term monitoring of each patient's progress. Further studies of a longer duration, may elucidate over time a more significant trend, than was found in this study.

5.2.4 Phase Angle

The median phase angle of higher body fat and BMI patients were consistently higher compared with those of the leaner patients, suggesting a healthier cell mass in the group with a higher body fat and BMI. This may be an important piece of the puzzle that has eluded scientists for over 30 years, namely, the reason the HD patients with a higher body fat and BMI have a better survival than their leaner counterparts.

5.2.5 Survival Benefit of a Higher Body Fat and BMI in Dialysis Patients

The reason for a survival benefit of a higher body fat % and BMI in HD patients has eluded scientists for the past 30 years. Patients with a body fat percentage ≥ 30 % and a BMI ≥ 28 kg/m², had a negative 3rd water space when compared to those with lower BF % and BMI. We postulate that this is an important factor in improving this sub-groups better survival amongst HD patients, and that it is due to greater perspiration, and consequent higher water and sodium losses in this group versus their leaner counterparts.

5.3 Study Limitations

The population size of this study was a limitation, however, it was addressed through conducting consecutive repeated measures over time. The duration of this study, was probably not sufficient to demonstrate a significant difference in the pre- and post-HD prediction marker. Future studies of at least 2 years may be more effective in determining the level of significance.

Chapter 6: Conclusion and Recommendations

6.1 Conclusion

The aim of the study was to compare the excess fluid volume to be removed in haemodialysis patients as estimated by the haemodialysis (HD) unit staff and the volume measured by a multiple frequency bioelectrical impedance analysis (BIA) machine. The outcome of which, would be used to inform future clinical practice for HD patients.

In this study it was hypothesized that the excess fluid estimated by the HD staff versus the amount determined by a multiple frequency BIA machine, the Bodystat Quadscan 4000® would differ. It was predicted that the BIA values are better indicators. In this study, there was a significant difference when comparing the excess fluid estimation by staff and the BIA method, even when volumes over different days of measurements were combined. In clinical practice, the difference between the excess fluid measured per BIA and the HD staff estimate (1.29 L difference) is profound. This difference was however, more profound in patients with a body fat percentage $\geq 30\%$ and a BMI $\geq 28 \text{ kg/m}^2$ when compared to their leaner counterparts. Also, within each of these groups, there is a significant difference between the staff estimation and the BIA measurements.

Multiple frequency BIA is an invaluable tool for guiding both HD staff and patients towards an optimal fluid status in HD patients, as both extracellular and 3rd water space can be accurately measured and monitored. Patient compliance in the management of end stage renal disease (ESRD) on HD is not only critical to their long-term survival, but may also impact on their quality of life, through limiting or preventing irreversible brain damage which is associated with cognitive impairment. It would also be concomitantly useful in monitoring HD patients' nutritional status, in terms of lean body mass and fat weight.

The findings (negative 3rd water space in patients with a body fat percentage $\geq 30\%$ and a body mass index (BMI) $\geq 28 \text{ kg/m}^2$ and positive 3rd water space in

their leaner counterparts) of this study suggest that there is a potential benefit to a higher body fat and BMI in ESRD patients on HD, versus the conventional perception of a healthy BMI and body fat, namely a BMI between 19 and 25 kg/m², and body fat percentage between 15 and 20%. It is of utmost importance, that further studies in a larger population with ESRD on HD be conducted, to confirm this finding. If confirmed, it may be pivotal in changing the dietary management of ESRD patients on HD. It is possible that current practice of aiming for a “healthy” body fat and BMI, maybe deleterious and is possibly negatively impacting on this patient populations risk for mortality, and long-term survival.

6.2 Recommendations

Further studies are necessary to evaluate South African ESRD patients on HD compliance in terms of salt/ sodium and fluid intake, and the modulation thereof, to achieve an improved long-term survival.

Both national and international further investigations on the difference in 3rd water space between ESRD patients on HD with a higher BMI and body fat versus their leaner counterparts are required to further validate the findings of this study. If confirmed, the current dietary management of this patient population needs to be reviewed.

A longitudinal study in a larger ESRD patient population on HD, would be useful in evaluating whether the usefulness prediction marker in this patient population.

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Chapter 8: Addenda

8.1 *Addendum 1: Procedure for Subject Consent Counselling, and Data Collection*

Procedure for Subject Consent Counselling and Conducting of BIA Measurements

1. Upon commencement of the study, the **study objectives & written consent forms shall be discussed with the subject**. If the subject agrees to participate in the study, he or she shall sign the written consent form.
2. On each day of data collection, the subject shall be reminded of **his/ her right to withdraw from the study**, at any given time during the three month period of data collection.
3. The **procedure of conducting the BIA shall be explained to the subject, before the procedure is commenced**.
4. The **subject shall be weighed** by the nursing sister (standard daily procedure); refer to addendum 3. Upon the commencement of data collection, the **subject's height** shall also be measured (refer to addendum 2). The weight shall be measured on an electronic scale, which shall be calibrated at the onset of the study, and weekly thereafter.
5. The **subject's blood pressure** shall be measured and recorded (standard daily procedure), by the nurse.
6. The **subject's shall lie flat on the bed**, and the **HD canula shall be connected to the dialysis machine**.
7. The **HD staff member shall calculate the amount of fluid to be removed during dialysis**; that is, current body weight minus previous post dialysis (dry) weight. Not more than 1 litre fluid per hour shall be removed (standard daily procedure/ protocol). The amount of fluid to be removed shall be recorded.
8. **BIA measurement procedure:**
 - 8.1 The procedure of the BIA measurement shall be explained to the subject.
 - 8.2 A Bodystat tab shall be attached to the subject's right wrist and right ankle.
 - 8.3 The connectors (positive and negative) of the Bodystat machine shall be connected to the tabs attached the subject.
 - 8.4 The machine shall be switched on and the readings recorded.
 - 8.5 Once the measurements have been recorded; the results shall be explained to the subject.

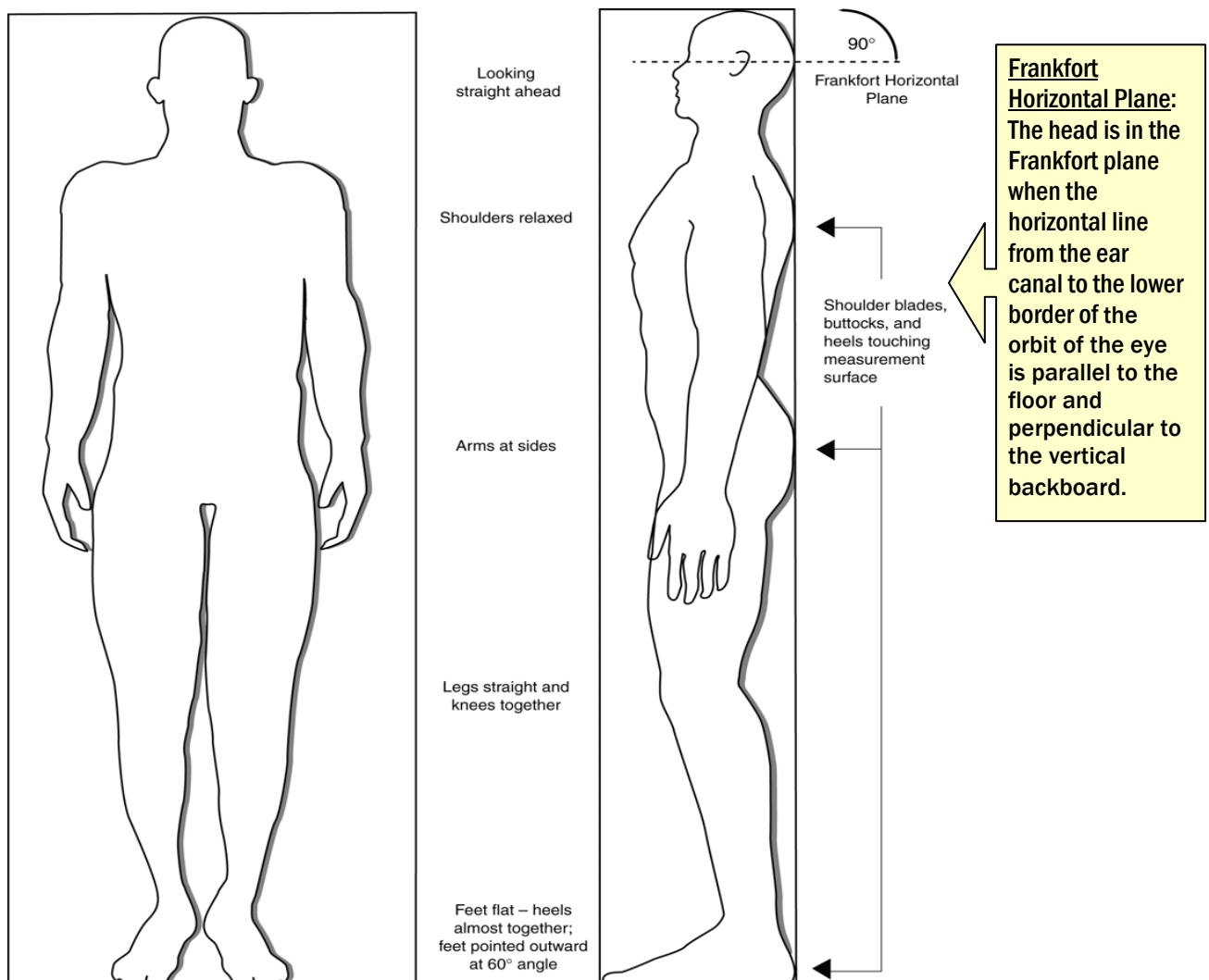
- 8.6 The procedure shall be repeated, 15 minutes after the HD has been completed.
9. During the dialysis, the **standard clinical practice shall be conducted**, namely:
- 9.1 constant measuring of the subject's blood pressure
 - 9.2 the HD machine shall be checked if any alarms are triggered
 - 9.3 the subject shall be monitored per standard clinical observation procedure

8.2 Addendum 2: Procedure for the Measurement of Standing Height

PROCEDURE FOR MEASURING STANDING HEIGHT POSITION

The Subject should:

- 1) Remove his/ her shoes.
- 2) Remove his/ her hat or cap or obstructing hair piece.
- 3) Have his/ her head, shoulder blades, buttocks, and heels touching measurement surface.
- 4) Have his/ her legs straight.
- 5) Have feet flat.
- 6) Have his/ her heels together.
- 7) Have his/ her feet pointed outward.
- 8) Be requested to inhale; take the measurement before he/ she exhales.



8.3 Addendum 3: Procedure for the Measurement of Body Weight

PROCEDURE FOR MEASURING BODY WEIGHT

Step 1: After the examiner shall **explain the procedure** to the subject.

Step 2: The examiner will request that the subject:

- 1) Void his/ her bladder.
- 2) Remove his/ her shoes.
- 3) Remove any additional heavy clothing (e.g. jacket/ jersey/ sweater), and shall only wear light in-door clothing.
- 4) Remove any items in his/ her pockets e.g. wallet or cellphone.
- 5) Stand in the center of the scale platform facing the scale reading screen.
- 6) Hands at his/ her sides.
- 7) Look straight ahead.
- 8) Weight shall be measured to the nearest 0.1 kg.
- 9) Weight measurements shall be repeated twice and the average of the two measurements shall be recorded.

8.4 Addendum 4: Calibration of Equipment

1. Calibration of Digital scale

1.1 A digital electronic scale with a 250kg capacity and a platform size of 305 mm x 305 mm to accommodate subjects with large feet shall be used.

1.2 Weight shall be measured to the nearest 0.1kg.

1.3 The scale shall be placed on a firm and flat surface, and calibrated with a one, two and five kilogram weight on a weekly basis for the duration of the study.

2. Calibration Bodystat Quadscan 4000

A separate **BODYSTAT** calibrator is supplied with each **QuadScan 4000** unit to enable the operator to independently verify that the unit remains in calibration at all times. This shall be done on a monthly basis. However, this is only an independent check and an operator will not be able to physically re-calibrate the unit. It is also recommended that the operator use their own body as another independent check. This should be performed on a subject whose body composition does not fluctuate greatly and remains fairly constant.

2.1 PROCEDURE

2.1.1 Attach one pair of red and black leads to any one terminal of the calibration unit.

2.1.2 Then attach the other pair of red and black leads to the other terminal of the calibration unit.

2.1.3 Switch the unit ON and enter any subject data or accept the default displays on the LCD screen.

2.1.4 Provided that the leads have been correctly attached to the calibrator and after "MEASURING" is displayed, scroll through the results until the Impedance values are reached.

2.1.5 The results at all four impedance values should reflect readings of between 496 to 503, approximately a 0.5% variance on either side of the high precision 500 ohm resistor in the BODYSTAT calibrator.

2.1.6 If the readings are outside of this range, the following should be

checked:

- Are the leads correctly attached as per the procedure above?
- If the results are still incorrect, first replace ALL six batteries with new Duracell or Procell batteries (see *BATTERY REPLACEMENT* section of the User's Guide).
- If the unit remains outside of the calibration range, contact BODYSTAT LTD or your dealer.

8.5 Addendum 5: Data Sheet – Allocation of Research Codes to Subjects

Allocation of Data Collection Codes		
Code	Subjects Name	Subjects Out-patient Number
X1		
X2		
X3		
X4		
X5		
X6		
X7		
X8		
X9		
X10		
X11		
X12		
X13		
X14		
X15		
X16		
X17		
X18		
X19		
X20		
X21		
X22		
X23		
X24		
X25		

8.6 Addendum 6: Subjects Demographics

Addendum 6: SUBJECTS DEMOGRAPHICS																												
Patient Code	Sex		Age	Age Range					Ethnic Group					No. of years on dialysis	Pre-HD Systolic BP				Other Conditions									
	M	F		19-29	30-39	40-49	50-59	60-69	A	W	C	I	Other		Well Controlled (130-159mm Hg)	Moderately controlled (101-130mm Hg)	Poorly controlled (>159mm Hg)	Poorly controlled (<100 mm Hg)	Cardiac Disease	Ischaemic HD	Angina	RVD (Not on Rx)	RVD (On Rx)	Dm I	Dm II	Severe Ascites	SLE	
1																												
2																												
3																												
4																												
5																												
6																												
7																												
8																												
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25																												

8.7 Addendum 7: Daily & Monthly Data Collection Spreadsheets

Addendum 7: DAILY/WEEKLY/ MONTHLY DATA SHEET																								
Patient Code: X	Height:								Age				Sex											
Date:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
HD Unit staff code																								
Bodystat Machine Code																								
Last Post Dialysis Wt																								
Predialysis Wt																								
Post Dialysis Wt																								
Fluid to be removed																								
No. of hrs on HD																								
Fat %																								
Fat % N Range - min																								
Fat % N Range - max																								
Fat wt in kg																								
Fat wt in kg range - min																								
Fat wt in kg range -max																								
Lean %																								
Lean % N Range - min																								
Lean % N Range - max																								
Lean wt (kg)																								
Lean wt range (kg) - min																								
Lean wt range (kg) - max																								
Total B wt (kg)																								
Total B wt N range - min																								
Total B wt N range - max																								
Dry Lean wt (kg)																								
TBW - Total Fluid (Pre) %																								
TBW Total Fluid N range % - min																								
TBW Total Fluid N range % - max																								
TBW Total Fluid (Pre) L																								
TBW Total Fluid N range L - min																								
TBW Total Fluid N range L -max																								
ECW %																								
Extracellular Fluid % N																								
ECW -Extracellular Fluid (Pre) L																								
ICW -Intracellular Fluid (Pre) %																								
ICW - Intracellular Fluid (Pre) % N																								
Intracellular Fluid (Pre) L																								
Body Cell Mass (kg)																								
Third Space (Fluid Overload Vol) L																								
Prediction/ Illness Marker (Pre)																								
BMR (Kcal)																								
BMR/ body wt (Kcal/ kg)																								
Est Average Req (Kcal)																								
BMI																								
BMI Range -min																								
BMI Range - max																								
Phase Angle 50K																								
BIA Machine code																								
TBW - Total Fluid (Post) %																								
TBW Total Fluid N range % - min																								
TBW Total Fluid N range % - max																								
TBW Total Fluid (Post) L																								
TBW Total Fluid N range L - min																								
TBW Total Fluid N range L - max																								
ECW - Extracellular Fluid (Post) %																								
Extracellular Fluid % N																								
ECW -Extracellular Fluid (Post) L																								
ICW -Intracellular Fluid (Post) %																								
ICW - Intracellular Fluid (Post) % N																								
Intracellular Fluid (Post) L																								
Body Cell Mass (kg)																								
Third Space (Fluid Overload Volume) L																								
Prediction/ Illness Marker (Post)																								
Phase Angle 50K																								
BP (Pre)																								
BP (Post)																								
Serum Albumin																								

8.8 Addendum 8: Subject Consent Forms – English and Zulu Version and UKZN and DOH Ethics Approval to Conduct the Study

CONSENT FORM AND INFORMATION REGARDING THE RESEARCH PROJECT AT YOUR HOSPITAL

TITLE OF THE RESEARCH PROJECT: To Determine the Difference in Extracellular Fluid (Excess) to be removed in Chronic Haemodialysis Patients, estimated by the Haemodialysis Unit Staff versus the Multiple Frequency BIA Measurement.

ETHICS REFERENCE NUMBER: BE041/14

INVESTIGATORS: Jane Downs (Chief Dietitian and HOD Dietetics Dept, King Edward VIII Hospital, Durban, KZN).

ADDRESS: c/o Dietetics Dept, King Edward VIII Hospital, Private Bax X01, Congella, Durban, 4013

CONTACT NUMBER: Jane Downs: 031-3603293

I would like to invite you to take part in this research project, which is part of my Dietetics Masters studies (MSc).

Please take some time to read the information presented here, which will explain the details

of this project. Please ask the researcher any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you will be involved. Also, your participation is **entirely voluntary** and you are free to decline to

participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do initially agree to participate.

This study has been approved by the Ethics BREC Committee (Medical School) of the University of KwaZulu-Natal and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

The study will be conducted at the King Edward VIII Hospital Haemodialysis unit. A non-invasive bioelectrical impedance assessment (measurement) shall be performed on each dialysis patient that agrees to participate in the study, before and after each dialysis treatment. A special machine (Quadscan) will be used in this research project, in which a small undetectable current will pass through your body from your right hand to your right foot.

This machine measures various measurements, namely, your fluid inside and outside the cells in your body (intra & extracellular fluid). It accurately measures of your excess fluid outside your body's cells (extracellular) fluid (which needs to be removed during dialysis). This will be compared to what the Haemodialysis unit staff estimate in terms of how much fluid should be removed. The bioelectrical impedance assessment measurement will be used to guide the HD unit staff, on how much fluid needs to remove during your dialysis.

All information collected will be treated as confidential.

Why have you been invited to participate?

This study is being conducted exclusively at King Edward VIII hospital and only the HD patients in the chronic program will be invited to participate.

What will your responsibilities be?

The collection of the data involves:

1. You will be weighed pre- and post-dialysis, as per your usual treatment program, by the HD nursing staff.
2. While the Haemodialysis staff prepare the haemodialysis machine for your dialysis, the dietitian/ researcher, shall attach 2 tabs on your right hand and 2 on your right foot, and connect the Quadscan to the tabs.

3. The machine will give various readings. One of which will be your extracellular fluid, which will be used to guide the haemodialysis staff on how much excess fluid outside the cells (extracellular) to remove.
4. At the end of your dialysis session the dietitian/ researcher will repeat the BIA measurement. This is to assess the change in the volume of your excess fluid outside the cells (extracellular), and to assess whether your illness marker has improved. The illness marker is an indirect measure that will help assess how healthy the cells in your body are. If your body fluid management improves with time, this marker will also improve with time.
5. No special blood tests are required in this study. Only the tests that are routinely carried out will be used as data for the study.
6. The tests will be repeated on each of your haemodialysis treatments (2 times per week) over a 3 month period.

Will you benefit from taking part in this research?

Yes, the research might benefit you, as well as, future patients that need haemodialysis. The main goal of this study is to assess whether the estimated amount of fluid to be removed, as estimated by haemodialysis staff is accurate. If not, to assess whether there is a need to implement the Quadscan measurements as standard practice, to improve haemodialysis patients' fluid management. Excess extracellular fluid (fluid outside the cells in the body) has been shown to cause heart failure and increase the risk or aggravate high blood pressure, amongst other possible side-effects.

Furthermore, the illness marker will be a helpful tool to show you how your body is responding to the haemodialysis treatment. If it significantly improves in most of the patients in this study, this will provide evidence to motivate for this assessment to be used not only in the King Edward Hospital VIII Haemodialysis unit, but in all the haemodialysis units throughout South Africa.

Are there in risks involved in your taking part in this research?

There are no risks associated with taking part in the study. The usual monitoring and clinical practice measures used for your haemodialysis treatment shall be conducted. This assessment has been scientifically validated as a tool, and is used as in standard practice in haemodialysis treatment centres in other countries, for example in the United Kingdom.

If you do not agree to take part, what alternatives do you have?

Participation in this study is entirely voluntary. Standard care will not be withheld in the event of you deciding not to participate. You are also free to withdraw at any time, even if you initially agreed to participate in the study, but later decide not to.

Who will have access to the information collected at your hospital?

All information collected in this research project, will be treated as confidential, and will be stored in a safe and secure location. When the data (information collected)

is reported, the hospital and patients/subjects will be referred to in coded format. The researchers are the only people who will have access to the information collected. If the data (information collected) is used in a publication or thesis, patient identification will be kept anonymous.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

As this study does not involve any invasive procedures or drug testing, it is highly unlikely that any injury will occur as a result of taking part in this study.

Will you be paid to take part in this study and are there any costs involved?

No, you will not be paid to take part in the study and there will be no costs involved for you, if you do take part. The measurements shall be conducted on your usual treatment days and times.

Is there anything else that you should know or do?

Should you have any further queries or encounter any problems regarding the study, you can contact **Ms Jane Downs** on telephone number **031-3603293**.

If you have any concerns or complaints, that have not been adequately addressed by the researcher, you can contact the UKZN BIOMEDICAL RESEARCH ETHICS COMMITTEE (BREC) at telephone number: 031 2604769. The full BREC contact details are:

University of KwaZulu-Natal

Research Office

Biomedical Research Ethics Administration

Westville Campus, Govan Mbeki Building,

Private Bag x54001, Durban, 4000

Tel: 27 31 2604769; Fax:27 31 2604609

E-mail: BREC@ukzn.ac.za

Website: <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>

You will receive a copy of this information and consent form for your own records.

INFORMED CONSENT FOR RESEARCH AT YOUR HOSPITAL

Declaration by Participant

By signing below, I agree to take part in a research

study titled "***To Determine the Difference in excess Fluid to be removed in Chronic Haemodialysis Patients, estimated by the Haemodialysis Unit Staff versus the Multiple Frequency BIA Measurement.***"

I declare that:

- I have read or had read to me this information and consent form and it is written in a language in which I am fluent and am comfortable with.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to **withdraw from the study at any time** and will not be penalised or prejudiced in any way as a result.
- I may be asked to withdraw from the study before it has finished, if the researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) on (*date*) 2014.

.....
Signature

.....
Signature of witness

.....
Designation

.....
Name of witness

Declaration by Investigator

I (name) declare that:

- I explained the information in this document to
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. *(If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (place) on (date) 2014.

.....
Signature of investigator

.....
Signature of witness

.....
Name of investigator

.....
Name of witness

IFOMU LEMVUME NOLWAZI MAYELANA NOCWANINGO ESIBHEDLELA SAKHO

ISIHLOKO SOCWANINGO: Ukuveza umehluko emanzini angaphandle kwamaseli (*excessr fluid*) (angaphezu kwesilinganiso) okumele asuswe ezigulini ezihlala nokuphila kwesifo sezinsu njengokokuhlambekisela kwabasebenzi basophikweni lwe-Haemodialysis lapho kuqhathaniswa ne-*Multiple Frequency BIA Measurement*.

IKHODI YOPHIKO LWEMIGOMO YOKUZIPHATHA: BE041/14

ABACWANINGI: Jane Downs (Oyinhloko yama-dietician aphinde abe ngumphathi ephikweni lwe-Dietetics esibhedlela iKing Edward VIII, eThekwini, KwaZulu;Natal).

IKHELI: c/o Dietetics Dept, King Edward VIII Hospital, Private Bag XO1, Congella, Durban, 4013

INOMBOLO YOCINGO: Jane Downs: 031-360 3293

Ngithanda ukukumema ukuba ube yingxenywe yalolu cwanningo, okuyingxenywa yezifundo zami za-Masters kwi-Dietetics (Msc).

Ngicela ukuba uthathe isikhathi ukuba ufunde lokhu okubhalwe lapha, okuzokucacisela ngemininingwane yalolu cwanningo. Ngicela ukuba umhlohle imibuzo umcwanningi nangonoma yini ongayiqondi ngalolu cwanningo. Kubalulekile ukuba waneliseke futhi ucaceliseleke kahle ukuthi lolu cwanningo lumayelana nani kanye nokwazi ukuthi luzodingani.

Okunye futhi okumele ukuqonde ukuthi ukuba yingxenywe yalolu cwanningo **akunampoqo** kanti futhi ukhululekile ukuba wenqabe ukuba yingxenywe yalo. Uma wenqaba ukuba yingxenywe yalo ucwanningo, Angeke uze ubukeke njengomuntu omubi. Uvumelekile futhi ukuba unгахoxa nanoma yinini ekubeni yingxenywe yalolu cwanningo yize noma kade wawuvumile ekuqaleni.

Lolu cwanningo lugunyazwe yi-Ethics BREC Committee yase-KwaZulu-Natal University Medical School kantu luzokwenziwa kulandelwa imigomo kanye nemithetho yokuziphatha ebekwe yi-International Declaration of Helsinki, yi-South African Guidelines for Good Clinical Practice kanye ne-Medical Research Council (MRC) Ethical Guidelines for Research.

Lumayelana nani lolu cwanningo?

Lolu cwanningo luzokwenziwa eSibhedlela iKing Edward VIII ophikweni lwe-Haemodialysis. Kuzosetshenziswa isikali sikagesi esingenabungozi kuzo zonke iziguli ezisohlelweni lokukhuculula izinso ezizovuma ukuba yingxenywe yalolu cwanningo, ngaphambi kanye nangemuva kokuba sezikhuculiwe izinso. Uhlobo oluthile lomshini olwaziwa nge-Quadscan luzokusetshenziswa kulolu cwanningo lapho kuzodedelwa

umbani (*current*) omncanyana ukuba udlule emzimbeni wakho kusukela esandleni sokudla kuye onyaweni lwakho losokudla.

Lo mshini uzokunikeza izikalo eziningi okubalwa kuzo, amanzi angaphakathi okanye angaphandle kwamasele (*cells*) asemzimbeni wakho. Lo mshini ukala ncimishi amanzi evile angaphandle kwamasele omzimba wakho adinga ukususwa lapho kukhucululwa izinso. Lokhu kuzobe sekuqhathaniswa nalokho abasebenzi base-Haemodialysis abakuhlambekisayo ekuthenini mangakanani amanzi okumele asuswe. Lokhu kuhlola kuzokusiza abasebenzi basophikweni lwe-Haemodialysis njengomhlahlandlela ekuthenini mangakanani amanzi okumele asuswe lapho kukhucululwa izinso.

Lonke ulwazi oluzotholakala luzothathwa njengoluyimfihlo.

Kungani umenywe ukuba yingxenywe yalolu cwaningo?

Lolu cwaningo luzokwenzenziwa eSibedlela iKing Edward VIII kuphela kanti yiziguli kuphela ezinesifo sezinsu ezingamahlalakhona ezizokuba yingxenywe yalolu cwaningo.

Kuzokuba yiliphi iqhaza lakho?

Ukuqoqwa kolwazi kuzodinga lokhu:

1. Njengnjwayelo, onesi abangabasebenzi basophikweni lwe-Haemodialysis bazokukala iziguli ngaphambi nangemuva kokukhucululwa izinso.
2. Ngesikhathi abasebenzi bohlelo lwe-Haemodialysis belungisa umshini wokukhuculula izinso, umcwaningi oyi-dietician uzokunamathisela izigqebhezana ezimbili esandleni sakho sokudla kanye nasonyaweni lakho lokudla bese exhuma umshini i-Quadiscan kuzo izigqebhezana.
3. Umshini lo uzokuveza imibhalo eyahlukene, enye yawo okungowamanzi angaphandle kwamasele ezokusetshenziswa ukwazisa abasebenzi bohlelo lwe-Haemodialysis ukuthi lingakanani inani lwamanzi eleqile olungaphandle kwamasele okumele lususwe.
4. Ukupheleni kohlelo lokukhucululwa izinso, umcwaningi oyi-dietician uzokuphinda futhi athathe izikalo ngohlelo lwe-BIA. Lokhu uzokwenza ukuhlola amazi eqile angaphandle kwamasele kanye futhi nokuhlola ukuthi isikali sakho sokugula sesigcono (*illness marker*) yini. Lokhu kuwukuhlola ngendlela ecashile isimo sempilo samasele asemzimbeni wakho. Uma kuwukuthi ukuphatheka kwamanzi asemzimbeni wakho kuba ngcono ngokuhamba kwesikhathi, lokho kusho ukuthi lesi sikali naso sizokuba ngcono ngokuqhubeka kwesikhathi.
5. Akukho ukuhlolwa kwegazi okukhethekile okuzokwenziwa kulolu cwaningo. Imininingwane yokuhlolwa okujwayelekile ezokusetshenziswa kulolu cwaningo.
6. Ukuhlolwa kuzokuphindwa njalo uma uze u ukuzokhucululwa izinso (kabili ngesonto) kuze kuphele izinyanga ezintathu.

Kukhona ozokuzuzisa ngokuba yingxenywe yalolu cwaningo?

Yebo, lolu cwaningo lungakuzuzisa, kanti futhi neziguli zangomuso ezidinga ukukhucululwa izinso, nazo zingahlomula. Injongo enkulu yalolu cwaningo ukuhlola ukuthi inani lamanzi elihlambikiselwe okumele lisuswe, njengokuhlambiselwa ngabasebenzi bohlelo lwe-haemodialysis, liyilo yini ncimishi. Uma kungenjalo, sikhona yini isidingo sokusebenzisa izikalo ze-Quadiscan njengomkhuba ukuphucula ukuphatheka kwamanzi emzimbeni weziguli lapho kukhucululwa izinso. Kweminye yemithelela emibi ebangwa ngamanzi evile angaphandle kwamasele (amanzi

angaphandle kwamaseli emzimbeni) kubalwa ukwehluleka kokusebenza kwenhliziyo kanye nengozi engenzeka yokwenyuka komfutho wegazi.

Ngaphezu kwalokhu, isikali sokugula sizokusiza ukukhombisa ukuthi umzimba wakho uzwana kanjani nokulashwa kusetshenziswa uhlelo lokukhucululwa izinso. Uma kuwukuthi iziguli eziningi ziyasizakala kulolu cwaningo, lokhu kuzokunikeza ubufakazi obuzokugqugquzela lolu hlelo ukuthi lungasetshenziswa ophikweni lwe-Haemodialysis lwaseSibhedlela iKing Edward VIII kuphela, kodwa lusetshenziswe eNingizimu Afrika yonkana.

Bukhona ubungozi ekubeni yingxenye yalolu cwaningo?

Abukho ubungozi obukhona obumbandakanywa nokuba yingxenye yalolu cwaningo. Kuzokukalwa ngendlela eyejwayelekile lapho kuzokukhucululwa izinso. Loluhlelo luhloliwe kanti lusetshenziswa mihla yonke ophikweni lwe-Haemodialysis kwamanye amazwe afana nelaseNgilandi.

Uma ungavumi ukuba yingxenye yalolu cwaningo, yini ongayenza?

Akusiyo neze impoqo ukuba yingxenye yalolu cwaningo. Angeke uze ubanjelwe igqubo uma ukhetha ukuba ungazibandakanyi nalolu cwaningo. Uvumelekile futhi ukuba uhoxe nanoma yinini, yize noma wawukade uvumile ekuqaleni bese unquma ukungazibandakanyi ngokuhamba kwesikhathi.

Ngubani esibhedlela ozolubona ulwazi oluqoqiwe mayelana nalolu cwaningo?

Lonke ulwazi oluqoqwe kulolu cwaningo luzokuthathwa njengemfihlo luphinde lugcinwe endaweni ephaphile. Uma selubikwa ulwazi oluqoqwe kulolu cwaningo, igama lesibhedlela kanye namagama eziguli angeke kuze kubhadlaze kodwa kuzobizwa ngamakhodi athile. Abacwaningi ukuphela kwabantu abazokwazi ukubona ulwazi oluqoqiwe. Uma lolu lwazi kwenzeka lusetshenziswa oshicilelweni oluthile, igama lesiguli angeke lize lidalulwe.

Kuzokwenzakalani uma kwenzeka ulimala ngenxa yokuba yingxenye yalolu cwaningo?

Njengoba bungekho ubungozi okanye izidakamizwa ezisetshenziswayo kulolu cwaningo, amathuba mancane kakhulu ukuthi kukhona ukulimala ongakuthola ngenxa yokuba yingxenye yalolu cwaningo.

Uzokukhokhelwa ngokuba yingxenye yalolu cwaningo okanye zikhona yini izindleko ngalolu cwaningo?

Cha angeke uze ukhokhelwe ngokuba yingxenye yalolu cwaningo kanti futhi azikho izindleko ozokhokhelwa zona. Izikalo zizokwenziwa ngezinsuku kanye nangezikhathi ezijwayelekile owelashwa ngazo.

Kukhona yini okumele ukwazi noma ukwenze?

Uma unemibuzo okanye uhlangabezana nezinkinga eziqondene nalolu cwaningo, ungathintana noNksz Jane Downs kule nombolo 031 360 3293.

Uma kukhona izinkinga okanye izikhalazo umcwaningi angazange akucacisele zona,

ungaxhumana ne- **UKZN BIOMEDICAL ETHICS COMMITTEE (BREC)** kule nombolo: **031 2604769**.

Uzokunikezwa ikhophi yalolu lwazi kanye nefomu lemvume ukuba uzigcinele wena.

Imininingwane ephelele yawa-BREC ithi:

iNyuvesi-YaKwaZulu-Natal

Research Office

Biomedical Research Ethics Administration

Westville Campus, Govan Mbeki Building,

Private Bag x54001, Durban, 4000

Tel: 27 31 2604769; Fax: 27 31 2604609

E-mail: BREC@ukzn.ac.za

Website: <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>

IMVUME YOKWENZA UCWANINGO ESIBHEDLELA SAKHO

Isifungo ikalowo ozokuba yingxeny yalolu cwaningo

Ngokusayinda ngenzansi, mina.....ngiyavuma ukuba yingxeny yalolu cwaningo olusihloko sithi **Ukuveza umehluko emanzini angaphandle kwamaseli (*extracellular fluid*) (angaphezu kwesilinganiso) okumele asuswe ezigulini ezihlala nokuphila kwesifo sezinsu njengokokuhlambekisela kwabasebenzi basophikweni lwe-Haemodialysis lapho kuqhathaniswa ne-Multiple Frequency BIA Measurement.**

Ngiyakufungela ukuthi:

- Ngikufundile okanye ngifundelwe lokhu okubhalwe lapha kanye nefomu lemsume. Lokhu kubhalwe ngolimi engilwaziyo nengiluqondayo kahle kakhulu.
- Nginikeziwe ithuba lokuphonsa imibuzo kanti nemibuzo yami iphendulekile ngokugculisayo.
- Ukuba yingxeny yalolu cwaningo **akusiyo impoqo** kanti name angizange ngiphogwe ukuba ngibe yingxeny yalolu cwaningo.
- Ngingazikhethela **ukuyeka ukuba yingxeny yocwaningo nanoma yinini** kanti angeke ngihlawuliswe okanye ngicwaswe ngokwenza njalo.
- Ngingacelwa ukuba ngiyeke ukuba yingxeny yalolu cwaningo ngaphambi kokuba luphele uma kuwukukuthi umcwaningi ubona sengathi ngizosizakala okanye ubona sengathi angiyilandeli imigomo yalo ucwaningo njengokwesivumelwano.

Isayindwe e-

(indawo).....mhlaka

(usuku).....2014.

.....

Sayinda

Ukusayinda kukafakazi

.....

.....

Isifungo sikamcwangingi

Mina
(igama).....ngiya

kufungela ukuthi:

- Ngiyichaze yonke imidanti ebhalwe lapha uku.....
- Ngibagqugquzelile abantu ukuba baphonse imibuzo kanti name ngichithe isikhathi esamele ukuyiphendula.
- Nganelisekile ukuthi abantu bayiqonde kahle kakhulu imidanti yalolu cwangingo njengoba ibaluliwe ngasenhla.
- Ngimusebenzisile/ angimsebenzisanga utolika. (Uma kuwukuthi umsebenzisile utolika, kumele asayinde lesisi fungo esingenzansi).

Isayindwe e-(indawo).....mhlaka

(usuku).....2014.

.....
.....

Ukusayinda komcwangingi

Ukusayinda kukafakazi

.....
.....

Igama lomcwangingi

Igama likafakazi

03 April 2014

Ms JH Downs
P O Box 50128
Musgrave Road
Durban, 4002
Jane.downs3@gmail.com

Dear Ms Downs

PROTOCOL: A comparison between the extracellular fluid (excess) to be removed in chronic Haemodialysis Patients, estimated by HD unit staff versus the multiple frequency BIA measurement. REF: BE041/14

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 10 January 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 28 March 2014 to queries raised on 18 March 2014 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 03 April 2014.

This approval is valid for one year from 03 April 2014. 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 13 May 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

Professor D Wassenaar (Chair)
Biomedical Research Ethics Committee
Westville Campus, Govan Mbeki Building

Postal Address: Private Bag X54001, Durban, 4000, South Africa

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Website: <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>

Founding Campuses:  Edgewood  Howard College  Medical School  Pietermaritzburg  Westville

INSPIRING GREATNESS





health

Department:
Health
PROVINCE OF KWAZULU-NATAL

OFFICE OF THE HOSPITAL CEO

KING EDWARD VIII REGIONAL HOSPITAL
Private Bag X02, CONGELLA, 4013
Corner of Rick Turner & Sydney Road
Tel.031-3603853/3015; Fax.031-2061457:
Email.rejoice.khuzwayo@kznhealth.gov.za:
www.kznhealth.gov.za

Ref.: KE 2/7/1/ (01/2014)
Enq.: Mrs. R. Sibiya
Research Programming

22 January 2013

Ms. JH Downs
P.O. Box 50128
Musgrave Road
DURBAN
4062

Dear Ms. Downs

Protocol: "A comparison between the extracellular fluids (excess) to be removed in chronic Haemodialysis Patients, estimated by HD unit staff versus the multiple frequency BIA Measurements" REF041/14

Permission to conduct research at King Edward VIII Hospital is provisionally granted, pending approval by the Provincial Health Research Committee, KZN Department of Health.

Kindly note the following:-

- The research will only commence once confirmation from the Provincial Health Research Committee in the KZN Department of Health has been received.
- Signing of an indemnity form at Room 8, CEO Complex before commencement with your study.
- King Edward VIII Hospital received full acknowledgment in the study on all Publications and reports and also kindly present a copy of the publication or report on completion.

The Management of King Edward VIII Hospital reserves the right to terminate the permission for the study should circumstances so dictate.

Yours faithfully

SUPPORTED/NOT SUPPORTED



DR. OSB BALOYI
ACTING CHIEF EXECUTIVE OFFICER



DATE

uMnyango Wezempilo . Departement van Gesondheid

Fighting Disease, Fighting Poverty, Giving Hope



health

Department:
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Health Research & Knowledge Management sub-component
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3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM 21/14
Enquiries: Mrs G Khumalo
Telephone : 033 – 395 3189

24 March 2014

Dear Ms Jane Downs

Subject: Approval of a Research Proposal

1. The research proposal titled 'A COMPARISON BETWEEN THE EXTRACELLULAR FLUID (EXCESS) TO BE REMOVED IN CHRONIC HAEMODIALYSIS PATIENTS, ESTIMATED BY HD UNIT STAFF VERSUS THE MULTIPLE, FREQUENCY BIA MEASUREMENT' was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

The proposal is hereby **approved** for research to be undertaken at King Edward VIII Hospital.

2. You are requested to take note of the following:
 - a. Make the necessary arrangement with the identified facility before commencing with your research project.
 - b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.
3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-395 3189.

Yours Sincerely

Dr. E Lutge
Chairperson, KwaZulu-Natal Health Research Committee

Date: 25/03/2014.

uMnyango Wezempilo. Departement van Gesondheid

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