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Impact of Dialysis Adequacy on Patient Outcomes

by

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A Research Report Submitted to



Faculty of Health Sciences
University of the Witwatersrand

in partial fulfilment of the requirements for the degree of Master in Medicine.

Johannesburg 2005

DECLARATION

I, Jules Kabahizi declare that this research report is my own work. It is being submitted for the degree of Master in Medicine, to the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

Jules Kabahizi

17th day of February 2005

DEDICATION

This work is dedicated to the following, especially those who have rested in peace:

- my parents,
- my brothers and sisters
- my nieces and nephews
- my wife and kids
- The victims of the Rwandan tragedy.

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ABSTRACT

Introduction: Numerous studies have confirmed the association between the delivered dose of haemodialysis and patients outcomes. There is thus some evidence regarding the relationship between dialysis dose and quality of life.

Objective: The study was designed to assess dialysis adequacy using urea kinetic modelling parameters and to determine the association between dialysis dose and patient outcomes.

Methods: A retrospective review of the demographic and biochemical data of 61 patients on chronic haemodialysis in the year 2003 was performed and a prospective component was added to the study for quality of life and evaluation of cardiovascular comorbidity.

Results: The mean delivered dose Kt/V was 1.34 ± 0.25. There was a statistically significant correlation ($p<0.05$) between dialysis dose and the following parameters: haemoglobin, physical dimension and its 3 scales, the SF-36 overall score, as well as between dialysis dose and sepsis.

Conclusion: The dialysis dose correlated with a significant number of parameters including Hb and the physical components of the SF-36; hence, the importance of measuring the delivered dialysis dose of patient on maintenance dialysis in accordance with DOQI guidelines for improved patient outcomes is confirmed.

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TABLE OF CONTENTS

TITLE i

DECLARATION ii

DEDICATION iii

ABSTRACT iv

ACKNOWLEDGMENT v

TABLE OF CONTENTS I

LIST OF TABLES 5

LIST OF FIGURES 6

LIST OF ABBREVIATIONS 7

CHAPTER 1. INTRODUCTION 10

1.1. HISTORY OF DIALYSIS 11

1.2. DIALYSIS ADEQUACY 15

1.2.1. Definition 15

1.2.2. Parameters considered for assessment of dialysis adequacy 15

1.2.2.1. Kt/V 16

1.2.2.2. The timed average urea concentration 18

1.2.2.3. Solute removal index 19

1.2.2.4. Non-normalised dialysis dose 19

1.2.2.5. Urea Reduction Ratio 19

1.2.2.6. Protein Catabolic Ratio 20

1.2.2.7. Other parameters of dialysis adequacy 21

1.2.3. Frequency of measurement of haemodialysis adequacy 22

1.2.4. Pitfalls in measuring dialysis adequacy 24

1.3. WHY IS DIALYSIS ADEQUACY IMPORTANT? 25

1.4. NUTRITIONAL STATUS IN HAEMODIALYSIS PATIENTS. 26

1.5. QUALITY OF LIFE OF PATIENTS ON MAINTENANCE HAEMODIALYSIS. 33

CHAPTER 2. MATERIALS AND METHODS 38

2.1. ETHICS..... 39

2.2. CONSENT..... 39

2.3. STUDY POPULATION..... 39

2.3.1. The inclusion criteria..... 39

2.3.2. The exclusion criteria 39

2.4. METHODS..... 40

CHAPTER 3. RESULTS 45

3.1. DEMOGRAPHIC DATA 46

3.1.1. GENDER..... 46

3.1.2. PATIENT POPULATION RACE GROUP..... 47

3.1.3. AGE..... 48

3.2. DURATION OF HAEMODIALYSIS (IN YEARS) 49

3.3. PRIMARY RENAL DISEASE..... 50

3.4. COMORBIDITIES..... 51

3.4.1. SMOKING STATUS..... 51

3.4.2. SERUM PTH LEVEL 52

3.4.3. BMI 53

3.4.4. HEPATITIS B&C AND HIV INFECTION 54

3.4.5. ECHOCARDIOGRAPHIC FINDINGS..... 55

3.4.5.1. Left Ventricular configuration 55

3.4.5.2. Left Ventricular function 56

3.4.5.3. Valvular heart disease 57

3.4.5.4. Pulmonary hypertension..... 59

3.4.6. LIPID STATUS. 60

3.4.6.1. DYSLIPIDAEMIA..... 60

3.4.6.2. LIPID PROFILES OF PATIENTS WITH DYSLIPIDAEMIA 61

3.5. VASCULAR ACCESS..... 62

3.6. INDICATORS OF DIALYSIS ADEQUACY 63

3.7. INDICATORS OF DELIVERED DIALYSIS DOSE (KT/V) AND PATIENT OUTCOMES..... 65

3.7.1. Correlation between Kt/V and Haemoglobin 65

3.7.2. Correlation between Kt/V and Albumin..... 66

3.7.3. Correlation between Kt/V and health related quality of life using questionnaire SF-36..... 67

3.7.4. Correlation between Kt/V and Physical Health 68

3.7.5. Correlation between Kt/V and Mental Health 69

3.7.6. Correlation between Kt/V and Physical Functioning..... 70

3.7.7. Correlation between Kt/V and Role Physical..... 71

3.7.8. Correlation between Kt/V and Bodily Pain..... 72

3.7.9. Correlation between Kt/V and General Health..... 73

3.7.10. Correlation between Kt/V and Vitality..... 74

3.7.11. Correlation between Kt/V and Social Functioning 75

3.7.12. Correlation between Kt/V and Role Emotional..... 76

3.7.13. Relationship between delivered dialysis dose (Kt/V) and hospitalisation, blood pressure control, sepsis and mortality..... 77

3.7.13.1. Kt/V and hospitalisation 77

3.7.13.2. Kt/V and blood pressure control 77

3.7.13.3. Kt/V and sepsis..... 77

3.7.13.4. Kt/V and mortality 77

CHAPTER 4. DISCUSSION 78

4.1. DEMOGRAPHIC DATA AND PRIMARY RENAL DISEASE 79

4.2. DIALYSIS ADEQUACY 81

4.3. DIALYSIS DOSE (KT/V) AND PATIENT OUTCOMES 91

4.3.1. Dialysis dose (Kt/V) and haemoglobin 91

4.3.2. Dialysis dose (Kt/V) and albumin 91

4.3.3. Dialysis dose (Kt/V) and health related quality of life (SF-36) 92

4.3.3.1. Dialysis dose (Kt/V) and physical dimension 92

4.3.3.2. Dialysis dose (Kt/V) and mental dimension 93

4.3.3.3. Dialysis dose (Kt/V) and overall SF-36 93

4.3.3.4. Dialysis dose (Kt/V) and other parameters: hospitalisation, sepsis, hypertension 94

CHAPTER 5. CONCLUSION 96

REFERENCES 98

APPENDICES 107

APPENDIX 1. ETHICS APPROVAL 120

APPENDIX 2. PATIENT INFORMATION SHEET. 108

APPENDIX 3. CONSENT FORM 110

APPENDIX 4. SHORT FORM 36 QUALITY OF LIFE SCALES AND DIMENSIONS 111

APPENDIX 5. HEALTH SURVEY FOR DIALYSIS PATIENTS (SF36) 112

LIST OF TABLES

Table 1 Anthropometry in haemodialysis patients 29

Table 2 Primary renal disease. 50

Table 3 Serum PTH levels. 52

Table 4 BMI 53

Table 5 Left ventricular configuration 55

Table 6 Left ventricular function 56

Table 7 Lipid profiles of patients with dyslipidaemia 61

Table 8 Indicators of dialysis adequacy. 63

Table 9 Causes of ESRD (SADTR, 1998) 81

LIST OF FIGURES

Figure 1 Correlation between dialysis dose and patient survival..... 26

Figure 2 Correlation between plasma albumin concentration and mortality in patient on MHD 30

Figure 3 Gender of patients on chronic haemodialysis..... 46

Figure 4 Patient population on chronic haemodialysis..... 47

Figure 5 Patients' ages (in years) on chronic haemodialysis. 48

Figure 6 Duration of haemodialysis (in years). 49

Figure 7 Smoking status. 51

Figure 8 Hepatitis B & C and HIV infection status..... 54

Figure 9 Valvular heart disease..... 57

Figure 10 Pulmonary hypertension..... 59

Figure 11 Patients with dyslipidaemia 60

Figure 12 Vascular access. 62

Figure 13 Correlation between Kt/V and haemoglobin..... 65

Figure 14 Correlation between Kt/V and albumin..... 66

Figure 15 Correlation between Kt/V and SF-36 67

Figure 16 Correlation between Kt/V and physical health 68

Figure 17 Correlation between Kt/V and mental health 69

Figure 18 Correlation between Kt/V and physical functioning 70

Figure 19 Correlation between Kt/V and role physical..... 71

Figure 20 Correlation between Kt/V and bodily pain 72

Figure 21 Correlation between Kt/V and general health 73

Figure 22 Correlation between Kt/V and vitality 74

Figure 23 Correlation between Kt/V and social functioning..... 75

Figure 24 Correlation between Kt/V and role emotional 76

LIST OF ABBREVIATIONS

%	Percentage
AR	Aortic Regurgitation
AS	Aortic Stenosis
A-V	Arterio-Venous
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
Ca	Calcium
CRF	Chronic Renal Failure
CRP	C-Reactive Proteins
DEXA	Dual-Energy X-ray Absorptiometry
DM	Diabetes Mellitus
DOPPS	Dialysis Outcomes and Practice Patterns Study
EF	Ejection Fraction
ESRD	End Stage Renal Disease
ESRF	End Stage Renal Failure
Fig	Figure
g	gram
GIT	Gastro Intestinal Tract
Hb	Haemoglobin
HD	Haemodialysis
HIV	Human Immunodeficiency Virus
ID	Interdialytic

K/DOQI	Kidney Dialysis Outcomes Quality Initiative
Ln	Natural logarithm
LV	Left Ventricle
LVH	Left Ventricle Hypertrophy
MAP	Mean Arterial Pressure
mg	milligram
MHD	Maintenance Haemodialysis
min	minute
ml	millilitre
mmol	millimol
MR	Mitral Regurgitation
MS	Mitral Stenosis
NCDS	National Cooperative Dialysis Study
NHANES	National Health and Nutritional Examination Survey
NKF	National Kidney Foundation
nPCR	Normalised Protein Catabolic Ratio
NY	New York
p	Probability
PAP	Pulmonary Artery Pressures
PCS	Physical Component Scale
PEM	Protein- Energy Malnutrition
PNA	Protein equivalent of Nitrogen Appearance
PO_4	Phosphate
PTH	Parathormone
RPA	Renal Physician Association

QOL	Quality Of Life
SADTR	South African Dialysis and Transplantation Registry
SD	Standard Deviation
SF-36	Short Form 36
SIP	Sickness Impact Profile
T	Time
TACurea	Time Average Urea Concentration
TR	Tricuspid Regurgitation
TS	Tricuspid Stenosis
UF	Ultrafiltration
UKM	Urea Kinetic Modelling
URR	Urea Reduction Ratio
USA	United States of America
USRDS	United States Renal Disease Symposium
V	Volume
W	Weight

CHAPTER 1.INTRODUCTION

1.1. History of dialysis

1.2. Dialysis adequacy

1.2.1. Importance of dialysis adequacy

1.2.2. Parameters considered for assessment of dialysis adequacy

1.2.3. Frequency of measurement of haemodialysis adequacy

1.2.4. Pitfalls in measuring dialysis adequacy

1.3. Why is dialysis adequacy important?

1.4. Nutritional status in dialysis patients

1.5. Quality of life

1.1. History of dialysis

Dialysis is a Greek word meaning "loosening from something else"; it is derived from the Greek dia (= through); and leuin (= to loosen); (Davison, 1998).

Nevertheless, it was the Romans who first used a form of dialysis therapy by giving hot baths to patients to remove urea. The action of the hot water made the patient sweat profusely and, this together with water removal resulted in removal of the toxins. Diffusion of toxins through the skin into the bath water would temporarily relieve symptoms. This treatment was still on occasions used into the 1950s, as the only hope.

Dialysis is not a recent discovery; in 1854 Thomas Graham a Scottish chemist (Graham, 1854) was the first to use the term `dialysis`. He demonstrated that 'crystalloids', but not 'colloids', diffused down a concentration gradient across a semi-permeable membrane separating two solutions (Davison, 1998; Nissenson *et al*, 1990). The membranes were made from a variety of substances, including parchment and colloidion (Eggrth, 1921)

In 1913, Abel Rowntree and Turner at the John Hopkins Medical School in Baltimore wrote the first article on the technique of haemodialysis, named the artificial kidney. Experimental dialysis was performed on nephrectomized dogs, by using variances in the composition of dialysis fluid (Abel *et al*, 1914). The main aim was the removal of salicylates. The removal of fluid and toxins that accumulated due to kidney disease were not at this time considered. However, difficulties in dialysis construction and anticoagulation control prevented further developments for about 7 years. Hirudin was the first anticoagulant used. In 1920, Georg Haas in Gissen, Germany performed the first dialysis on a human, in a uraemic patient. Hand-made colloidion membranes were used and clotting was prevented by using Hirudin and, later, a crude form of heparin. Haas used multiple dialysers to increase the surface area of blood exposed to the dialysis fluid, but the

arterial pressure of the blood was insufficient to propel the blood through the entire extracorporeal circuit. He therefore introduced a pump into the circuit (Smith *et al*, 2002, p3). George Haas was consequently honoured as the pioneer of dialysis. As his institution and his colleagues did not support him, he gave up and the work was stopped.

Despite all the above developments, until 1940, patients with uraemic symptoms could be offered nothing more than bed rest and salt free diet composed mainly of vegetables, carbohydrates and fat to reduce protein metabolism. Nevertheless, the American scientist William Thalhimer worked on the use of cellophane and the purification of heparin (Thalhimer, 1938). These two advances gave rise to the next stage of development, which took place between 1940-1950.

Willem Kolff, a physician working in Groningen in Nazi-occupied Holland, built a rotating drum dialyser, which provided sufficient surface for human haemodialysis. After the war in 1945, Kolff`s technique was widely used, particularly in Sweden and the United States of America .The treatment was mainly used for acute renal failure when kidney function could be expected to return to normal, following a short period of dialysis treatment; it was just a bridging dialysis (Kolff, 1950).

For his great contribution, Willem Kolff is the acknowledged father of modern kidney dialysis. However vascular access limited dialysis to patients with acute renal failure who only needed renal replacement therapy for a short period of time (Kolff *et al*, 1965)

Thereafter, the rotating drum dialyser was modified by Dr Carl Walter, at the Brent Brigham Hospital together with Edward Olson, an engineer from Renwal, to create a new

version of the Kolff device, the Kolff-Brigham kidney dialysis machine and over 40 of these machines were built and exported all over the world.

Jack Leonards and Leonard Skeggs produced a plate dialyser, which permitted a reduction in the priming volume and allowed negative pressure to be used to remove fluid from the patient's system (Skeggs *et al*., 1949). Larger dialysers followed, which necessitated the introduction of a blood pump.

It was in the late 1950s when Fredrik Kiil of Norway developed a parallel plate dialyser with a large surface area (1 m^2) requiring a low priming volume (Smith *et al*, 2002, p8).

Finally, Baxter was the first to manufacture a commercial dialyser, which was based on the Kolff kidney. It was the equivalent to today's dialysers and was on the coil design. It provided a urea clearance of approximately 140 ml/min. In 1960, Richard Stewart produced the true forerunner of today's capillary flow dialyser. It was a hollow-fibre dialyser with a low priming volume and minimal resistance to flow.

The vascular access problem for chronic patients was solved by Scribner's shunt and strongly promoted home dialysis in the United Kingdom.

In 1960 in the USA, George Quinton, an engineer and Belding Scribner, a physician, created the arterio-venous (AV) shunt and James Cimino developed the subcutaneous radial artery to cephalic vein AV Fistula (Cimino & Brescia, 1962).

Up-to-date, monitoring and total control of the patient's therapy became more important as dialysis became widespread, and so equipment development continued. Hence, the introduction of dialysis as a life saving treatment for kidney failure was not the result of any large-scale research program; rather it resulted from the activities of scientists, pioneers who were able to utilise ideas, materials and methods from a range of developing technologies.

The 21st century has been set to enhance dialysis adequacy, in attempts to improve patients' quality of life. Good nutrition has also emerged as playing a vital role in reducing dialysis morbidity and mortality. World- wide, currently more than 500 000 people are undergoing haemodialysis treatment.

1.2. Dialysis adequacy

1.2.1. Definition

Dialysis adequacy is the recommended quantity of haemodialysis delivered which is required for adequate treatment of end stage renal disease (ESRD), such that the patient receives full benefit of haemodialysis (RPA, 1993). Adequacy of haemodialysis is an important determinant of patient morbidity and survival.

To ensure that ESRD patients treated with chronic haemodialysis receive a sufficient amount of dialysis, the delivered dose should be measured and monitored routinely and regularly.

1.2.2. Parameters considered for assessment of dialysis adequacy

Simply following the blood urea nitrogen (BUN) is insufficient because a low BUN can reflect inadequate nutrition rather than sufficient dialytic urea removal. Furthermore, to monitor the patients' symptoms alone is not sufficient i.e. the combination of dialysis plus erythropoietin to correct anaemia can eliminate most uraemic symptoms even if the patient is under-dialysed.

Urea kinetic modelling is widely used in clinical practice to quantify and deliver adequate doses of dialysis, as reported by Gotch *et al*. 1975. Urea is the substance that is most often monitored in clinical practice as a surrogate for measurement of the clearance of small solutes. The reasons are that urea:

- Is a small readily dialysed solute that is the catabolite of dietary protein (Gotch, 1995; Yeun, 2000)[3, 4]?
- Constitutes 90% of waste nitrogen accumulated in body water between haemodialysis treatments (Gotch, 1995; Yeun *et al*, 2000).
- Is easily measured in blood, and the fractional clearance of urea in body water correlates with patient outcomes, such as mortality and morbidity (Hakim *et al*, 1994; Lowrie *et al*, 1981; Lowrie, 1994).

Furthermore urea is unequivocally recognised as a marker of solute retention and removal in dialysed patients. The degree of urea clearance correlates with clinical outcomes of patients undergoing maintenance haemodialysis (Fernandez, 1992). Thus, urea kinetic modelling is used to estimate and, if necessary, to provide the correct dialysis dose.

Conventional methods of quantifying the prescribed or delivered haemodialysis dose began by estimating the difference in predialysis and postdialysis urea concentration by sampling patients before and after a single dialysis session. According to DOQI guidelines, the practice of sampling to measure the haemodialysis dose consists of slowing the blood pump to 50 ml/min and to obtain the blood sample for BUN estimation 15 seconds later (Silvester, 1997). This earlier measurement is thought to be the most accurate method to support formal kinetic modelling, and to ensure consistent values; the measurement of the postdialysis BUN should be performed in exactly the same way each time it is assessed (NKF-DOQI guidelines)

The adequate delivered dose of solute removed is assessed by the following parameters:

1.2.2.1. Kt/V :

K: Dialyser urea clearance supplied by the manufacturer in litres per minute (l/min)

t: The duration of dialysis in minutes(min).

V: The volume of distribution of urea in litres (l).

Kt/V is calculated as follows:

$$Kt/V = -Ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times {}^{UF}\!/_{W}$$

In which:

- *Ln* is the natural logarithm
- R is the *postdialysis BUN ÷ predialysis BUN*
- t is the length of the dialysis session in hours
- UF is the ultrafiltration volume in litres
- W is the patient's postdialysis weight in kilograms

As per the above formula, the value of Kt/V should be at least 1.3 for stable patients dialysed thrice weekly (DOQI guidelines, 2000). This is important to prevent the delivered dose of HD from falling below the recommended dose.

In terms of URR, (urea reduction ratio) a Kt/V of 1,3 corresponds to an average URR of 70%. However the URR corresponding to a Kt/V of 1.3 can vary substantially as a function of ultrafiltration. Different target values are needed for patients who are dialysed more or less frequently.

Nevertheless, because of the complexity of the formulae to calculate the Kt/V by UKM there are other methods to calculate it in order to assess dialysis adequacy, such as

computer models and statistical models. Moreover, there are other alternative methods for calculating Kt/V for assessing adequacy. These include:

1.2.2.2. The timed average urea concentration (TACurea): It has been suggested that the timed average urea concentration is preferable to Kt/V because it also measures urea generation, thereby allowing the estimation of the PCR (Held, 1996). The TACurea has a major limitation in that poor nutrition often due to inadequate dialysis may lead to a low predialysis BUN and therefore to a low TACurea that misleadingly suggests adequate dialysis. It is the reason why TACurea must be evaluated in concert with the protein catabolic rate which estimates protein intake.

$$\text{TACurea} = \frac{(\text{Td} \times [\text{C1} + \text{C2}]) + (\text{Id} \times [\text{C2} + \text{C3}])}{2 \times (\text{Td} + \text{Id})}$$

Where:

- C1 and C2 are the predialysis and postdialysis BUN
- C3 is BUN at the beginning of the next dialysis
- Td is the dialysis time
- Id is the interval between the two dialyses

A TACurea of 50 mg/dl is roughly equivalent to a Kt/V of 1.2 (Held, 1996). According to the National Cooperative Dialysis Study (Held *et al*, 1996), dialysed patients with TACurea of 52 mg/dl have a better outcome than patients with TACurea of 100 mg/dl.

1.2.2.3. Solute removal index: This is another method of measuring dialysis adequacy. With this method, the total amount of urea removed during haemodialysis is measured by multiplying urea concentration in the dialysate by the volume of used dialysate. However the DOQI clinical workgroup for haemodialysis adequacy has been focusing their recommendations exclusively on blood-based measures of adequacy. Thus, studies are lacking that correlate patient outcomes with the values obtained with this index.

1.2.2.4. Non-normalised dialysis dose (Kt): The correction of total urea removal (Kt) for the volume of distribution resulting in Kt/V is important. However, according to Kt/V formulae it is assumed that V does not alter patient outcomes despite its effect on the clearance of urea. This is important because some evidence suggest that the assumption is not true. For example, black dialysis patients, although they have a relatively lower URR, have superior survivals compared with white patients (Owen *et al*, 1998). A retrospective study of more than 17,000 haemodialysis patients showed that increasing Kt, independent of body size was associated with a lower risk of mortality. Further studies are required to determine whether the Kt alone is a superior measure of dialysis dose.

1.2.2.5. Urea Reduction Ratio (URR): The HD adequacy work group acknowledges the ease of calculation of URR (Baltimore, 1998; Bethesda, 1996).

In fact of the three methods for measuring haemodialysis adequacy and the delivered dose of haemodialysis, which are the Kt/V, the Protein catabolic rate (PCR) and the URR, the URR is the simplest to use.

$$\text{URR} = \frac{\text{Predialysis BUN} - \text{Post dialysis BUN}}{\text{Predialysis BUN}} \times 100$$

The URR has been proven to be a statistically significant predictor of mortality for ESRF patients (Held, 1996; Owen *et al*, 1993). In contrast to formal urea kinetic modelling and the Kt/V natural logarithm formulae (Daugirdas, 1993; Depner, 1993; Sherman *et al*, 1995), the URR does not account for the contribution of ultralfiltration to the final delivered dose of dialysis. This is because the convective transfer of urea that occurs by ultralfiltration does not result in a decrease in the BUN concentration, although urea removal into the dialysate has occurred. Thus the URR is less accurate in estimating the delivered dose of haemodialysis than the Kt/V and the URR does not take into consideration the contribution of residual kidney function to urea clearance.

Furthermore there is a curvilinear relationship between Kt/V and URR, hence a URR of 65% corresponds to a Kt/V of 1.2 and URR of 70% is equivalent to a Kt/V of 1.3. According to the DOQI guidelines, a URR should be at least 70% (Sehgal *et al*, 1998).

1.2.2.6. Protein Catabolic Ratio (PCR)

The PCR is also called the protein equivalent of nitrogen appearance (PNA). It is used in most HD units to assess dietary protein intake in patients who are in a steady state regarding nutritional status, as it is a function of protein intake which should reflect dialysis adequacy.

The PCR is determined by measuring the interdialytic appearance of urea in body fluids plus any urea lost in urine in patients with residual renal function. The PCR is of value in prospectively predicting morbidity in haemodialysis patients (Laird *et al*, 1983).

The PCR is usually expressed as g/kg per day, a parameter that is also called the normalised PCR (nPCR). Less commonly, the PCR is not normalised to weight and is expressed as g/day.

The National Cooperative Dialysis Study (NCDS) recommended a minimal nPCR of 0.8g/kg per day (Laird *et al*, 1983), but a target of 1.0 to 1.2g/kg per day or higher is currently recommended (Dumler *et al*, 1992; Gombe *et al*, 2000; Hakim, 1990).
Formal UKM permits calculation of the nPCR. The volume of distribution term may be used to calculate the nPCR as follows:

$$nPCR(g/kg/day) = (PCR,g/day)(meanV/0.58)$$

More importantly, the nPCR can be useful to identify patients who might benefit from counselling about their dietary protein intake. Furthermore, it is used as a marker of HD adequacy. In the NCDS, a PCR greater than 1g/Kg/day has been associated with low morbidity and mortality (Laird *et al*, 1983).
DOQI guidelines recommend nPCR of at least 0.8g/kg per day. The ideal, being nPCR value between 1g/kg per day to 1.2gr/kg per day.

1.2.2.7. Other parameters of dialysis adequacy:

There are other parameters, which are suggestive of dialysis adequacy:

- Predialysis BUN between 25 to 32 mmol/L
- Low requirement for erythropoietin and antihypertensive drugs
- Plasma albumin greater than 40 g/L

- Predialysis plasma creatinine concentration more than 1100 μmol/L (Bommer, 2001; Iseki, 1993; Lowrie *et al*, 1990; Owen *et al*, 1993). The improved outcome associated with higher plasma creatinine concentration is probably a reflection of muscle mass and adequate nutrition.
- Interdialytic weight gain
- Haemoglobin level
- Serum parathormone level
- Dialysis session time more than 4 hours
- Number of hospitalisations

1.2.3. Frequency of measurement of haemodialysis adequacy

To ensure that ESRD patients treated with chronic HD receive a sufficient amount of dialysis, the delivered dose should be measured and monitored routinely by every haemodialysis unit; the NKF-DOQI guidelines recommend an assessment of the haemodialysis dose once per month for stable patients haemodialysed thrice weekly for at least for four hours per session.

However, the frequency of measurement of the delivered dose of haemodialysis should be increased when:

- Patients are non-compliant with their haemodialysis prescriptions (missed treatments, late for treatments, early sign-off from haemodialysis treatment).
- Frequent problems are noted in delivery of prescribed dose of haemodialysis (such as variable poor blood flow rates, or treatment interruptions because of hypotension or angina pectoris).

- Wide variability in urea kinetic modelling results is observed in the absence of prescription changes.
- The haemodialysis prescriptions are modified.

Dialysis adequacy impacts on outcomes of patients on dialysis as discussed previously. Other independent predictors of dialysis outcomes include:

- **Primary renal disease**: Evidence has shown the best survival in haemodialysis patients with chronic glomerular diseases and polycystic kidney disease, intermediate survival in ESRD secondary to hypertension and the worst survival with diabetic nephropathy (Mailloux et al, 1994; USRDS, 1998).
- **Comorbid conditions:** The presence of comorbid conditions is a common problem in haemodialysis patients; left ventricular hypertrophy, metabolic abnormalities, atherosclerosis, dyslipidaemia, diabetes affects overall survival (Ganesh *et al*, 2001).
- **Age:** Studies have shown that survival declines with increasing age (Chara *et al*, 1992; Mailloux *et al*, 1994).
- **Race:** African-Americans and Asian-Americans have a lower mortality rate than whites (Daugirdas, 1998; Tanna *et al*, 2000, Wong *et al*, 1999). This finding persists even after adjustment of patient characteristics, comorbidities and laboratory values. There is no data on this in South Africa.
- **Psychosocial factors:** Increased level of social support results in enhanced compliance and good acceptance of the illness have been associated with lower relative risk of mortality (Kimmel *et al*, 1998).

- **Nutrition:** Increased mortality and morbidity have been observed in under-nourished patients as evidenced by different levels of hypoalbuminemia. Furthermore, the presence of malnutrition prior to the initiation of dialysis is strongly predictive of increased mortality.

1.2.4. Pitfalls in measuring dialysis adequacy

Urea kinetic modelling is probably the most objective way of measuring dialysis adequacy. In fact, urea is unequivocally recognised as a marker of solute retention and removal in dialysed patients. The degree of urea clearance also correlates with clinical outcomes of patients on maintenance haemodialysis.

However, high blood concentration of urea may not necessarily correlate with poor outcomes in certain circumstances:

- High serum concentrations of urea due to adequate protein intake that are compensated by adequate removal is a marker of adequate dialysis and is different from the high urea levels secondary to inadequate dialysis (Blumenkrantz, 1982).
- Low urea levels related to poor nutrition reflect dialysis inadequacy and may negatively affect the patient prognosis (Lowrie *et al*, 1990).

It has also been suggested that the kinetics of urea is representative of the behaviour of other uraemic toxins. However, data suggests that the dialytic removal of lipophilic protein-bound compounds, as well as that of several other water-soluble compounds, is different from that of urea (Lesaffer *et al*, 2000; Vanholder *et al*, 1992).

Some investigators have therefore asked whether there should be a search for marker molecules that are representative of middle, large or lipid-soluble compounds. In fact the haemodialysis work group recognises that an increasing body of evidence suggests that the clearance of larger molecular weight solutes may have an independent effect on patient survival that is not fully reflected in the Kt/V_{urea} .

In addition, many different factors influence the correct determination of Kt/V such as urea sequestration in different body compartments, vascular access and cardiopulmonary recirculation. These factors, together with the single-pool instead of the double-pool effects are responsible for urea rebound after the end of haemodialysis sessions causing poor Kt/V estimation.

Furthermore, some patients with residual renal function may have significant urea loss from the native kidneys. This should be measured and added to the measured Kt/V to achieve an effective Kt/V.

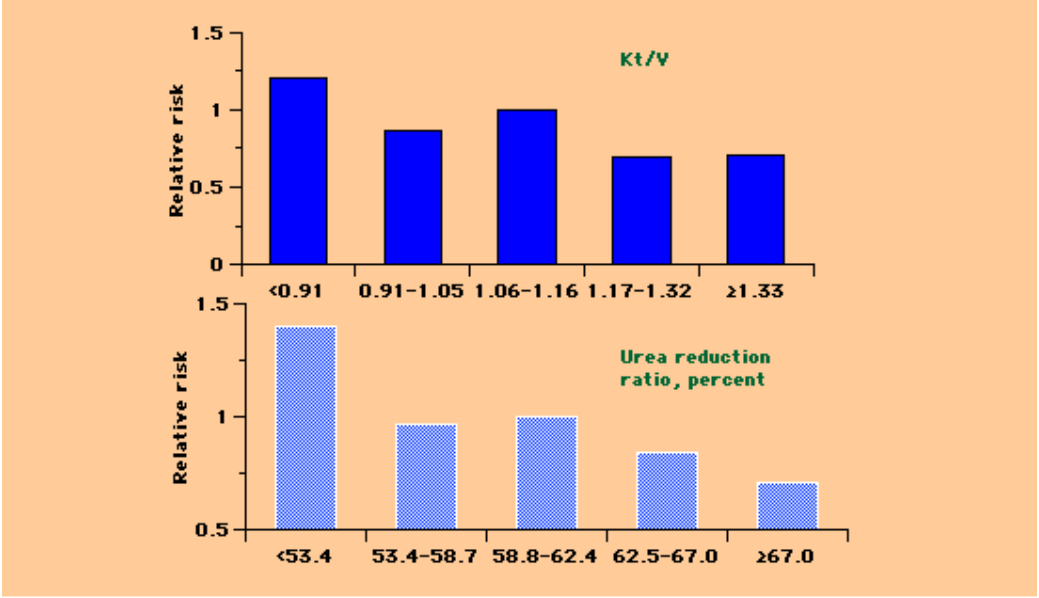
1.3. Why is dialysis adequacy important?

Uncontrolled observations suggest that increasing the intensity of dialysis to achieve a Kt/V of at least 1.3 is associated with improved survival, which is the Kt/V value recommended by the DOQI guidelines.

Furthermore, numerous outcome studies have shown a correlation between the delivered dose of haemodialysis and patient morbidity and mortality (Collins *et al*, 1994; Fernandez *et al*, 1992; Gotch *et al*, 1997; Hakim *et al*, 1994; Held *et al*, 1996; Lowrie *et al*, 1981;

Lowrie, 1994; Owen *et al*, 1993; Owen *et al*, 1998; Parker *et al*, 1994). The evidence demonstrates that mortality among ESRF patients is lower when sufficient haemodialysis treatments are provided. This can be explained by the fact that dialysis efficiency has been related to better control of arterial blood pressure, anaemia and serum phosphorus levels, and to improvement in patients' nutritional status.

Figure 1 SHOWING THE CORRELATION BETWEEN DIALYSIS DOSE AND PATIENT SURVIVAL



Increasing dialysis dose improves survival The relative risk of mortality by delivered dose of dialysis as measured by quintiles of Kt/V (top panel) or urea reduction ratio (bottom panel, in percent) among a random sample of 2311 patients on dialysis for more than one year at the end of 1990. Increasing the dialysis dose improved survival with apparent maximum benefit at a Kt/V of 1.3 and urea reduction ratio of 70. (Data from Held, PJ, Port, FK, Wolfe, RA, Kidney Int 1996; 50:550.)

1.4. Nutritional status in haemodialysis patients.

Malnutrition is an important problem in patients treated with chronic haemodialysis. The most common cause of inadequate nutrition in many patients is underdialysis, which can lead to decreased food intake because of diminished appetite, vomiting.

Evidence has shown that dialysis adequacy and nutrition have an effect on mortality and morbidity. It has been observed that the presence of malnutrition prior to the initiation of dialysis is strongly predictive of increased mortality with dialysis (Chung *et al*, 2000). Studies have also demonstrated that, unlike the general population, there was no positive correlation between blood pressure and body mass index (B.M.I); thus underweight rather than overweight is associated with a higher prevalence of hypertension. Therefore, assessment of the adequacy of dialysis necessitates the evaluation of patients' nutritional status.

Protein-energy malnutrition (PEM) is very common in patients undergoing maintenance dialysis. Different reports suggest the prevalence of this condition to be between 18 % to 70% in adults on maintenance HD. In adults the presence of PEM is one of the strongest predictors of morbidity and mortality.

There are many causes of PEM in patients with advanced chronic renal failure (CRF). These include:

- Inadequate food intake secondary to: anorexia caused by the uraemic state, altered taste sensation. It has also been postulated that hyperleptinaemia observed in patients with end stage renal failure may contribute to anorexia and malnutrition (Daschner *et al*, 1998; Fouque *et al*, 1998; Johansen *et al*, 1998).
- Uraemia is a catabolic state associated with frequent illnesses, and a state of chronic inflammation
- The dialysis procedure itself may remove nutrients i.e. amino acids, peptides, protein, glucose , water-soluble vitamins; protein catabolism due to bio-incompatibility of the dialysis membranes

- Medications such as phosphate binders can impair nutrient absorption.
- Other factors predisposing to malnutrition in haemodialysis patients include gastroparesis (for example, in diabetic patients) (Rothstein *et al*, 1992), which in some cases do not respond to increases of the dialysis dose. Gastroparesis may occur in non-diabetic patients on maintenance haemodialysis (De Schoenmakere *et al*, 2001; Grodstein *et al*, 1979).

In order to prevent PEM in patients on MHD, the provision of adequate nutrition is important. Nutritional status should be evaluated periodically.

The methods used to assess nutritional status:

1. History and physical examination can provide important clues to the patient who might be malnourished:
   - Symptoms such as nausea, anorexia, weight loss or gain.
   - Concomitant problems such as alcoholism, DM, hyper- or hypothyroidism, GIT pathologies etc may affect the nutritional status.
   - Socio-economic issues: financial problems, unemployment, signs and symptoms of depression which can result in disinterest and in a decrease in caloric intake.
2. Patients' food intake is an important component of the nutritional assessment (Wolfson, 1999). The protein intake can be estimated by calculating the PCR, utilising kinetic modelling (Hakim *et al*, 1993). The PCR is a reflection of protein intake only if the patient is in neutral nitrogen balance (Hakim *et al*, 1993).

3. Anthropometric measurements help to evaluate body fat and muscle mass. Body fat is estimated by measuring skin fold thickness at the triceps or subscapular areas, while mid-arm circumference can provide an estimate of the muscle mass. The results of these measurements are compared to reference standards obtained from healthy adults during the National Health and Nutrition Examination Surveys (NHANES II) from 1986 to 1980 (Table 1). Anthropometry has the advantage of being simple, non-invasive and quick to carry out.

Table 1 Anthropometry in haemodialysis patients

Parameter	Normal	Patients	P value
Relative body weight, percent	100	93.2 ± 16.3	<0.05
Triceps skinfold thickness, mm	12.0 ± 5.9	7.2 ± 3.9	<0.001
Subscapular skinfold thickness, mm	15.9 ± 7.7	11.2 ± 5.3	<0.001
Mid-arm circumference, cm	31.8 ± 3.4	28.9 ± 3.6	<0.001
Mid-arm muscle circumference, cm	28.0 ± 0.4	26.7 ± 3.0	NS

Anthropometry in hemodialysis patients Anthropometric measurements in normal subjects compared to 30 stable patients on maintenance hemodialysis. (Data from Wolfson, M, Strong, CJ, Minturn, D, et al, Am J Clin Nutr 1984; 39:547.)

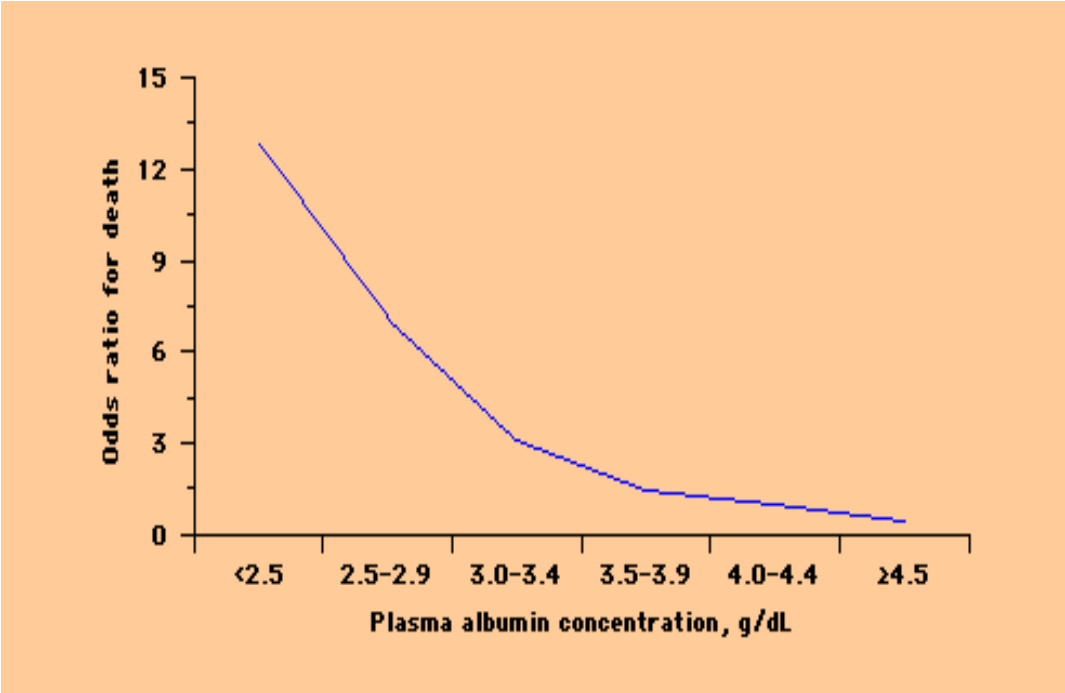
4. The nutritional status can also be assessed by bioelectric impedance analysis (BIA) and dual-energy x-ray absorptiometry (DEXA) (Segal *et al*, 1991; Vanitallie *et al*, 1990) but they are reserved for selected patients because they are sophisticated techniques and not available in the majority of the health centres. Unfortunately, these techniques do not distinguish between fat mass and body water.

5. Plasma protein measurements:

   Albumin: several studies have shown a negative correlation between the plasma albumin and mortality in patient on MHD (shown on *Figure 1-2*) (Goldwasser *et al*,

1993; Lowrie *et al*, 1990; Owen *et al*, 1993; Rocco *et al*, 1993; Teehan *et al*, 1990). However, albumin is not a specific marker of malnutrition as it is an acute phase protein with a half-life of 21 days; and hepatic stores are significant. Moreover, changes in extracellular volume represent a potential source of error in assessing the plasma albumin concentration.

Figure 2 SHOWING CORRELATION BETWEEN PLASMA ALBUMIN CONCENTRATION AND MORTALITY IN PATIENT ON MHD



Hypoalbuminemia and reduced survival in haemodialysis odds ratio for death, adjusted for age, sex, race, and underlying disease, according to the plasma albumin concentration in patients on maintenance haemodialysis. The likelihood of dying was inversely related to the plasma albumin concentration being greatest at a plasma albumin concentration below 3.0 g/dL (30 g/L). All values are significantly different ($p<0.001$ to 0.03) from the odds ratio of 1.0 a normal plasma albumin concentration of 4.0 to 4.4 g/dL (40 to 44 g/L). (Data from Owen, WF Jr, Lew, NL, Liu, Y, et al, N Engl J Med 1993; 329:1001).

The increase in mortality associated with hypoalbuminaemia is observed in 60 to 67 percent of patients on chronic haemodialysis (Lowrie *et al*, 1990; Owen *et al*, 1993).

It appears to occur even with an almost normal serum albumin (35 g/L). However, the mortality is further increased with more severe hypoalbuminaemia (less than 30 g/L). The DOQI guidelines recommend the measurement of albumin on a monthly basis (DOQI Guidelines, 2000).

Like albumin, a significant number of plasma proteins can also be used to evaluate nutritional status:

Transferrin concentration: Low transferrin levels have been described in dialysis patients and have been found to be associated with malnutrition (Buchwald *et al*, 1989; Owen *et al*, 1993; Young *et al*, 1991). However, plasma transferrin levels may be decreased in renal failure and with erythropoietin therapy for the treatment of anaemia of renal failure.

Prealbumin: Plasma concentrations of prealbumin may vary with the state of nutrition in patients with normal renal function. However as prealbumin is excreted and metabolised by the kidney, it tends to accumulate in renal failure (Cano *et al*, 1988). It explains why a single value of prealbumin may not be an accurate indicator of nutrition, and serial measurements should be monitored once a baseline level has been established for the particular patient. Unlike albumin, prealbumin has a short half-life and changes rapidly in response to alterations in nutritional status. It has been found that a value below 30mg/dl is a parameter of malnutrition for patients on haemodialysis (Hakim *et al*, 1993). As per albumin, prealbumin is also an acute phase protein, and its value must be interpreted with caution in situations of acute inflammation.

Cholesterol: As cholesterol concentration is reduced in undernourished patients with normal renal function, it is also lower with end-stage renal disease. The evidence has shown an inverse relationship between mortality and cholesterol concentration (Degoulet *et al*, 1982; Lowrie *et al*, 1990).

Blood urea nitrogen: Low predialysis BUN levels have been found to be associated with increased mortality (Hakim *et al*, 1993); low values of BUN related to decreased protein intake may be misleading in the prescription of dialysis dose causing underdialysis, which will then lead to worsening of the nutritional status, in view of loss of appetite and subsequently, to decline in protein intake; hence, the role of monitoring the protein catabolic rate in dialysis patients.

Creatinine production: Creatinine is also a marker of nutrition as it is a product of muscle breakdown. Studies have shown a reduction in survival in patients on chronic haemodialysis with lower plasma creatinine concentration levels (Lowrie *et al*, 1990; Rocco *et al*, 1993; Teehan *et al*, 1990).

A variable plasma amino acid pattern has been also found in end-stage renal disease. In general, the essential amino acids are decreased, while the nonessential amino acids are either within the normal range or increased (Bergstrom *et al*, 1990; Kopple *et al*, 1975). These changes may be due to uraemia itself, rather than reflecting malnutrition.

Obviously there is no one measure which can be used to accurately assess patients' nutritional status. Therefore, patients on chronic haemodialysis should undergo a

variety of measurements in order to develop a profile, which can be used to assess the nutritional status.

1.5. Quality of life of patients on maintenance haemodialysis.

Patients on maintenance haemodialysis often show a significant decrease in quality of life. Haemodialysis patients experience numerous symptoms in terms of medical outcomes and also in terms of potential reduction in functioning and wellbeing.

In fact, despite technical progress in therapy, haemodialysis patients continue to report health- related quality of life, which is substantially lower than that of the general population. Patients often report that they are limited by their physical functioning and by multiple dialysis-related symptoms i.e. cramps, symptomatic hypotension, anaemia and other symptoms related to dysautonomia. Hence, patient perception of health is an important outcome measure in the assessment of the influence of chronic disease and its treatment. Moreover, perception of health-related quality of life influences compliance by the patients.

Research findings from Europe and U S A demonstrated that patients who are treated with successful renal transplantation experience a quality of life, which is superior to that achieved with any dialysis modality and which is very close to the quality of life scores of the general population.

Different studies have shown a better quality of life with predialysis clinic attendance. This may result from opportunities for patient education, dietary counselling, modality selection, permanent dialysis access creation and management of comorbid conditions

i.e. the importance of early predialysis correction of anaemia by the use of erythropoietin and iron management has been emphasised in different trials (Zehnder *et al*, 1992). In fact several studies have proved that earlier initiation of erythropoietin therapy may improve patient morbidity and mortality by retarding or preventing the development of cardiomyopathy secondary to anaemia. The DOQI guidelines recommend an Hb between 11 to 12 g/l

Furthermore, delayed diagnosis, late referral and delay in commencing dialysis are commonly observed in developing countries and also probably in the developed nations (Ratcliffe *et al*, 1984). In fact, these patients have a higher frequency of clinical complications, metabolic disturbances, long term access problems and a higher mortality rate than patients with a regular follow-up at the renal clinic.

Other independent predictors of quality of life:

- Age: older age being associated with a relatively poor quality of life may be related to the presence of significant comorbities.
- Gender: Evidence has shown that female patients have a poorer quality of life than their counterpart male patients.
- Race: Different studies have demonstrated that African- American patients on chronic haemodialysis have a better quality of life than non-African-American patients (Mark *et al*, 2004).
- Education: higher education level has been found to be associated with a better quality of life. This may be explained by a better understanding of the disease and consequently better compliance.

- Dialysis adequacy: Increased dialysis dose has been associated with a better quality of life (Benz *et al*, 2000). In another study, increased dialysis dose was found to be associated with a decrease number of awakenings at night (Benz *et al*, 2000).
- Nutritional status: Evidence has shown a correlation between nutrition and quality of life even after controlling for comorbidities and dose of haemodialysis, hence providing an additional reason for maximising patients' nutritional status and health (Dwyer *et al*, 2002).
- Dialysis dose: Evidence has shown either a correlation between dialysis dose and quality of life or a lack of correlation between two elements (Manns *et al*, 2002; Morton *et al*, 1996).
- Dialysis modality: Some studies have shown that quality of life depends upon dialysis modality (Merkus *et al*, 1999).
- Others: Psychosocial factors, vascular access, duration of haemodialysis, number of hospitalisations, primary renal diseases, comorbities.

Assessing the quality of life for patients with end stage renal disease treated by haemodialysis has been considered an important aspect of therapy. Many quality of life measures have been used in dialysis patients. Among them are the following:

- Medical Outcomes Study Short Form 36 (SF-36).
- Sickness Impact Profile (SIP).
- Index of Well Being, Index of Overall Life Satisfaction.
- Index of Psychological Affect.
- General Health Questionnaire.
- Simmons Self Esteem Scale.
- Profile of Mood States.

- Multidimensional Health Locus of Control.
- Modality Specific Stresses Scale.
- General Treatment Stress Scale.
- Global Illness Stress on Self and Others, Global Adjustment to Illness Scale.
- Quality of Life (QL 100 mm) Analogue Scale.
- Dialysis Relationship Quality Scale.
- Social Leisure Activities Index, Social Support Satisfaction Scale.
- General Well-Being Index.
- Index of General Affect, Overall Life Satisfaction.
- Katz Activities of Daily Living.
- Time Trade-off Measures.

Unfortunately, many of these instruments do not have enough evidence for reliability and validity. A popular generic measure is the ***Short Form 36 (SF36***), which is a health survey, well-validated self- report questionnaire that assesses quality of life of patients on maintenance haemodialysis (Kalantar-Zadeh *et al*, 2001)

It may be difficult however, to compare results from different population cultures in view of how different people interpret and rate their quality of life. Nevertheless, the score of the SF36 has been used in different studies showing statistically significant correlations between serum albumin, haemoglobin and quality of life and subsequent correlation with morbidity and mortality with the above two parameters.

The study will help us to identify the parameters of dialysis adequacy and possible association in view of laboratory markers of haemoglobin, albumin and the quality of

life. Moreover the association between dialysis dose and other outcomes such as blood pressure control, sepsis and mortality will be considered.

CHAPTER 2.MATERIALS AND METHODS

2.1. ETHICS

Human ethics clearance for the study was obtained from the Medical Ethics Committee of the University of the Witwatersrand: clearance certificate number M040325.

2.2. CONSENT

Voluntary consent was obtained from patients willing to participate in the study. The consent form is attached as *Appendix 2*.

2.3. STUDY POPULATION

A retrospective review of 61 patients who were on chronic haemodialysis at Johannesburg Hospital during January-December 2003 was performed.

2.3.1. The inclusion criteria:

Patient on maintenance haemodialysis for at least three months; these were outpatients receiving haemodialysis three times per week, for an average of four hours for each session.

2.3.2. The exclusion criteria:

Patients on temporary haemodialysis i.e. on holiday haemodialysis as well as patients who required bridging haemodialysis for continuous ambulatory peritoneal dialysis related complications.

2.4. METHODS

2.4.1 The following information was obtained from the patients' records:

- Demographic data: Age, gender, race
- Aetiology of chronic kidney diseases
- Duration of haemodialysis
- Vascular access
- Comorbid conditions: Body mass index, viral hepatitis B & C, HIV infection, diabetes mellitus. The body mass index (BMI) was calculated as the ratio of weight to height squared; the dry weight was used to calculate the BMI of patients on maintenance haemodialysis. The measurements of the weight and height were performed using "Detecto-scale (Brooklyn. N.Y—USA)".

2.4.2 A smoking history was obtained and accordingly three groups of patients were established:

2.4.2.1 Current smoker

2.4.2.2 Former smoker

2.4.2.3 Never smoked (= non smoker)

2.4.3 The records of monthly blood results, which were analysed by the National Health Laboratory Service (NHLS), were also reviewed for:

2.4.3.1 Laboratory values of:

- Haemoglobin
- Serum albumin
- Serum cholesterol

- Parathyroid hormone

2.4.3.2 Parameters of haemodialysis adequacy:

- Calculated Kt/V
- Urea reduction ratio (URR)
- Normalised protein catabolic rate (nPCR)

These were calculated according to the following formulae:

$$Kt/V = -\ln(R - 0.03) + [(4 - 3.5R) \times (UF \div W)]$$

Where:

UF: Is the ultrafiltration volume in litres

W: Is the post dialysis weight in kg

R: Is the ratio of the post dialysis to predialysis BUN

$$\mathbf{U}RR = \frac{\text{Predialysis BUN} - \text{Predialysis BUN}}{\text{Predialysis BUN}} \times 100$$

$$nPCR = 0.22 + \frac{(0.036 \times \text{ID rise in BUN} \times 24)}{\text{ID interval (hours)}} (\text{g/kg/day})$$

Where:

ID (Interdialytic rise in BUN) = Predialysis BUN minus immediate post dialysis BUN from the preceding dialysis in mmol/l.

For these calculations, a calculator EL-531VH (SHARP Corporation) also capable of performing natural logarithms was used. Furthermore, for weight measurement a Detecto-scale (Brooklyn N.Y –USA) was used.

2.4.4 The prospective aspects of this study included:

2.4.4.1 A quality of life questionnaire assessment, using the short form health survey with 36 questions (SF36) which is a well documented scoring system that has been used and validated as a QOL (Quality Of Life) tool for the general population as well as the patients on maintenance haemodialysis, was submitted to every patient and a self-assessment of quality of life was then measured by the SF-36. For patients who could not read or write English, the questionnaire was administered by myself with the assistance of an interpreter.

The SF-36 encompasses eight scales (annexed SF-36 questionnaire):

1. Physical functioning (10 items)
2. Role physical (4 items)
3. Bodily pain (2 items)
4. General health (5 items)
5. Vitality (4 items)
6. Social functioning (2 items)
7. Role emotional (3 items)
8. Mental health (5 items)

The above 8 scales are divided into two dimensions (physical and mental):

- The physical component aggregates items from the physical functioning, role physical, bodily pain, general health, vitality, and social functioning.

- The mental component aggregates items from role-emotional, mental health, and also includes elements of general health, vitality, and social functioning.

- The scales vitality and general health are part of both dimensions. Hence every dimension includes three specific and two overlapping scales.

In SF36 scoring system, the scales are assessed quantitatively, each on the basis of answers to two to ten multiple choice questions, and a score between 0 and 100 is then calculated on the basis of well-defined guidelines, with a higher score indicating a better state of health

The scores of the SF-36 dimensions range from 0 to 100, higher scores representing better quality of life.

2.4.4.2 Each patient underwent echocardiography performed by the Cardiology Unit using SEQUOIA C_{256} (SIEMENS) echocardiograph machine.

The following parameters were recorded for every patient:

- Left ventricle hypertrophy (LVH): Concentric or eccentric
- Left ventricle dilatation
- Ejection fraction (EF)
- Left ventricle diastolic dysfunction
- Pulmonary pressures
- Others: wall motion abnormalities; valvular heart disease

2.4.5 Statistical analysis:

Statistical analyses were performed as follows:

- Descriptive statistics, which included percentages and graphical presentation of the data.
- Correlation of dialysis dose (Kt/V) and laboratory markers such as haemoglobin (Hb) and serum albumin. The short-form 36 (SF-36) scoring results were also correlated with Kt/V.
- Statistical inference including:
    - Mean confidence intervals of indicators of dialysis adequacy of adult patients on chronic haemodialysis at Johannesburg hospital in 2003. This involved Kt/V, Urea Reduction Rate (URR) and normalised Protein Catabolic Rate (nPCR).
    - Chi-square tests of association between hypertension and diastolic dysfunction and also between aetiology of ESRD and LVH.
    - Two-sample t-tests were performed to study the relationship between:
        i) LVH and duration of haemodialysis, aetiology of ESRD, Hb status.
        ii) Diastolic dysfunction and anaemia, duration of haemodialysis
        iii) Valvular heart disease and serum PTH, Ca x P product, serum PO_4 , serum Calcium, duration of haemodialysis.
        iv) Influence of Kt/V on BP control, hospitalisation and sepsis.

Conclusions were made at 95% confidence levels. That is, differences and relationships were considered statistically significant when the probability value, p, was less than 0.05 ($p<0.05$).

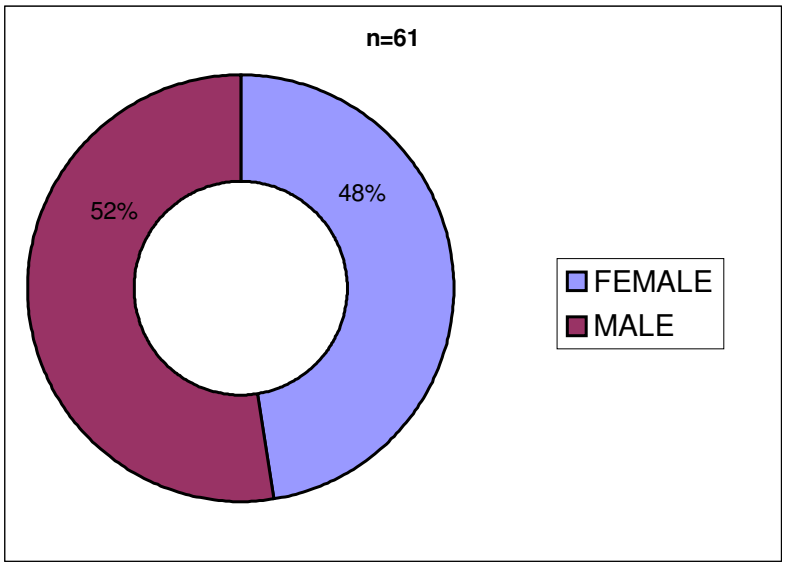
CHAPTER 3. RESULTS

3.1. DEMOGRAPHIC DATA

At the initiation of the study, 61 patients were enrolled. During the course of the study, four patients passed away and three patients were transplanted. All these events happened at different periods of time. Therefore, they were obviously ruled out for some of the study parameters. Furthermore, only patients who have been on maintenance haemodialysis for at least three months duration were considered for the study.

3.1.1. GENDER

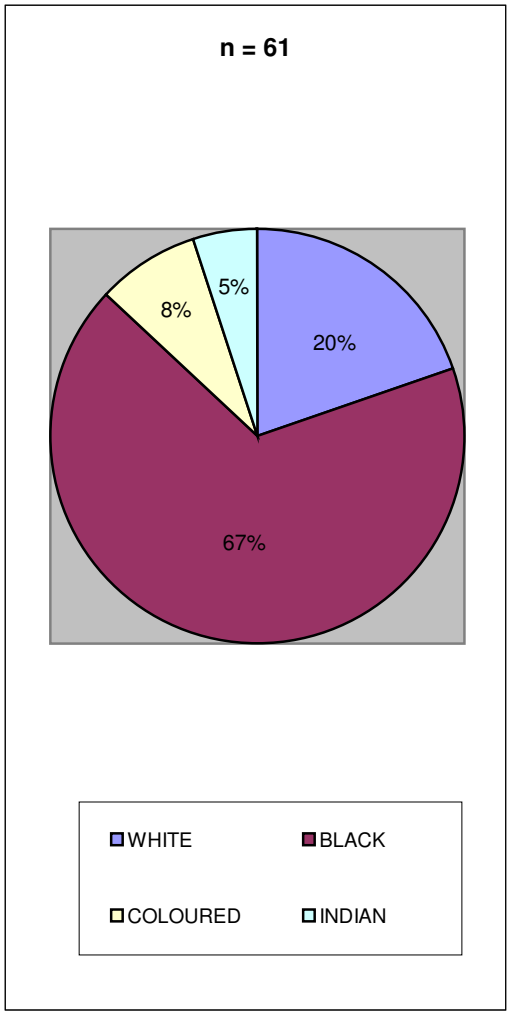
Figure 3 GRAPH SHOWING THE GENDER OF ADULT PATIENTS ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003.



52% of adult patients on chronic haemodialysis at Johannesburg Hospital during 2003 were male and 48% were female.

3.1.2. PATIENT POPULATION RACE GROUP

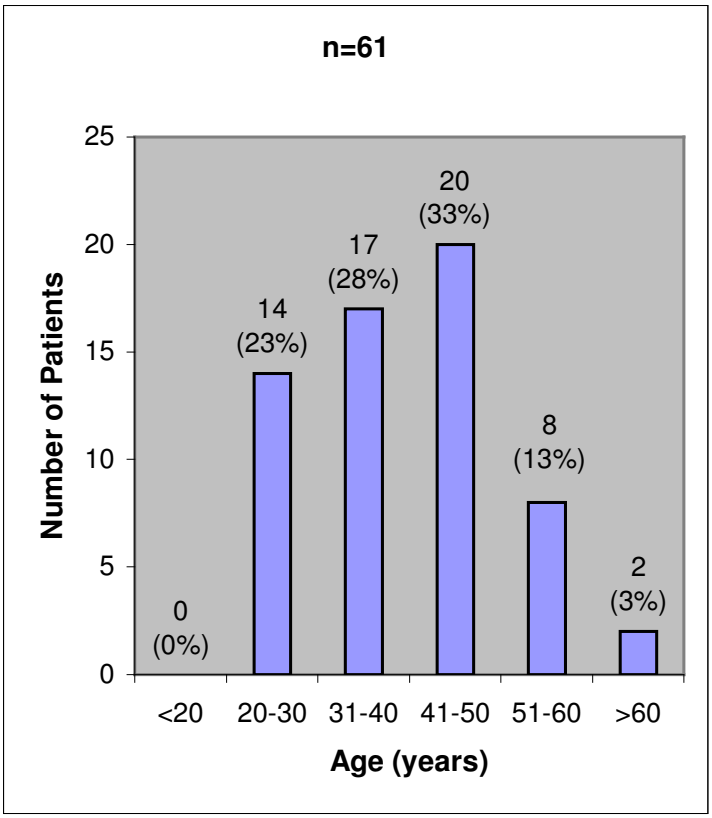
Figure 4 GRAPH SHOWING THE ADULT PATIENT POPULATION ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003.



The majority of patients on chronic haemodialysis at Johannesburg Hospital in 2003 were black Africans (67%), the rest being 20% Caucasian, 8% coloured and 5% Indian.

3.1.3. AGE

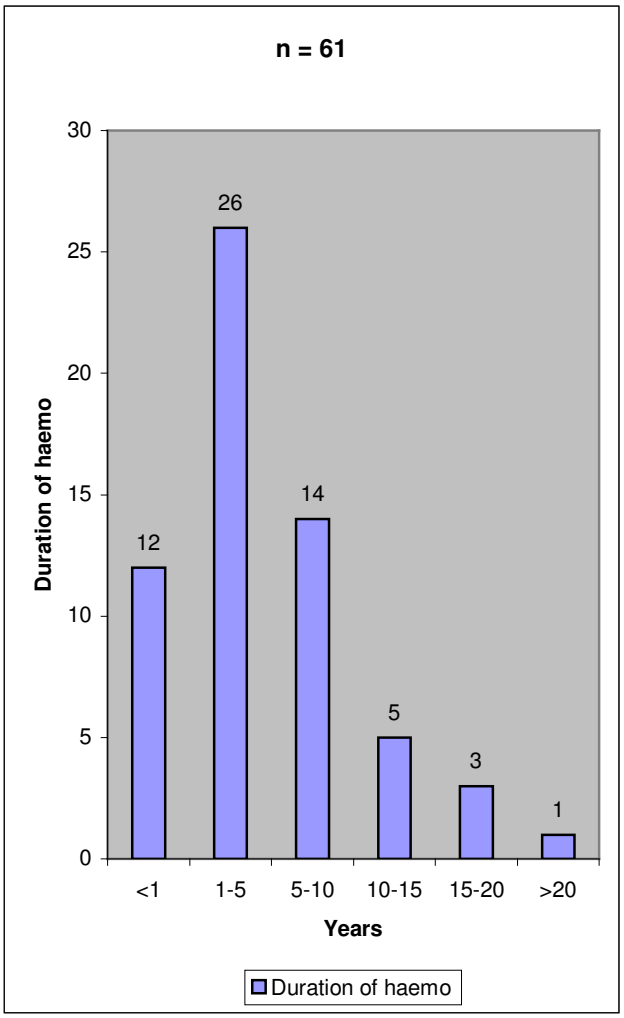
Figure 5 HISTOGRAM OF PATIENTS' AGES (IN YEARS) ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003.



Most of the adult patients on chronic haemodialysis at Johannesburg Hospital in 2003 were between the age group 20-50 years, the biggest group belonging to the age group 40 to 50 year old. Only two patients were more than 60 years old and none were less than 20 years.

3.2. DURATION OF HAEMODIALYSIS (IN YEARS)

Figure 6 HISTOGRAM SHOWING THE DURATION OF HAEMODIALYSIS (IN YEARS) OF ADULT PATIENTS AT THE RENAL UNIT AT JOHANNESBURG HOSPITAL IN 2003.



The duration of haemodialysis of most of the patients was between less than one year to 10 years; only one patient was on chronic haemodialysis for more than 20 years.

3.3. PRIMARY RENAL DISEASE

Table 2 PRIMARY RENAL DISEASE RESULTING IN END STAGE RENAL FAILURE (ESRF) IN ADULT PATIENTS (n= 61) ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003.

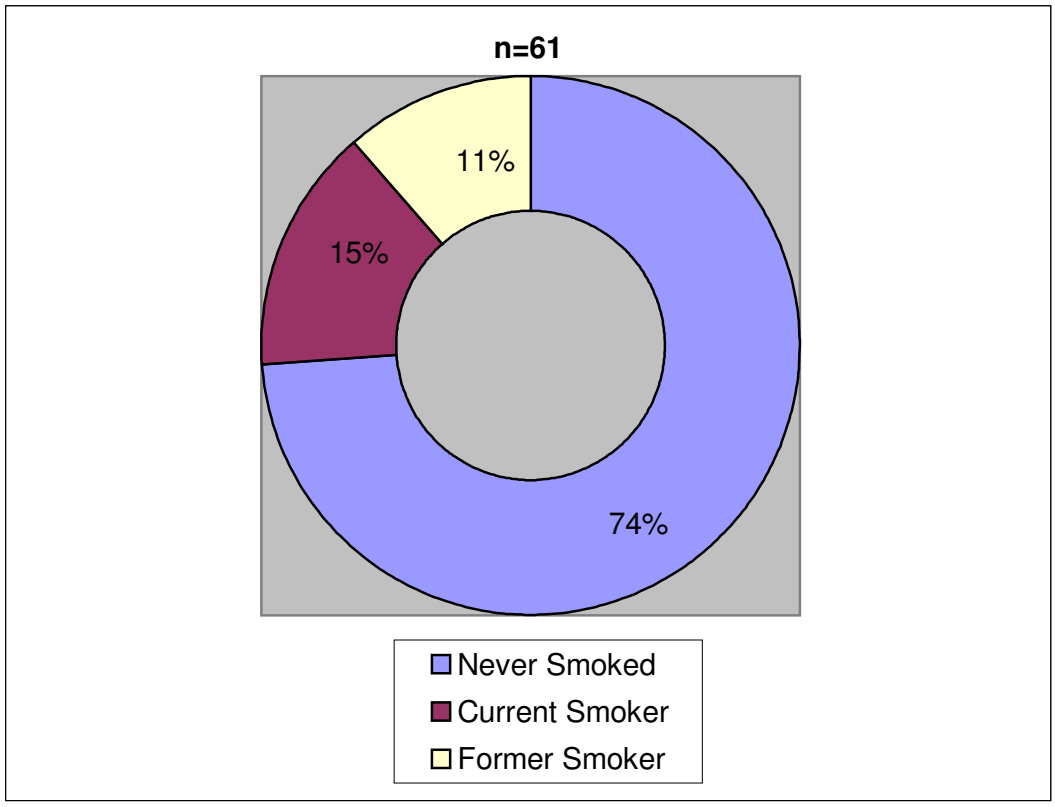
AETIOLOGY	NUMBER OF PATIENTS	PERCENTAGE
Hypertension	26	42.62%
Glomerulonephritis	11	18.03%
Polycystic kidney disease	1	1.64%
Diabetes	4	6.56%
Reflux	5	8.20%
Congenital kidney disease	3	4.92%
Trauma-surgery	2	3.28%
Unknown	9	14.75%

Hypertension remains the most common presumed cause of ESRF, followed by glomerulonephritis. A significant number of patients have ESRF of unknown aetiology. Of note, diabetes was in the 5th position of primary renal disease; this is related to selection-bias, as only those patients deemed suitable for renal transplantation were offered chronic dialysis.

3.4. COMORBIDITIES

3.4.1. SMOKING STATUS

Figure 7 GRAPH SHOWING THE SMOKING STATUS OF ADULT PATIENTS ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003.



74% of patients (n=45) never smoked, 15% (n=9) were current smokers and 11% (n=7) were former smokers. Among the smokers 89% were male and 11% were female. In addition, the smokers were all in the age group between 25-50 years. They were all moderate smokers (1 to 5 per day), trying hard to quit smoking.

3.4.2. SERUM PTH LEVEL

Table 3 SERUM PTH LEVELS OF ADULT PATIENTS (n=58) ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003. 3 PATIENTS' DATA ON SERUM PTH LEVELS WERE NOT FOUND DURING THE STUDY.

SERUM PTH (pg/ml)	NUMBER OF PATIENTS	PERCENTAGE
<150	17	29%
150-300	7	12%
300-1000	26	45%
≥1000	8	14%

According to K/DOQI guidelines which recommends a serum PTH level between

150-300 pg/ml, 59% (n=34) of patients had hyperparathyroidism

(PTH level ≥300pg/mL), 14% having PTH levels of more than 1000 pg/ml.

It is the intact serum PTH that was measured during our study.

3.4.3. BMI

Table 4 BMI (kg/m^2) OF ADULT PATIENTS ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003

BMI (kg/m^2)	NUMBER OF PATIENTS	PERCENTAGE
<18.5	4	6.6%
18.5-24.9	40	65.6%
25.0-29.9	12	19.7%
30.0-34.9	2	3.3%
35.0-39.9	2	3.3%
≥40	1	1.6%

65.6% (n=40) of patients had a normal BMI, 19.7% (n=12) were overweight (pre-obese) and the rest of the patients were obese with 1.6% (n=1) having morbid obesity.

World Health Organisation classification of overweight and obesity based on BMI:

Underweight: <18.5 kg/m^2 Normal weight: 18.5-24.9 kg/m^2

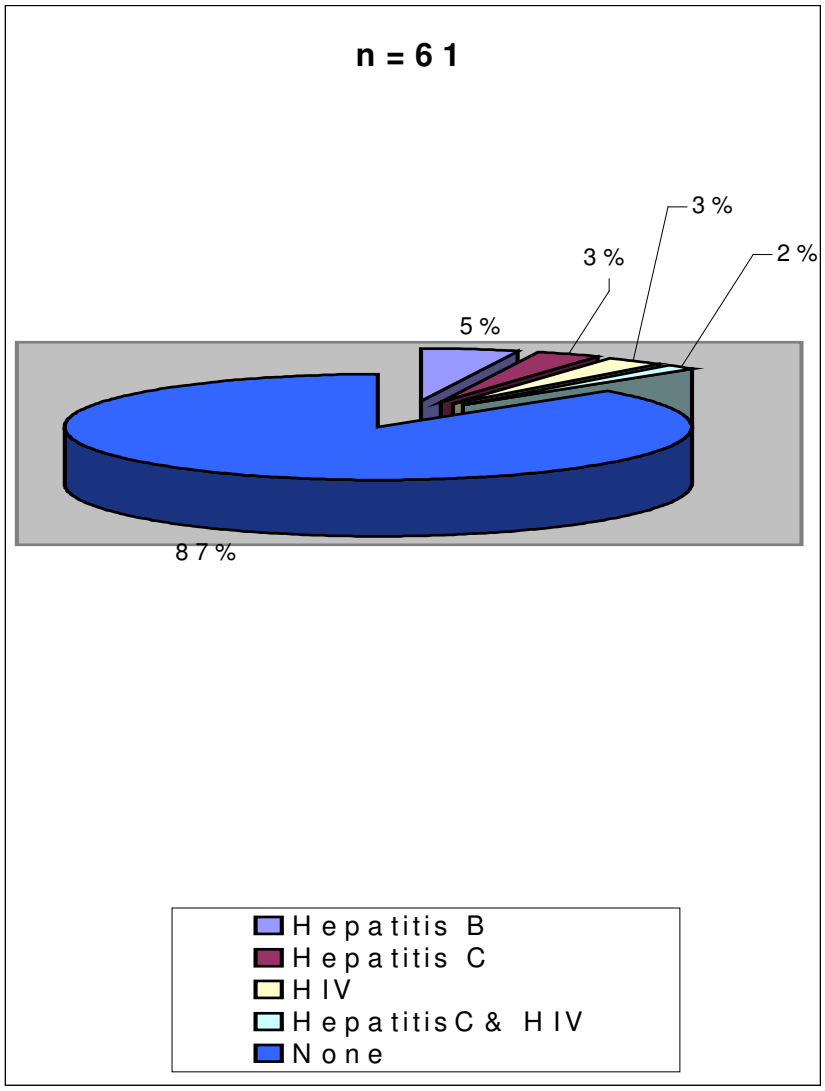
Pre-obese (overweight): 25.0 - 29.9 kg/m^2 Obese Class I: 30.0-34.9 kg/m^2

Obese Class II: 35.0-39.9 kg/m^2

Obese Class III (morbid obesity): ≥40.0 kg/m^2

3.4.4. HEPATITIS B&C AND HIV INFECTION

Figure 8 GRAPH SHOWING HEPATITIS B & C AND HIV INFECTION STATUS OF ADULT PATIENTS ON CHRONIC HAEMODIALYSIS



3% (n=2) of patients were HCV positive, 5% (n=3) were HBV positive, 3% (n=2) were HIV positive, and 2% (n=1) had co-infection Hepatitis C & HIV.

3.4.5. ECHOCARDIOGRAPHIC FINDINGS IN ADULT PATIENTS (n=59) ON CHRONIC HAEMODIALYSIS AT JHB HOSPITAL IN 2003

Two patients had already died and their echocardiographic data were not available.

3.4.5.1. Left Ventricular configuration

Table 5 LEFT VENTRICULAR CONFIGURATION

LV CONFIGURATION		NUMBER OF PATIENTS	PERCENTAGE
Hypertrophy	Concentric	40	68%
	Eccentric	4	7%
Dilated		6	10%
Normal		9	15%

75% (n=44) of patients had LVH, with 68% (n=40) having concentric LVH; 10% (n=6) had dilated LV. The mean EF was 63.16%; range 29.63% to 87.77%.

The statistical analysis of the association between LV configuration and the parameters of haemodialysis duration, aetiology of ESRD and haemoglobin shows the following:

- Using Fisher's- exact test (Chi-squared test), there is an association between LVH and hypertension; $p<0.05$.
- Using T-test the effect of haemoglobin on LVH is not statistically significant ($p=0.4307$). Similarly, there is no effect of haemodialysis duration on LVH ($p=0.9788$).
- The analysis for dilated LV and the above parameters was not performed due to the sample size, which is very small.

3.4.5.2. Left Ventricular function

Table 6 LEFT VENTRICULAR FUNCTION

LV FUNCTION	NUMBER OF PATIENTS	PERCENTAGE
Diastolic dysfunction	35	59%
Systolic dysfunction	3	5%
Systolic & Diastolic dysfunction	4	7%
Normal	17	29%

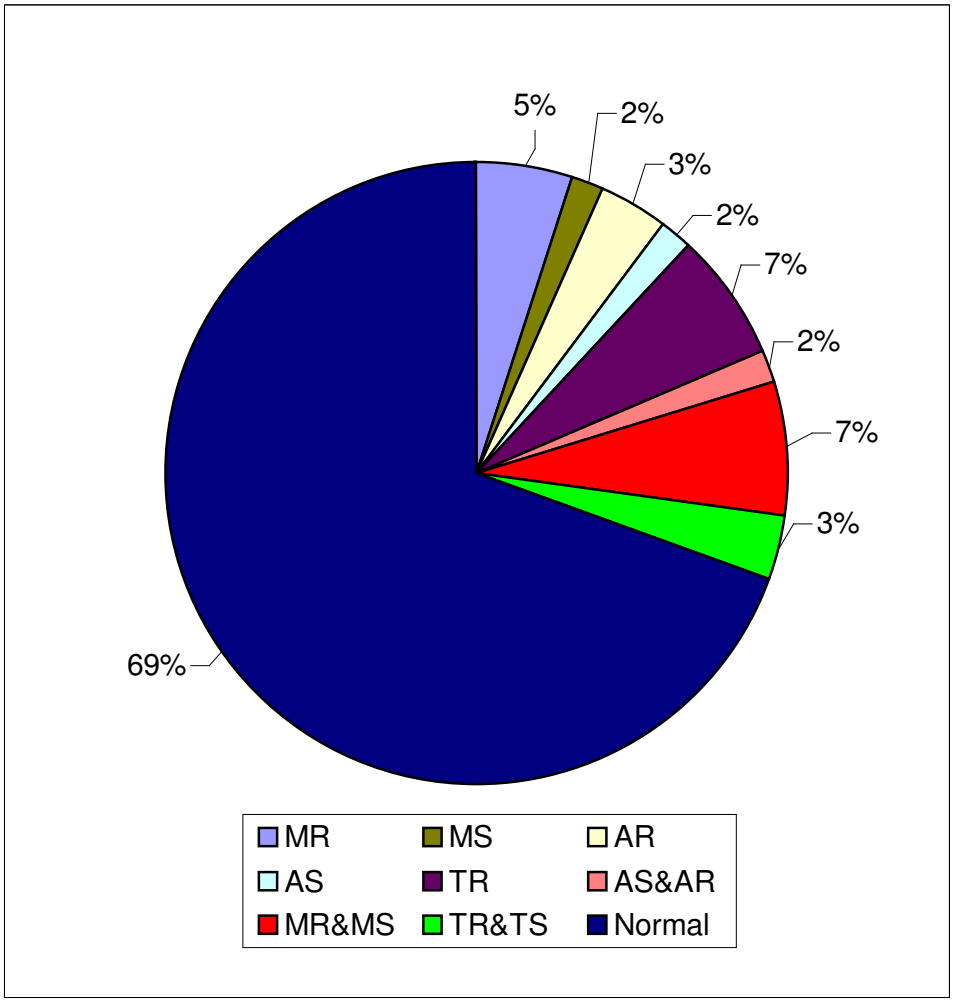
59% (n=35) of patients had diastolic dysfunction, 5% (n=3) had systolic dysfunction, whereas 7% (n=4) had mixed systolic and diastolic dysfunction.

The statistical analysis association between LV function and the parameters of hypertension, haemoglobin, duration of haemodialysis duration shows the following:

- Using Fisher's- exact test (Chi-squared test), there is a statistically significant association between hypertension and diastolic dysfunction; $p<0.05$.
- Using the T-test there is no effect of haemodialysis duration and serum haemoglobin levels on the diastolic dysfunction.
- Since the sample size for systolic dysfunction was very small (n = 3), no formal statistical inference was performed. The same observation applies to the analysis concerning the effect of Hb and haemodialysis duration on combined systolic and diastolic dysfunction (n = 4).

3.4.5.3. VALVULAR HEART DISEASE

Figure 9 VALVULAR HEART DISEASE



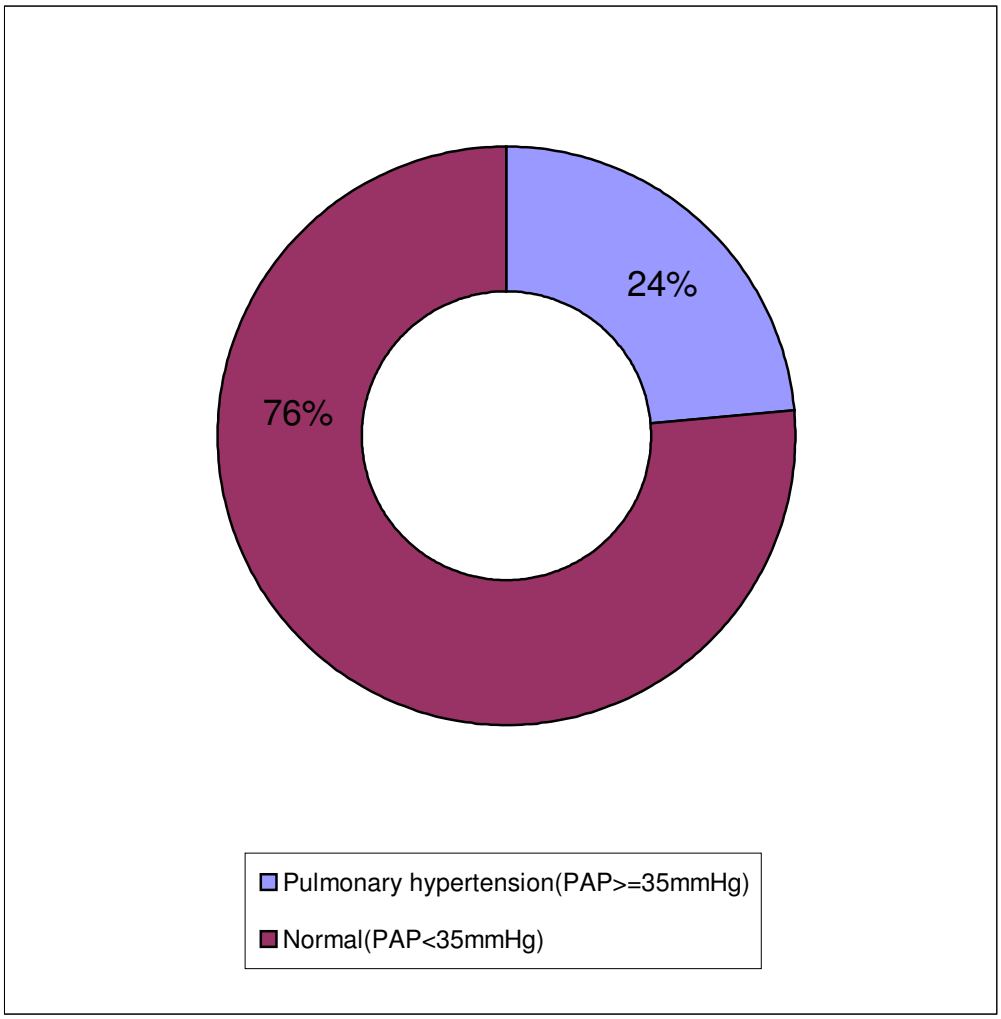
7% (n=4) had tricuspid regurgitation (TR), 7% (n=4) had mixed mitral valve disease, 5% (n=3) had mitral regurgitation, 3% (n=2) had aortic regurgitation, and the same number (n=2) with mixed tricuspid valve disease. One patient each had aortic stenosis, mitral stenosis and mixed aortic valvular disease.

The statistical analysis of the association between valvular heart disease and duration of haemodialysis, Ca x P product and plasma PTH shows the following:

- Using T-test, there is a statistically significant effect of haemodialysis duration on valvular heart disease ($p=0.0182$). Using the T-test there was no effect of Ca x P product on valvular heart disease ($p=0.8116$). The same applies ($p>0.05$) for the following: plasma PTH , serum PO_4, serum calcium.

3.4.5.4. Pulmonary hypertension

Figure 10 PULMONARY HYPERTENSION



24% (n=14) had pulmonary hypertension, with pulmonary artery pressures ranging from 35 to118mmHg; 76% (n=45) had normal pulmonary pressure.

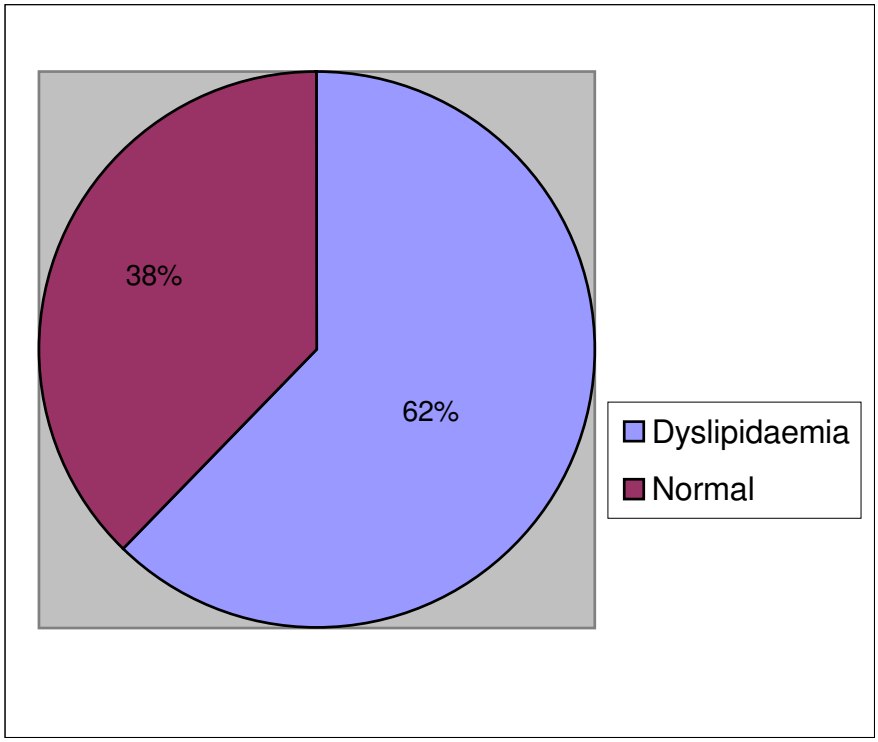
Pulmonary hypertension was defined as pulmonary artery systolic pressure of more than 35mmHg and was determined by two-dimensional doppler echocardiography imaging.

3.4.6. LIPID STATUS OF ADULT PATIENTS (n=53) ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003.

8 patients' data for serum lipids were not available.

3.4.6.1. DYSLIPIDAEMIA

Figure 11 GRAPH SHOWING PATIENTS WITH DYSLIPIDAEMIA



62% (n=33) had dyslipidaemia, whereas 38% (n=20) had normal lipograms.

3.4.6.2. LIPID PROFILES OF PATIENTS WITH DYSLIPIDAEMIA

Table 7 LIPID PROFILES OF PATIENTS WITH DYSLIPIDAEMIA

LIPID PROFILES	NUMBER OF PATIENTS	PERCENTAGE
Triglycerides (>1.5 mmol/l)	10	19%
LDL - Cholesterol (>3 mmol/l)	7	13%
HDL - Cholesterol (<1.2 mmol/l)	27	51%
Total - Cholesterol (>5 mmol/l)	3	6%

Most of the patients had low HDL-cholesterol (51%), with mean 1.13mmol/l and range 0.5 to 2.4mmol/l and hypertriglyceridaemia (19%) with mean 1.28mmol/l and range 0.5 to 4.9mmol/l. A significant number of patients had high LDL cholesterol (13%) with mean 2.12mmol/l and range 0.8 to 4.5mmol/l

Normal ranges for Total cholesterol: ≤ 5.0 mmol/l

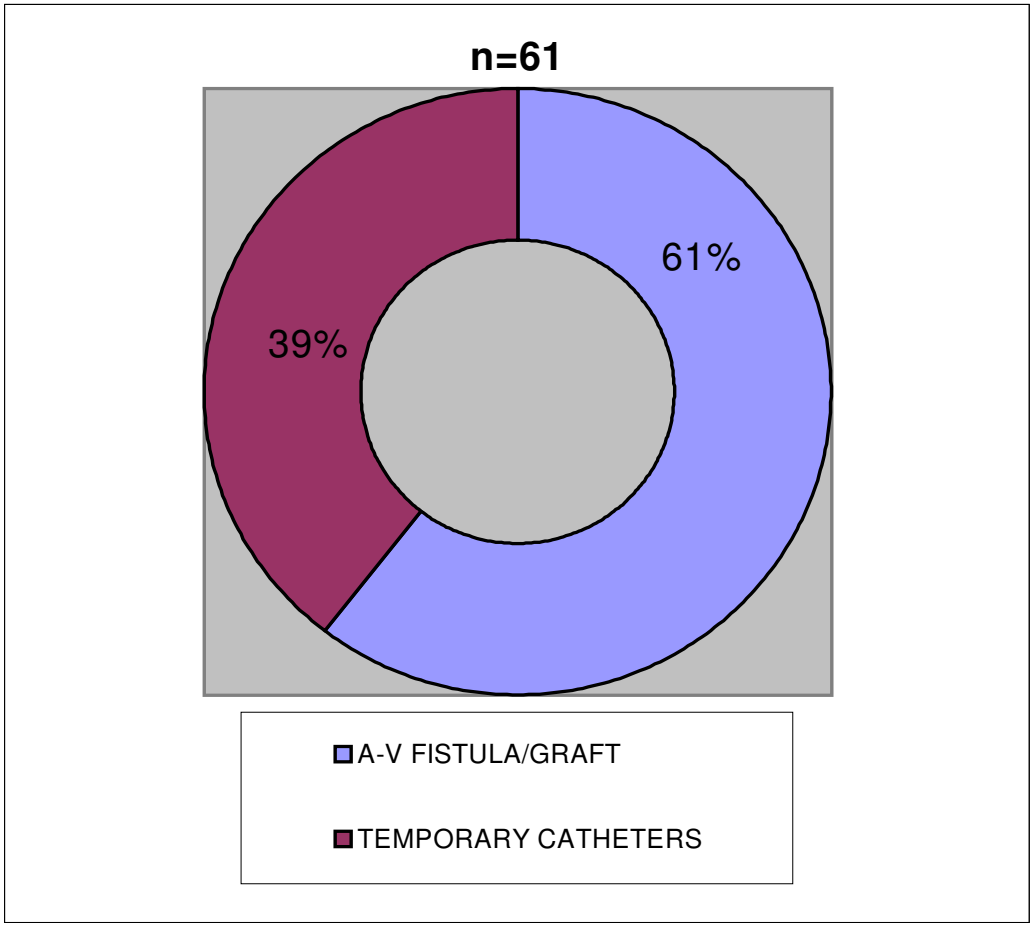
Triglycerides: ≤ 1.5 mmol/l

HDL-Cholesterol: ≥ 1.2 mmol/l

LDL- Cholesterol: ≤ 3.0 mmol/l

3.5. VASCULAR ACCESS

Figure 12 GRAPH SHOWING VASCULAR ACCESS OF ADULT PATIENTS ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003.



Although 61% (n=37) of patients on chronic haemodialysis at Johannesburg Hospital in 2003 have a permanent access (A-V fistula/graft), a significant number of patients (39%, n=24) were still being dialysed with temporary catheters.

3.6. INDICATORS OF DIALYSIS ADEQUACY OF ADULT PATIENTS (n=58) ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003.

3 patients' data on indicators of dialysis adequacy were not available.

Table 8 INDICATORS OF DIALYSIS ADEQUACY OF ADULT PATIENTS (n=58) ON CHRONIC HAEMODIALYSIS AT JOHANNESBURG HOSPITAL IN 2003.

Kt/V (1.34 ± 0.25)				**URR** (68.82 ± 9.19)%				**nPCR** (0.82±0.20) g/kg/day	
≥1.2	<1.2	≥1.3	<1.3	≥65%	<65%	≥70%	<70%	≥0.8	<0.8
74% (n=43)	26% (n=15)	60% (n=35)	40% (n=23)	74% (n=43)	26% (n=15)	55% (n=32)	45% (n=26)	50% (n=29)	50% (n=29)

An acceptable number of patients were adequately dialysed:

- 74% of patients (n = 43) had Kt/V ≥1.2
- 60% of patients (n = 35) had Kt/V ≥1.3
- 74% of patients (n=43) had URR ≥ 65%
- 55% of patients (n = 32) had URR ≥70%
- 50% of patients (n = 29) had nPCR ≥0.8 g/kg/day

Parameters considered for dialysis adequacy:

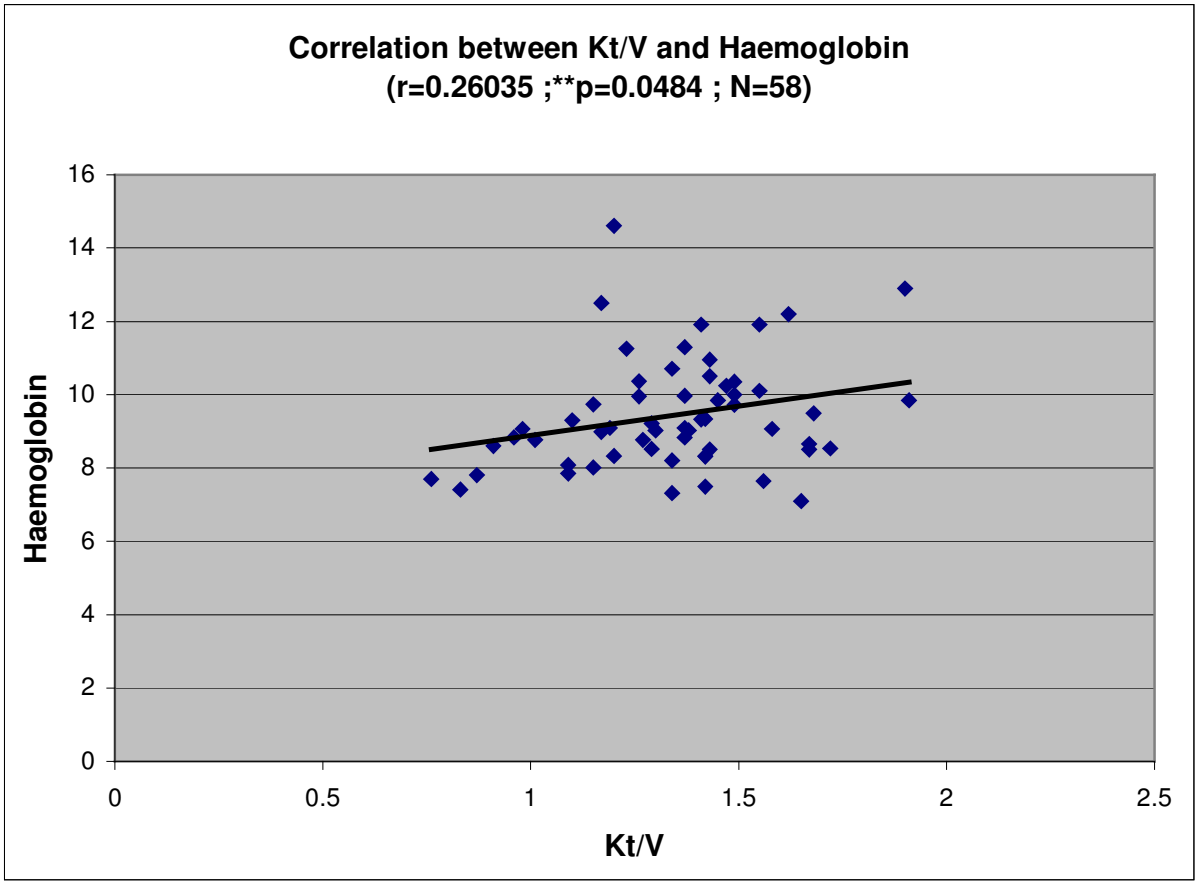
1. **Kt/V** (Urea Kinetic Modelling) DOQI: ≥1.3
2. **URR** (Urea Reduction Ratio) DOQI: ≥70%
3. **nPCR** (Normalised Protein Catabolic Rate) in gram/kg/day (NCDS: ≥0.8).

These parameters, plus signs and symptoms are important indicators for dialysis adequacy and they should be checked monthly (haemodialysis work group recommendation).

3.7. INDICATORS OF DELIVERED DIALYSIS DOSE (Kt/V) AND PATIENT OUTCOMES IN 2003.

3.7.1. Correlation between Kt/V and Haemoglobin (Mean Hb: 9.43±1.51) g/dl

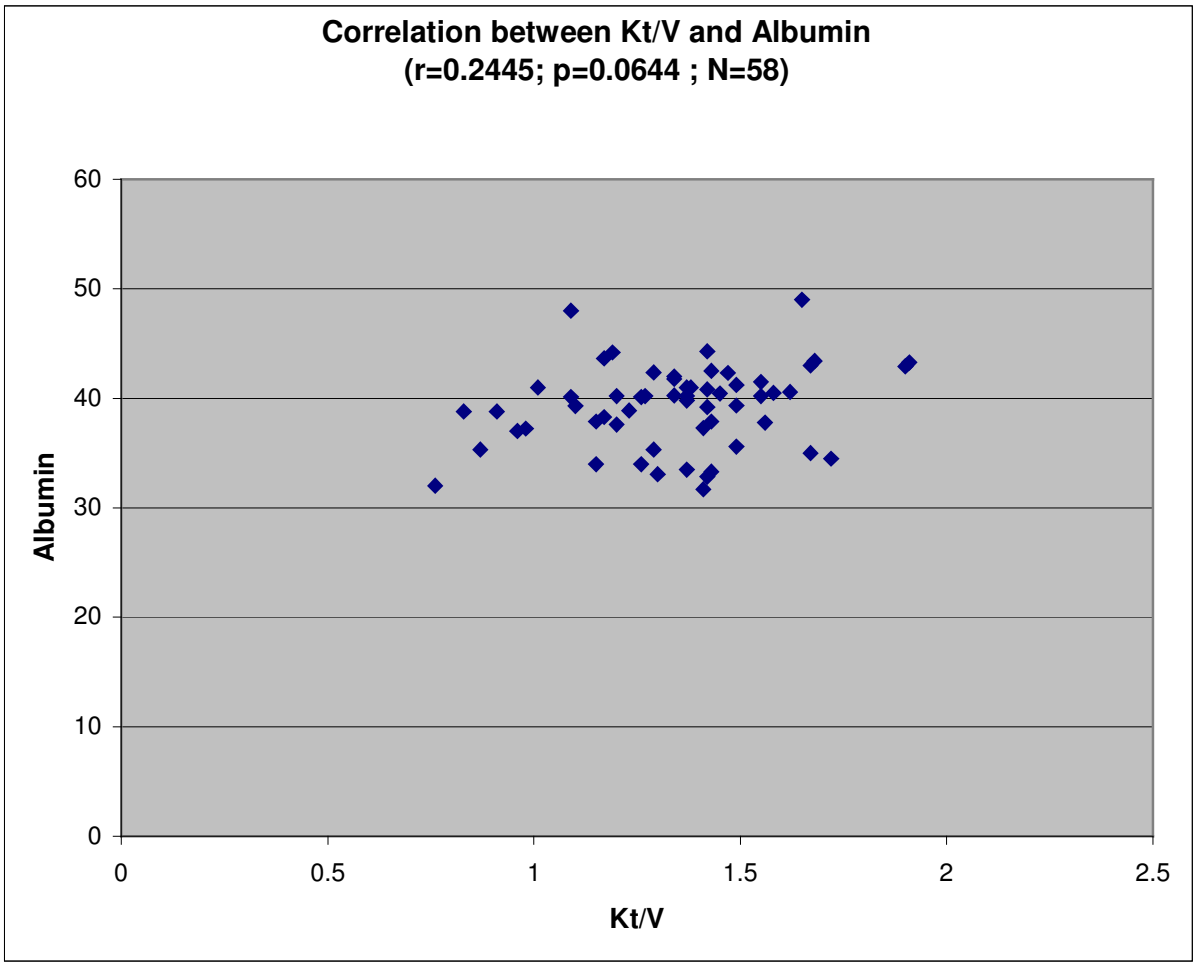
Figure 13 CORRELATION BETWEEN Kt/V AND HAEMOGLOBIN



The correlation between dialysis dose (Kt/V) and Hb is statistically significant ($p<0.05$).

3.7.2. Correlation between Kt/V and Albumin (Mean Albumin: 38.75±4.06) g/l

Figure 14 CORRELATION BETWEEN Kt/V AND ALBUMIN



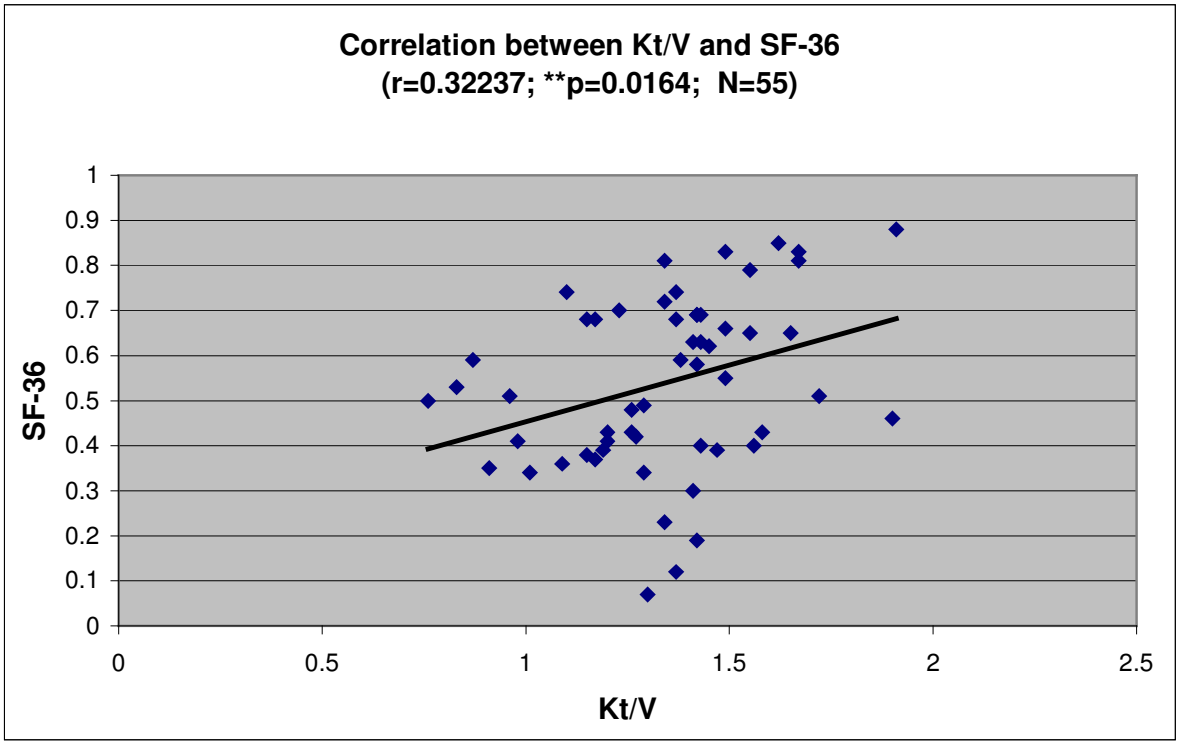
The correlation between dialysis dose (Kt/V) and Albumin was not statistically significant at the 95% confidence level.

3.7.3. Correlation between Kt/V and health related quality of life using questionnaire SF-36.

During this prospective component of the study, three patients had already passed away and 3 others patients had received kidney transplants, and therefore they did not participate in the study.

The SF-36 questions, health related quality of life questions are grouped into eight scales: physical functioning (10 items), role physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role emotional (3 items) and mental health (5 items). See *Appendix 4&5*.

Figure 15 CORRELATION BETWEEN Kt/V AND SF-36

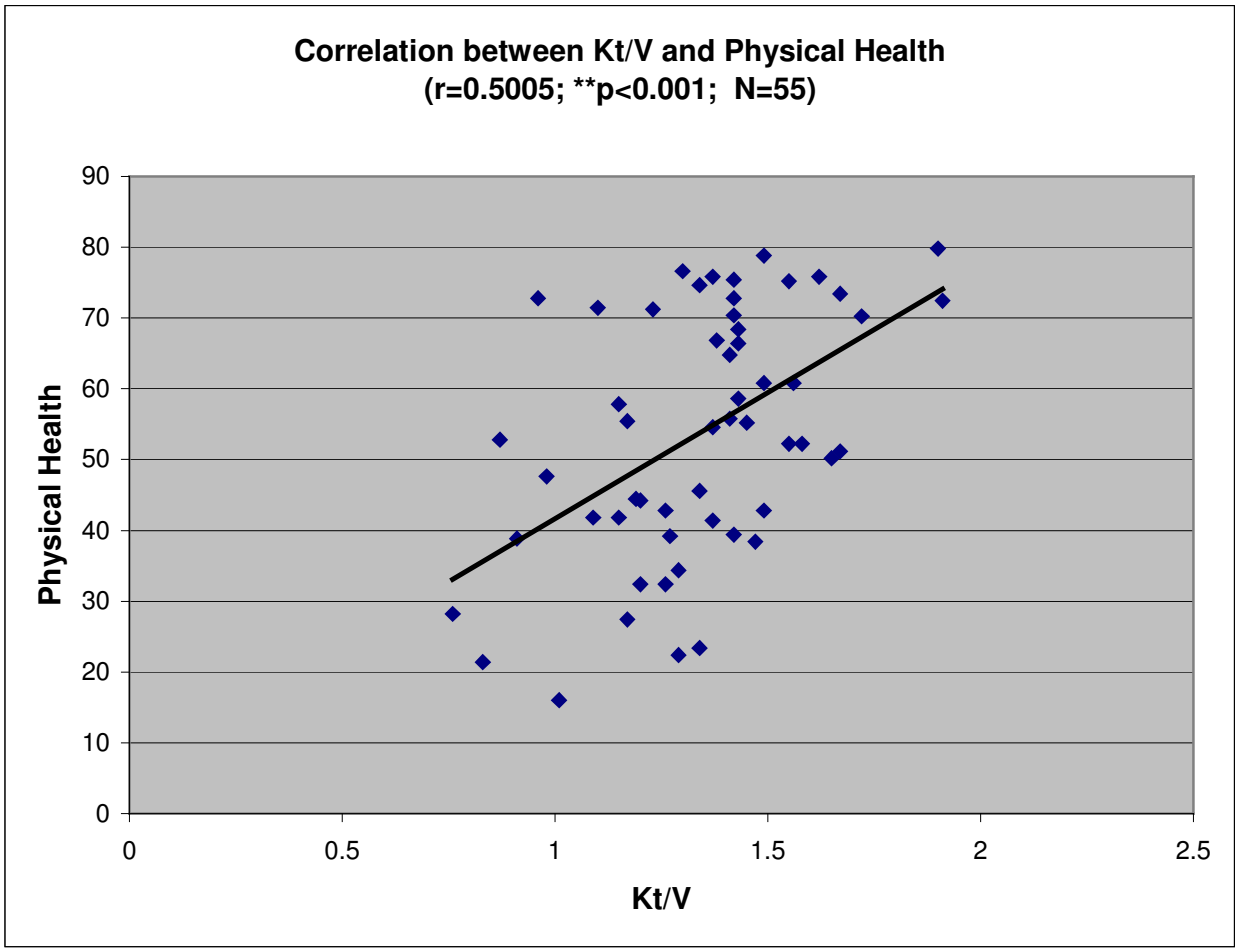


There is a statistically significant correlation ($p<0.05$) between dialysis dose (Kt/V) and SF-36.

3.7.4. Correlation between Kt/V and Physical Health

Physical health is one of the two dimensions with the mental health of the SF-36 and consists of five scales: physical functioning (10-question scale), role physical (4-item scale), bodily pain (2-item scale), vitality (4-item scale), and general health (5-item scale). (See *Appendix 4&5*)

Figure 16 CORRELATION BETWEEN Kt/V AND PHYSICAL HEALTH

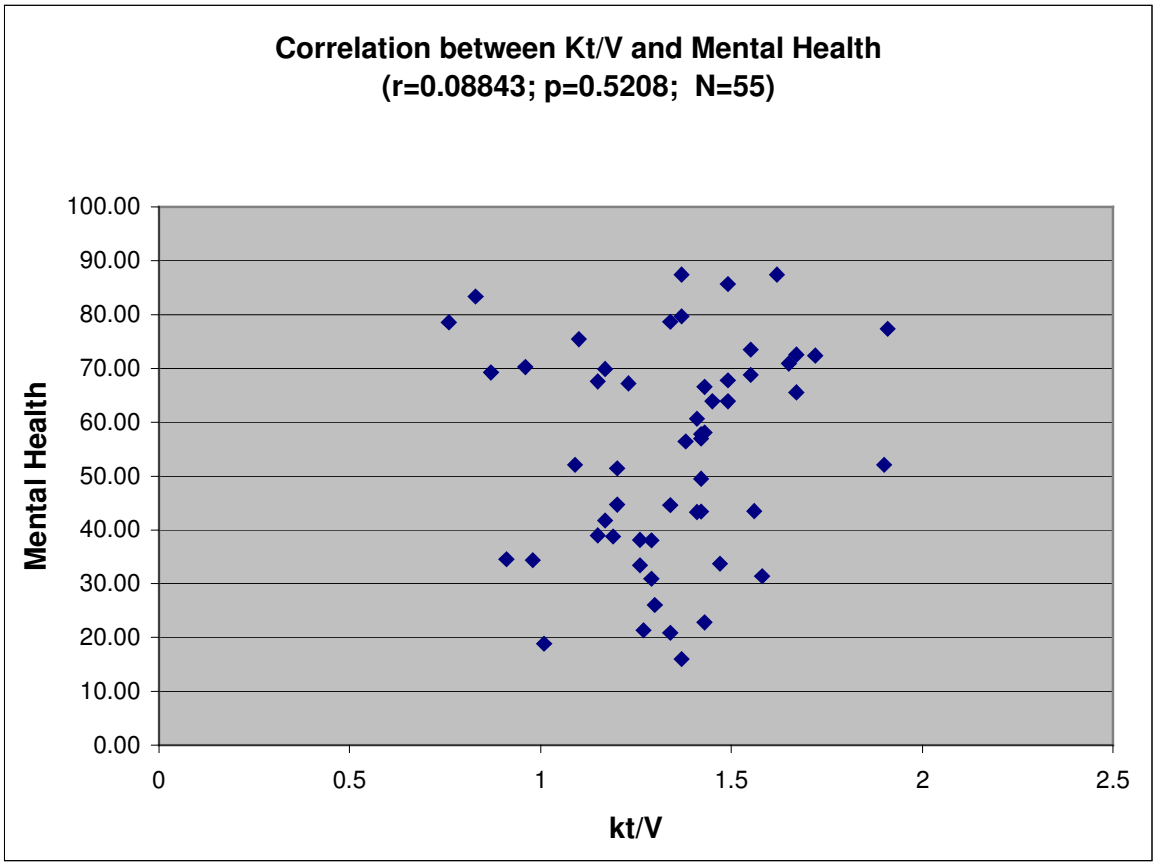


The correlation between dialysis dose (Kt/V) and physical health is statistically significant ($p<0.05$).

3.7.5. Correlation between Kt/V and Mental Health

Mental health is one of the two dimensions of SF-36 together with physical health and it aggregates role-emotional (2 -item scale), mental-health (5 -item scale), general health (5-item scale), vitality (4- item scale), and social functioning (2- item scale).

Figure 17 CORRELATION BETWEEN Kt/V AND MENTAL HEALTH

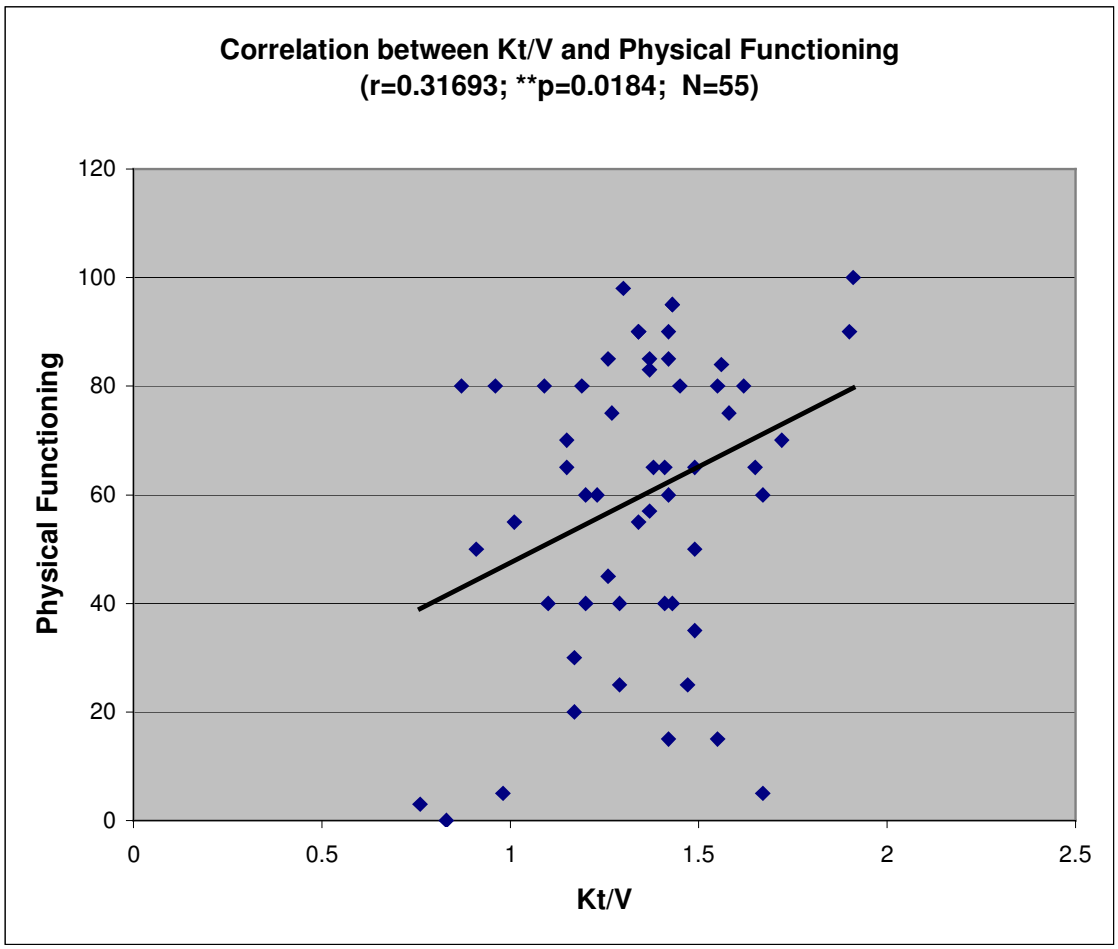


The correlation between the dialysis dose (Kt/V) and mental health was not statistically significant (p=0.5208).

3.7.6. Correlation between Kt/V and Physical Functioning

Physical functioning is one of the 5 scales of physical health; it is a 10-question scale that captures the ability to deal with the physical requirements of life, such as attending to personal needs, walking and flexibility. (See *appendix 4&5*).

Figure 18 CORRELATION BETWEEN Kt/V AND PHYSICAL FUNCTIONING

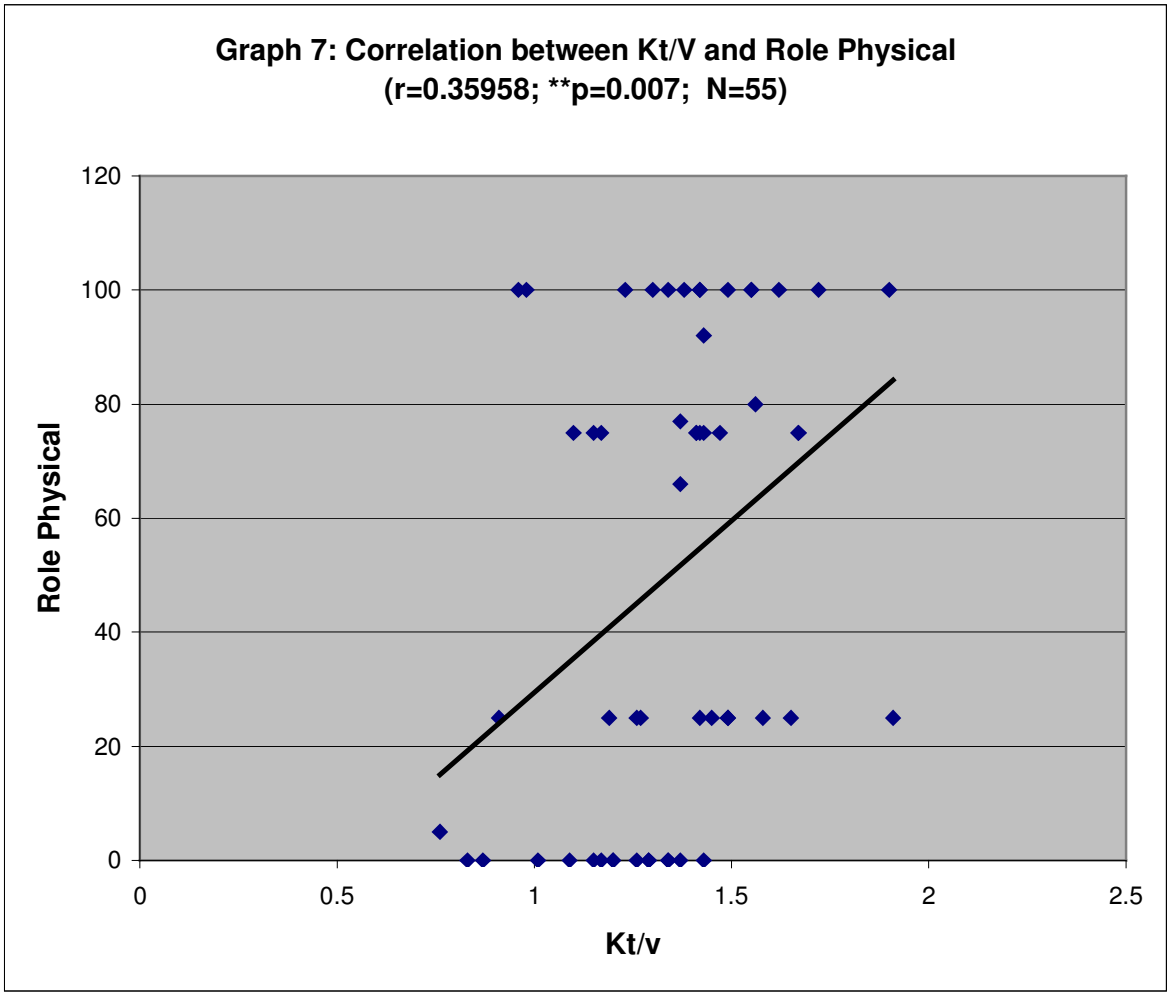


There is a statistically significant correlation between dialysis dose (Kt/V) and physical functioning ($p<0.05$).

3.7.7. Correlation between Kt/V and Role Physical

Role physical is one of the 5 scales of the physical health dimension; it is a 4-item scale that evaluates the extent to which physical capabilities limit activity.(See *appendix 4 &5*).

Figure 19 CORRELATION BETWEEN Kt/V AND ROLE PHYSICAL

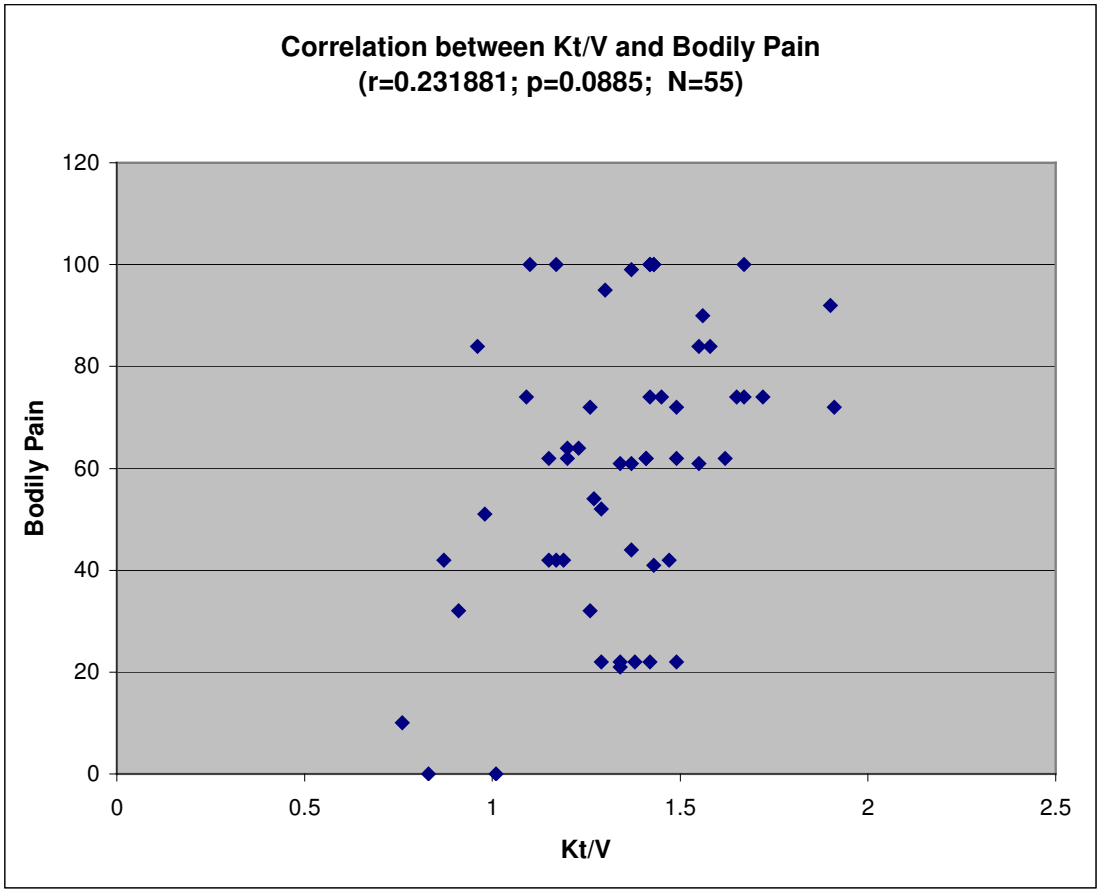


The correlation between dialysis dose (Kt/V) and role physical is statistically significant (p=0.007).

3.7.8. Correlation between Kt/V and Bodily Pain

Bodily pain is one the 5 scales of physical health and it is a 2-item scale that evaluates the perceived amount of pain experienced during the previous four weeks and the extent to which that pain interfered with normal work activities. (See *Appendix 4&5*)

Figure 20 CORRELATION BETWEEN Kt/V AND BODILY PAIN

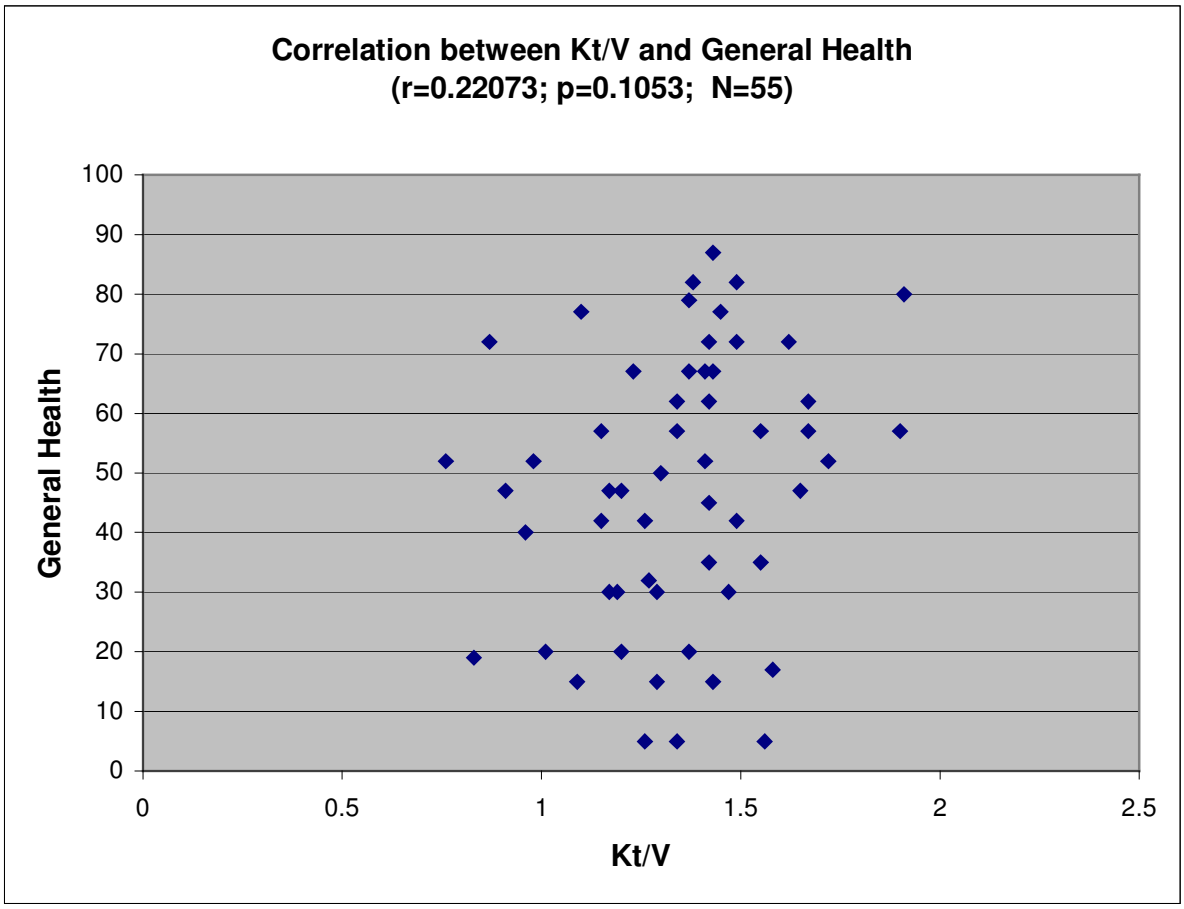


The correlation between the dialysis dose (Kt/V) and bodily pain is not statistically significant (p=0.0885).

3.7.9. Correlation between Kt/V and General Health

General health is one of the two overlapping components of both physical health and mental health dimensions; it is a 5-item scale that evaluates general health in terms of personal perception. (See *Appendix 4&5*).

Figure 21 CORRELATION BETWEEN Kt/V AND GENERAL HEALTH

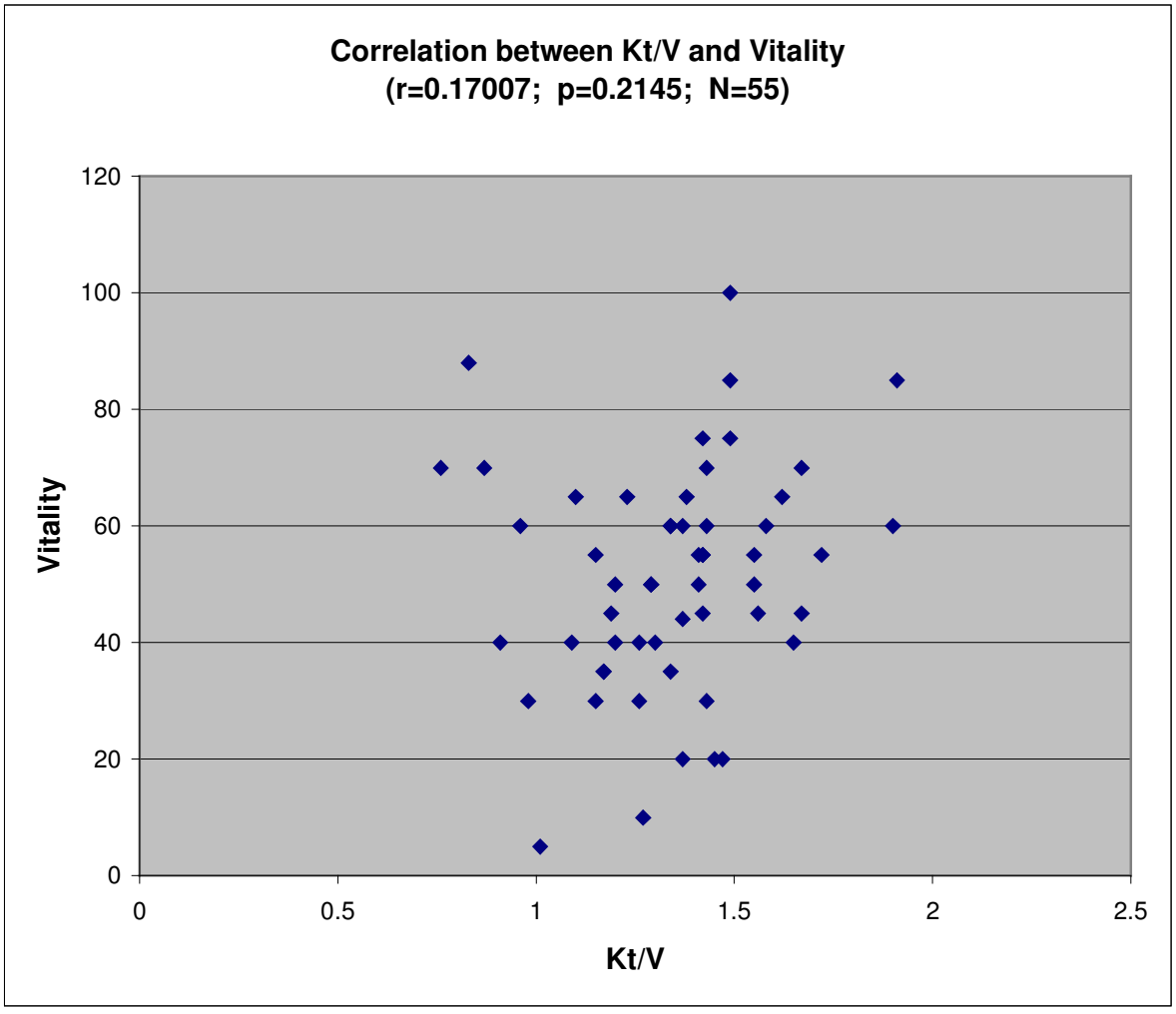


There is no correlation between dialysis dose (Kt/V) and general health (p=0.1053).

3.7.10. Correlation between Kt/V and Vitality

Vitality is one of the overlapping scales of both general health and physical health; it consists of a 4-item scale that evaluates feelings of pep, energy and fatigue. (See *Appendix 4&5*).

Figure 22 CORRELATION BETWEEN Kt/V AND VITALITY

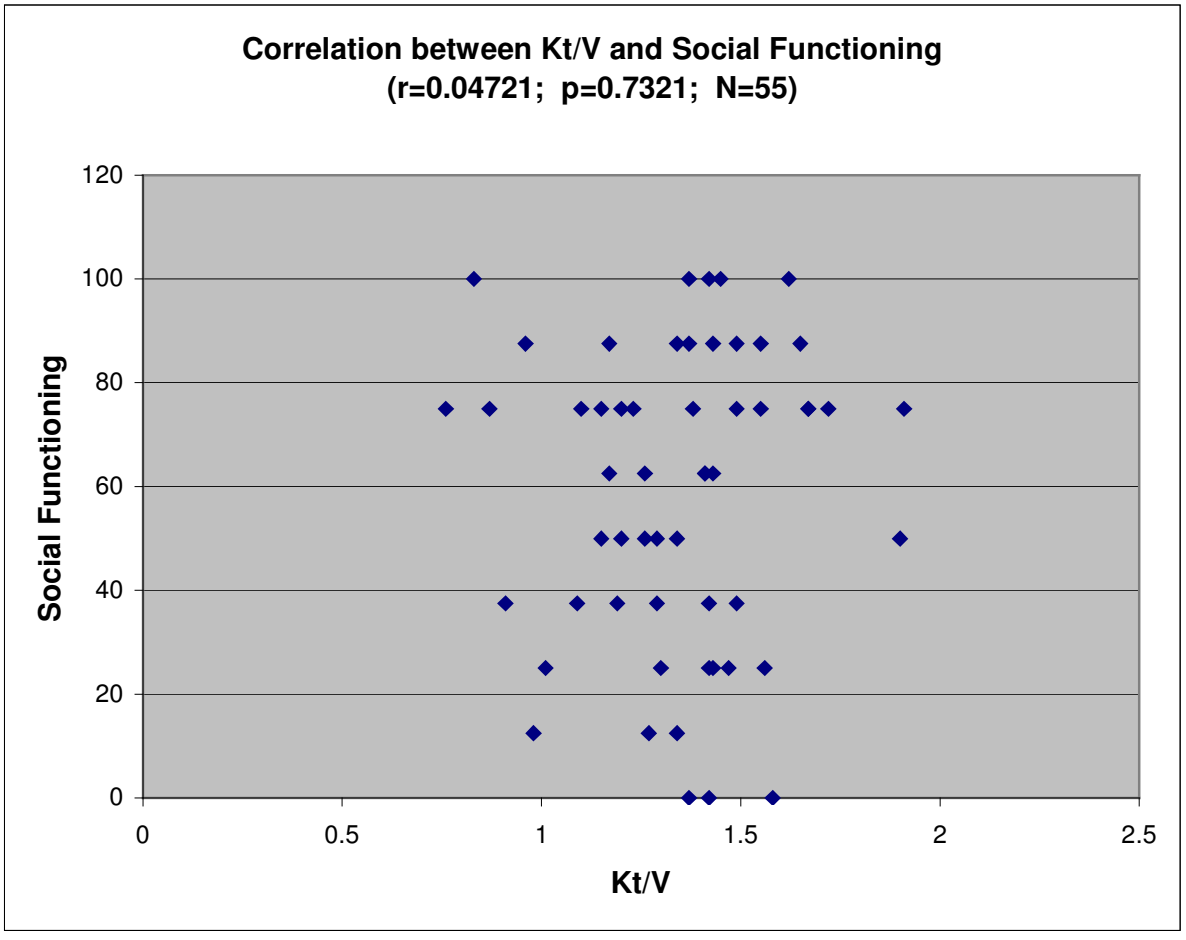


There is no correlation between dialysis dose (Kt/V) and vitality (p=0.2145).

3.7.11. Correlation between Kt/V and Social Functioning

Social functioning is a 2-item scale that evaluates the extent and amount of time, if any, that physical health or emotional progress interfered with family, friends, and social interactions during the previous 4 weeks. (See *Appendix 4&5*).

Figure 23 CORRELATION BETWEEN Kt/V AND SOCIAL FUNCTIONING

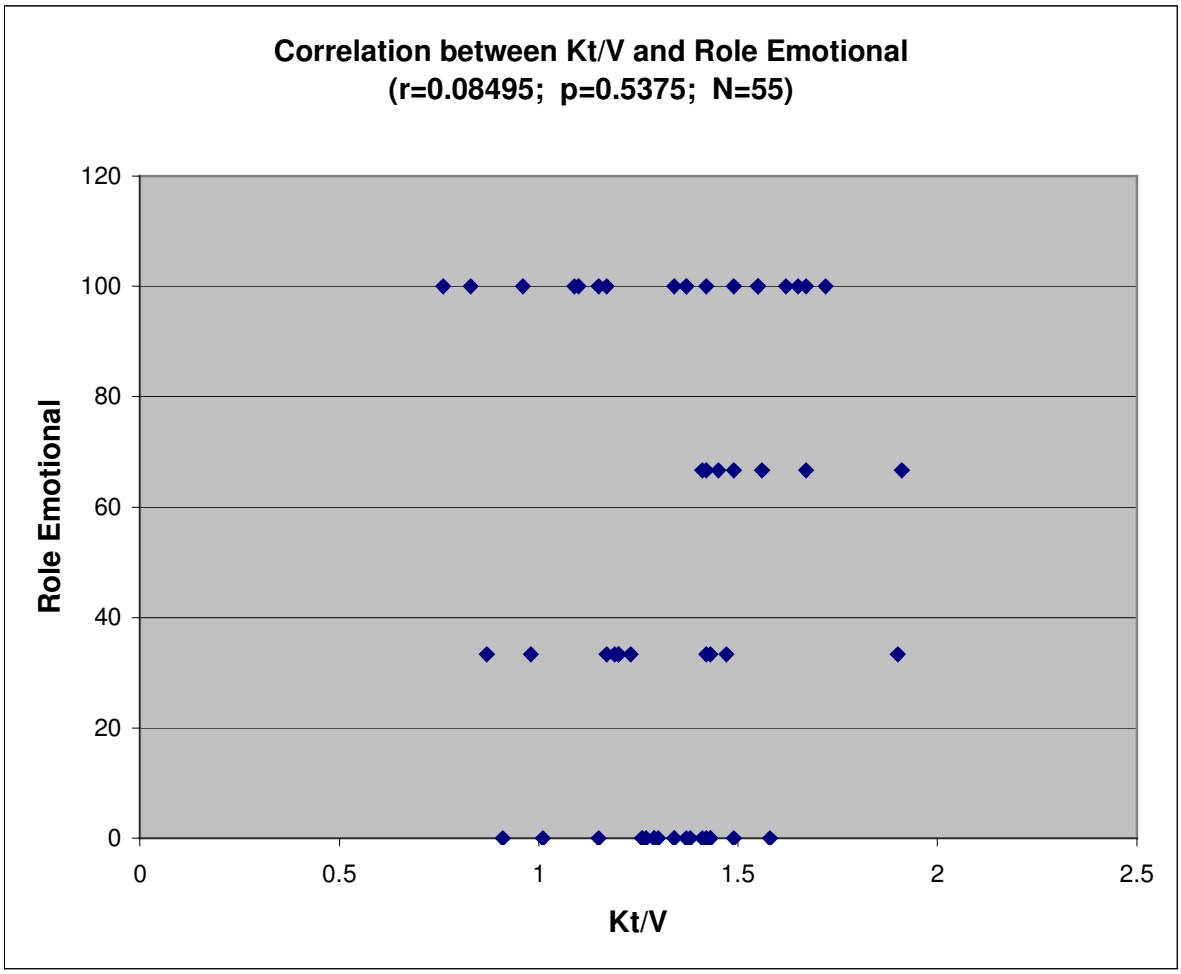


There is no correlation between dialysis dose (Kt/V) and social functioning (p=0.7321).

3.7.12. Correlation between Kt/V and Role Emotional

Role emotional is a 3-item scale that evaluates the extent, if any, to which emotional factors interfere with work or other activities. (See *Appendix 4&5*).

Figure 24 CORRELATION BETWEEN Kt/V AND ROLE EMOTIONAL



There was no correlation between dialysis dose (Kt/V) and role emotional.

3.7.13. Relationship between delivered dialysis dose (Kt/V) and hospitalisation, blood pressure control, sepsis and mortality

3.7.13.1. Kt/V and hospitalisation

The main causes of hospitalisation were sepsis and vascular access creation; there was no statistically significant effect of Kt/V on hospitalisation ($p=0.1534$; T-test).

3.7.13.2. Kt/V and blood pressure control

Hypertension is defined as predialysis blood pressure $\geq$ 140/90 (MAP>106 mmHg) when the patient is believed to be at so-called "dry weight". The effect of Kt/V on pre-haemodialysis blood pressure control was not statistically significant ($p=0.4819$; T-test).

3.7.13.3. Kt/V and sepsis

In 2003, there were in total 25 cases of sepsis and more than 90% were catheter-related sepsis; there was a statistically significant effect of Kt/V on sepsis ($p<0.05$; T-test). In fact the mean Kt/V for patients with sepsis was 1.1809 and mean Kt/V of patients without sepsis was 1.3763.

3.7.13.4. Kt/V and mortality

4 patients on chronic haemodialysis died during 2003. The statistical analysis of the association between Kt/V cannot be performed due to the sample size, which is very small. However, 50% of deaths were caused by vascular access problems and 50% of deaths were caused by sepsis. Overall, all the patients who died were underdialysed, with Kt/V of less than 1.2.

CHAPTER 4. DISCUSSION

4.1. Demographic data and primary renal disease

A total of 61 patients attending chronic haemodialysis at Johannesburg General Hospital in 2003 were included in the study. This number excludes patients on bridging haemodialysis for continuous ambulatory peritoneal dialysis-related complications as well as patients on holiday haemodialysis.

During the study, 4 patients died and 3 patients had received cadaver kidney transplantation and were therefore included in the study for only a certain number of parameters and they were ruled out especially from the prospective components of the study, which are echocardiography and the quality of life assessment using the SF-36 questionnaire. In addition, a certain number of data of the patients' results could not be found.

The number of male patients was slightly higher than that of the female patients on maintenance haemodialysis (52% versus 48%). The mean age of the patients was 40.02 ± 10.79 years. This age of the patients on chronic haemodialysis is different from that of Europe (60.2 ± 15.2 years), Japan (58.6 ± 12.5 years) and USA (60.5 ± 15.5 years) (Goodkin *et al*, 2004); as only those patients who were eligible for kidney transplantation were offered chronic dialysis. The gender difference was also observed in favour of male preponderance: the European haemodialysis population was 58% male versus 62% in Japan and 53% in the United States (Goodkin *et al*, 2004).

Concerning the age difference between our chronic haemodialysis patients in 2003 at Johannesburg Hospital, it is most likely related to stringent selection criteria for our chronic dialysis program, which does not apply in developed countries where the financial

resources are not as limited as in South Africa or in other underdeveloped or developing nations.

As should be expected in South Africa, the majority of patients on maintenance haemodialysis were black-Africans. This is a reflection of several factors:

- The fact that in South Africa, black- Africans constitute the majority of the population: they constitute about 73% of the South African population.
- Hypertension, which is the leading cause of end stage renal disease in the South African black population (Veriava and Milne, 2002) was also the most common cause of ESRD in our study population. This is also the reflection of the statistics derived from the South African Dialysis and Transplantation Registry (SADTR), which stipulates that hypertensive renal disease is clearly the most important cause of ESRD in black South Africans, and malignant as well as non-malignant hypertension is responsible for ESRD (see *Table 9*). It also reports that the three leading causes of ESRD in South Africans are hypertension, glomerulonephritis and unknown aetiology. This is similar to the USA, where hypertension was found to be the most common cause of ESRD in the African-American population (Grundy *et al*, 1999), contributing to 29% of patients with ESRF and is secondary to diabetes mellitus. Overall in the USA and Europe, diabetes was the most common cause of ESRD of patients on MHD, followed by hypertension and glomerulonephritis (Grundy *et al*, 1999).

  The number of patients on MHD with diabetes mellitus as the primary cause of renal disease in our study population was relatively small (7%). This is because of stringent selection criteria for renal replacement therapy and the frequently associated co-morbidities of patients with diabetes mellitus when they reach the stage

for renal replacement therapy such as congestive cardiac failure, ischaemic heart disease, peripheral vascular disease with subsequent vascular access problems, cerebro-vascular diseases such as strokes, and others such as dysautonomia, etc. This study found a significant number of patients on maintenance haemodialysis with ESRD of unknown aetiology (15%). This figure is different from the South African Dialysis and Transplant Registry report (SADTR) of 1998 on the causes of chronic renal failure, which showed that 19.5% of patients with ESRD were of uncertain aetiology.

Table 9 Report of causes of ESRD (SADTR, 1998)

Aetiology	**Percentage**
CRF - Uncertain aetiology	19.5
Glomerulonephritis	23.2
Pyelonephritis	8.0
Drug induced CRF	5.7
Cystic disease	5.5
Hereditary/congenital	1.7
Vascular (includes hypertension)	20.7
Systemic disease	11.8
Other/miscellaneous	4.1

4.2. Dialysis adequacy

Concerning parameters of dialysis adequacy, it was found that most of the patients were reasonably well dialysed, although a significant number of patients on maintenance haemodialysis were underdialysed according to the parameters of dialysis adequacy. See *Table 8* on indicator of dialysis adequacy of adult patients on

chronic haemodialysis at Johannesburg Hospital in 2003. In fact, 74% of our study patients on chronic haemodialysis had a Kt/V ≥ 1.2 and 60% had a Kt/V ≥ 1.3. The K/DOQI recommendation (Rajiv *et al*, 2004) is a Kt/V ≥ 1.3.

Some of the following factors plus a number of comorbid conditions may explain the cases of dialysis inadequacy, which were observed:

1. **Vascular access problems**:

The status of vascular access of the patients on chronic haemodialysis in year 2003 were as follow:

- 61% permanent access (A-V Fistula and Graft)
- 39% temporary catheters.

The problem of vascular access is more likely the result of the fact that most of the patients elected for haemodialysis did not have permanent vascular access at the initiation of haemodialysis. On the contrary, K/DOQI clinical practice guidelines (Rayner *et al*, 2004) for vascular access sets goals of primary AV fistulae being constructed in at least 50% of all new kidney failure patients electing to receive haemodialysis as their initial form of renal replacement therapy and 40% of prevalent haemodialysis patients with a native AV fistula and only less than 10% of chronic maintenance haemodialysis patients being maintained on catheters as their permanent haemodialysis access. In this context, chronic catheter access is defined as the use of a dialysis catheter for more than 3 months in the absence of a maturing permanent access. Furthermore, the study of Rayner *et al* in the Dialysis Outcomes and Practice Patterns Study (DOPPS) has shown that performance against these guidelines varies widely among countries. Japan, Italy, Germany Spain, and France

average more than 75% of their patients dialysing through AV fistulae. In the USA, however, the ratio is 30% fistulae to 42% grafts and around 10% or less of their patients using temporary catheters. The lack of vascular surgery and theatre time has been responsible for inadequate vascular access creation. This is very crucial in view of the K/DOQI vascular access guideline, which recommends referral for vascular access surgery within 1 month of commencing dialysis or when creatinine clearance is less than 25ml/min (Rayner *et al*, 2004).

2. **Poor compliance**: For different reasons, not every patient attended all dialysis sessions as recommended (three sessions per week for four hours each): lack of transport and social problems were the culprits for non-compliance.

3. **Lower than prescribed time of dialysis** especially for complications related to haemodialysis i.e. cramps, symptomatic hypotension, vascular problems during haemodialysis etc.

4. **Type of dialysis membranes**: There were no high flux membranes in the chronic haemodialysis unit in 2003. Although the HEMO Study (Rajiv *et al*, 2004) showed that neither more dialysis nor high-flux filters reduced hospitalisation or deaths among trial participants as a whole, findings for certain groups of patients are intriguing. In fact, the higher dialysis dose appeared to reduce the risk of death and hospitalisation among women and the high- flux filter appeared to reduce the risk of death among patients who had been on haemodialysis for longer than 3,5 years when they entered the study; further study is needed before conclusions can be drawn (Rajiv *et al*, 2004). Similarly to the HEMO study, the first major

National Institute of Health clinical trial for dialysis in more than 20 years, confirms that the minimum dose recommended by treatment guidelines is adequate and that, in general, a higher dose and special filters provide no added benefit to patients.

At this point in time, one is awaiting the conclusions of the membrane permeability outcome study, which is a randomised controlled clinical trial in progress at 9 clinical centres in Europe that has been designed to prospectively evaluate the long-term effect of membrane permeability (i.e. flux) on clinical outcomes such as mortality, morbidity, vascular access survival, and nutritional status.

5. Other important markers of haemodialysis adequacy including associated comorbidities:

5.1 Anaemia

The mean haemoglobin (Hb) was found to be 9.43±1.51 **g/dl** in our patients on chronic haemodialysis. This value is lower than the recommended DOQI guideline, which recommends a Hb of 11g/l to 12g/l and the haematocrit of 33% to 36%. The mean Hb in our study population was lower, compared to other countries: Mean Hb levels were 12g/dl in Sweden; 11,6 to 11,7g/dl in the United States, Spain, Belgium, and Canada; 11,1 to 11,5 g/dl in Australia, New Zealand, Germany, Italy, The United Kingdom, and France; and 10,1g/dl in Japan (Pisoni *et al*, 2004). The factors, which are responsible for the low haemoglobin levels in our patients, compared to the DOQI guidelines and other countries' haemoglobin levels, are the following:

- *Loss of blood due to* gastro-intestinal bleeding is often observed in uraemia; multiple venesections, blood sequestered in the extracorporeal circuit.

- *The lack of consistent supplies of erythropoietin,* which has been a frequent problem in the chronic haemodialysis unit, despite many meetings involving the nephrology unit, the pharmacy and administration of the hospital in order to discuss the problem and to highlight the importance of uninterrupted availability of erthropoietin in patients with ESRD on maintenance haemodialysis.
  Erythropoetin in patients on chronic haemodialysis helps to correct the anaemia, and consequently decreases the rate of cardiovascular complications, especially left ventricular hypertrophy (Ter Arkh, 2004). This issue can partially explain our study finding of patients with LVH (75%). Hypertension is the main risk factor for LVH in dialysis patients, followed by age and anaemia (Stewart GA *et al*, 2004). Moreover, anaemia is a risk factor for LVH, dilated cardiomyopathy and a non-classical risk of ischemic heart disease.
  This is meaningful, in view of our finding that in our study population 21% of patients had uncontrolled pre-haemodialysis blood pressure.

- *Insufficient dialysis dose*: There is good evidence that dialysis adequacy has resulted in better control of anaemia and other parameters correlating with dialysis adequacy such as hypertension and patients' nutritional status (Panagoutsos and Yannatos, 2002). This was not demonstrated in this study.

- *Dialysis membrane*: High- flux haemodialysis membranes were not used in the chronic haemodialysis unit. Evidence has shown that high-flux dialysis use is

effective in controlling renal anaemia and this beneficial effect of high- flux dialysis is probably mediated by the improved clearance of moderate and high molecular weight toxins (Ayli *et al*, 2004).

- *Hyperparathyroidism*: In our study population, according to K/DOQI guidelines, 59% of patients on chronic haemodialysis had hyperparathyroidism (intact PTH ≥ 300pg/ml), whereas 29% had hypoparathyroidism (intact PTH ≤ 150pg/ml). This study has shown that secondary hyperparathyroidism may contribute to inadequate anaemia control, and may result in larger doses of erythropoietin being required or resistance to erythropoetin therapy in haemodialysis patients. The evidence has shown that there was an inverse correlation between intact PTH with haematocrit and haemoglobin levels, and between alkaline phosphatase and haemoglobin (Baradaran and Nasri, 2001). It is suggested that PTH, when present in excessive amounts, interferes with normal erythropoiesis by down-regulating erythropoietin receptors on erythroid progenitor cells in the bone marrow (Sikole, 2000). Furthermore, besides the involvement of serum PTH in anaemia and mineral bone metabolism together with serum phosphorus, calcium, and calcium-phosphorus product, it has been found to participate in other pathologic processes such as cardiovascular abnormalities: cardiac structural diseases, pulmonary hypertension. In fact, adverse effects of secondary hyperparathyroidism on LV function and structure in this study supports the role of excess PTH in the development of left ventricular (LV) hypertrophy as well as low LV ejection fraction in patients with end-stage renal disease on haemodialysis. Hence, PTH needs more stringent control, in order to reduce the risk of cardiovascular morbidity and mortality in haemodialysis patients

(Baradaran and Nasri, 2004). It is most likely that secondary hyperparathyroidism, in concert with hypertension and low haemoglobin levels, has contributed to the magnitude of LVH observed in our patients on chronic haemodialysis. In addition, serum PTH has been proposed to play a role in pulmonary hypertension and in cardiovascular disease (Amin *et al*, 2003). In our study neither Ca x PO_4 product nor calcium and phosphorus had an impact on valvular heart disease ($p>0.05$). Although, with echocardiography results there was no evidence of rheumatic heart valve disease or elements of infective endocarditis as the background, it is important according to Schonenberger *et al* to rule out the role of chronic inflammation in haemodialysis patients with valvular heart disease.

Concerning cardiovascular comorbidity, the study has demonstrated a high prevalence (39.7%) of pulmonary hypertension among patients with ESRD receiving long-term haemodialysis with surgical arteriovenous access (Yigla *et al*, 2003). Both ESRD and long-term haemodialysis via arteriovenous access may be involved in the pathogenesis of pulmonary hypertension by affecting pulmonary vascular resistance and cardiac output (Yigla *et al*, 2003). Moreover, the evidence has shown significant improvement of pulmonary hypertension after ligation of brachiocephalic arteriovenous fistulae (Clarks *et al*, 2002). This may explain our finding of 24% of patients on chronic haemodialysis with pulmonary hypertension. This relatively lower prevalence, compared to the above study of 39,7%, may be secondary to the presence of a significant number of patients on chronic haemodialysis without permanent vascular access (39% of patients without AV fistulae, receiving haemodialysis with temporary catheters). The

study by Unger *et al*, 2004 has shown that closure of large and/ or symptomatic AVF causes long-term regression of LV hypertrophy.

Infection or inflammation: The anaemia in these HD patients is most frequently the result of anaemia of chronic disorder as well as erythropoietin deficiency. In fact studies have proven that these conditions are associated with higher concentrations of proinflamatory cytokines and higher levels of erythropoietin hyporesponsiveness and poor clinical outcome, including a 4-fold increase in mortality, greater hospitalisation rate, and a poor quality of life in maintenance haemodialysis patients (Kalantar-Zadeh *et al*, 2004).

- *Other possible factors causing anaemia in chronic haemodialysis patients*:
  - Iron deficiency, although unlikely in view of the patients' iron status in our study, which is a mean serum ferritin of 567.76±309.93 µg/l, although the presence of infection/inflammation has to be excluded.
  - Vitamin deficiency: B12 and Folate, although unlikely to be the cause of anaemia as the patients on chronic haemodialysis were all on vitamin therapy: B complex, ascorbic acid and Folate.

5.2. Nutritional status

5.2.1 Albumin

The mean plasma albumin level (± SD) for the patients on chronic haemodialysis was 38.75±4.06 g/l**.** This is an acceptable value, comparable with other countries' mean plasma albumin levels: USA (36 g/l), France (38.7 g/l), Italy (39.8 g/l), Spain (37.2 g/l); (Combe *et al*, 2004).

Serum albumin, which is one of the markers of nutrition, is however non-specific, in fact it is a negative acute phase reactant protein and falsely low results can occur in relation to infection or inflammation, decreased protein synthesis secondary to liver disease or urinary losses (albuminuria), and overhydration. In addition, serum albumin is slow to change (the half-life is 20 days).

Despite the above limitations, albumin remains an important indicator of both nutritional status and mortality risk. Evidence has shown that plasma albumin is the single laboratory finding most closely associated with an increased probability of death. The increase in risk is rising modestly at a plasma albumin concentration of 35 to 39 g/l but being much greater at values below 30g/l (Owen *et al*, 1993).

5.2.2 nPCR (normalised Protein Catabolic rate)

The mean nPCR (± SD) of our patients on chronic haemodialysis was 0.82 (±0.20) g/kg/day. This is in concordance with the NCDS recommendation of a minimal nPCR of 0.8/g/kg/day. In comparison to other countries, it is relatively low: USA (1.0 g/kg/day), France (1.12g/kg/day), Spain (1.09g/kg/day), UK (1.03g/kg/day).

5.2.3 BMI (Body Mass Index)

In our study population, only 5% of patients on chronic haemodialysis were underweight (BMI≤18,5kg/m), 65% being in the normal range (BMI between 18,5 to 24,9kg/m), whereas a significant number of patients (30%) belonged to the zone of overweight and obese patients. Fortunately, although obesity confers an increased risk of mortality in the general population, observational studies have shown that high BMI was associated with increased survival in dialysis patients (Kirsten et al.,

2004). Moreover the evidence has shown that there is no positive correlation between BP and increasing BMI in haemodialysis patients (Abdulla *et al*, 2004). In comparison to the mean BMI (± SD) (23.90±5.07 kg/m^2) of our patients on chronic haemodialysis, it was found by DOPPS I that the BMI in France and in Italy is 23.2 and 23.5 kg/m^2 respectively, which is almost equal to our patients' BMI (Combe C. *et al*, 2004).

5.2.4 Plasma cholesterol

Plasma cholesterol levels are lower with ESRD and studies have demonstrated an inverse relationship between mortality and cholesterol concentration (Lowrie and Lew; 1990).

In the context of cardiovascular risk in patients on chronic haemodialysis, the uraemic dyslipidaemic syndrome is characterised by an abnormal lipoprotein profile that results in: an elevation of triglyceride rich lipoproteins, very low density lipoproteins, intermediate density lipoprotein, and a reduction in high density lipoprotein levels. This is very similar to our results where a significant number of patients had hypertriglyceridaemia (TG>1,5mmol/l) and low density lipoprotein cholesterol (>3mmol/l). As also expected, most of the patients (51%) had low HDL cholesterol, and a small number of patients (6%) had a total cholesterol of more than 5 mmol/l.

Yet, paradoxically, evidence has shown that overweight, hypertension, and hyperlipidaemia, which are cardiovascular risk factors in the general population, have been reported to correlate with better patient survival in haemodialysis. This

might be due to the fact that in patients on haemodialysis, the positive effect of higher BMI and hyperlipidaemia but not of hypertension, could be partially explained on the basis of the accompanying better nutrition.

4.3. Dialysis dose (Kt/V) and patient outcomes

4.3.1. Dialysis dose (Kt/V) and haemoglobin

During the study of association between dialysis dose (Kt/V) and haemoglobin, a statistically significant correlation was found between the two parameters ($p<0.05$). This result is supported by the evidence that showed that in patients with end stage renal disease, inadequate haemodialysis is associated with a suboptimal response to erythropoetin therapy. Increasing the intensity of dialysis in patients with anaemia who are receiving inadequate dialysis results in a significant increase in the haematocrit (Ifudu and Friedman, 1996).

4.3.2. Dialysis dose (Kt/V) and albumin

During the study, there was no correlation between Kt/V and serum albumin at a 95% confidence interval, although a correlation was only found at a p-value of 10%. This outcome is more or less the same as the HEMO study about the effect of dialysis dose and membrane flux on nutritional parameters in haemodialysis patients, which showed that while the dose and flux interventions may subtly influence certain nutritional parameters, neither intervention prevented deterioration in nutritional status over time (Rocco *et al*, 2004).

However, other evidence has demonstrated that daily haemodialysis improves nutritional status by increasing serum albumin levels, and arm muscle area (Spanner E. *et al*, 2003). The lack of correlation between dialysis dose and albumin may be related to the fact that albumin may change in different circumstances as it is a negative acute phase reactant. In this matter, the measurement of CRP (as a marker of inflammation) would have helped in reaching a more valid conclusion.

4.3.3. Dialysis dose (Kt/V) and health related quality of life (SF-36)

The SF-36 quality of life scoring system is composed of two dimensions (physical and mental) and each one with 5 scales, each of these with 2 scales, which are overlapping between the two dimensions.

4.3.3.1. Dialysis dose (Kt/V) and physical dimension

The correlation between the dialysis dose and physical dimension, one of the two components of the two dimensions of the SF-36, was statistically significant ($p<0.05$) in 2 of its 5 components and the correlation was also statistically significant ($p<0.05$) between dialysis dose and physical dimension itself which has 5 scales (physical functioning, role physical, bodily pain, general health, vitality). The two scales of the physical health to which the correlation was positive are physical functioning and role physical. It is interesting to find that the correlation was overall statistically significant ($p<0.05$) between dialysis dose and physical health because the correlation was not statistically significant ($p>0.05$) between the dialysis dose and three other scales which are overlapping between physical dimension and mental dimension (bodily pain, general health, vitality).

4.3.3.2. Dialysis dose (Kt/V) and mental dimension

The study did not show any correlation (p>0,05) between the dialysis dose (Kt/V) and any of the scales of mental health (role emotional, general health, vitality, mental health and social functioning). This implies that there are factors other than haemodialysis dose, which influence the mental dimension such as primary renal disease, degree of family support, financial status (transport, nutrition) etc.

4.3.3.3. Dialysis dose (Kt/V) and overall SF-36

Nevertheless, the study demonstrated a positive correlation (p<0.05) between dialysis dose and the overall scoring results of the SF-36.

All of the above results of the association between dialysis dose and the different components can partially be explained by some of the parameters of dialysis adequacy which improve with increase of dialysis dose, such as the serum haemoglobin. In fact, evidence has confirmed that normalisation of haematocrit/ haemoglobin significantly improves the physical and psychosocial dimensions of quality of life and the patient's functional self-sufficiency. In fact, the study by Besarab *et al*, 1998 showed that an increase in haematocrit from 30 to 42% was associated with a clinically meaningful increase of 7,2 points in the score of the physical function scale (Fuesanta *et al*, 2000). This finding is interesting because our study showed a statistically significant correlation between dialysis dose and haemoglobin. This may explain why there was a statistically significant correlation between dialysis dose and physical health in particular and its 2 component scales (physical functioning and role physical). In our study there was a statistically significant correlation between dialysis dose and the physical component scale (PCS).

The above results imply meaningful clinical implications, according to DOPPS data which suggest that the HRQOL measures, particularly physical component scale (PCS), have a greater capacity to identify patients at risk for death and hospitalisation than serum albumin, which has been recognised as a key marker of risk of death among dialysis patients. Moreover, HRQOL predicts both shorter- term and longer- term outcomes. In the same context of DOPPS results, regardless of whether or not the relationship is causal, the data indicates that HRQOL can serve as a sensitive indicator of subsequent patient mortality and morbidity (Mapes *et al*, 2004). Obviously, if the relationship is causal, then interventions that can improve HRQOL might also effectively decrease the risk of death and prevent other adverse outcomes in haemodialysis patients.

However, the study Morton *et al*, 1996 showed that there is no statistically significant association between the dialysis dose (expressed by Kt/V) and any of the domains of HRQOL. Thus, HRQL seems to be influenced by factors other than dialysis adequacy, enhancing its role as an independent measure of patient problems otherwise undetected by traditional objective parameters (Morton *et al*, 1996).

4.3.3.4. Dialysis dose (Kt/V) and other parameters: hospitalisation, sepsis, hypertension

There was no correlation between dialysis dose ($p>0.05$) and hospitalisation, despite evidence which showed that underdialysed patients have a higher hospitalisation and mortality rate (Obialo *et al*, 1998). Nevertheless, there was a statistically significant correlation between dialysis dose (Kt/V) and sepsis, which was among the two main causes of hospitalisation in our patient population study. Statistical analysis of the correlation between dialysis dose and mortality was not possible in view of the small number of deaths

during our study period (4 patients), although, all the patients who passed away had inadequate dialysis (Kt/V < 1.2).

Our study of the relationship between dialysis dose and outcomes are not different from that of the HEMO study findings, which showed that patients who received a dialysis dose higher than the recommended minimum or who used high-flux filters neither lived longer nor stayed out of the hospital more than people who received the standard dose or used low-flux filters (Rajiv *et al*, 2004). Obviously, it is not easy to compare the results of the HEMO study with our study, because of a significant number of our patients with lower than the standard recommended dialysis dose (Kt/V <1.2). At the same time, we did not show an effect of dialysis dose on blood pressure control ($p>0.05$). This differs from other studies which showed that increased dialysis dose results in both clinical and laboratory improvement regarding hypertension, nutritional status and control of HD patients' anaemia (Panagoutsos *et al*, 2002).

CHAPTER 5.CONCLUSION

- Using the urea kinetic modelling, the indicators of dialysis adequacy on patient on chronic haemodialysis in year 2003 were acceptable. In fact the mean delivered dialysis dose Kt/V was 1.34 ± 0.25 (K/DOQI recommends a minimum of Kt/V = 1.3).
- There are factors responsible for the insufficient delivered haemodialysis dose which should be improved, like permanent vascular access creation (AV fistula, graft), compliance.
- The other way to improve Kt/V would be either by increasing K (clearance), or t (dialysis session length).
- Considering some of the pertinent laboratory markers of dialysis adequacy, our study found a relative low mean value of Hb (9.43 ± 1.51 g/dl). This result should be improved by ensuring regular supplies of erythropoietin and also by providing a sufficient dialysis dose ($Kt/V \geq 1.3$) for most of the patients on chronic haemodialysis.
- The other important findings from our study which proves the importance of dialysis adequacy was the relationship between dialysis dose and the following parameters outcomes:
    - The correlation between dialysis dose and Hb was statistically significant ($p<0.05$).
    - At the same time the correlation was also statistically significant between dialysis dose and the following markers of quality of life in patient on chronic haemodialysis:

- Physical dimension
- Physical functioning
- Role physical
- Vitality
- SF-36 overall results

♦ In addition, the study found the following associations to be statistically significant ($p<0.05$):
  - Dialysis dose (Kt/V) and sepsis
  - Valvular heart disease and duration of haemodialysis
  - Hypertension and diastolic dysfunction, which is a well-known association.

♦ It is important to note that all the patients who passed away (4), were underdialysed with a Kt/V < 1.2.

♣ In view of all above results of dialysis adequacy and patient outcomes, it is important to regularly measure the parameters of dialysis adequacy in order to assess whether targets are achieved in accordance with DOQI guidelines, in an effort to achieve improved long term outcomes in patients on chronic haemodialysis.

♣ Nevertheless, in view of many contradictions in the studies of dialysis dose and related outcomes, randomised multicentre studies are needed for the purpose of reviewing the actual guidelines objectively.

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APPENDICES

APPENDIX 1. ETHICS APPROVAL

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Jules

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M040325**
PROJECT outcomes	Impack of Haemodialysis adequacy on patient
INVESTIGATORS	Dr K Jules
DEPARTMENT	Dept of Medicine
DATE CONSIDERED	04.03.26
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 04.05.03 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof S Naicker

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

12.03.2004

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2. PATIENT INFORMATION SHEET.

STUDY TITLE: IMPACT OF DIALYSIS ADEQUACY ON PATIENT OUTCOMES.

Hello, my name is Dr KABAHIZI JULES, I am training to be a specialist in the Department of Medicine at Wits University.
I am doing a MMed program, as a part of my training; I am carrying out a study on the impact of the amount of dialysis on patient outcomes, such as well being, and hospitalisation.

The research involves asking you some questions about your general health, especially with regards to the impact of dialysis treatment on your quality of life. The questionnaire will take approximately 10 minutes to complete. In addition, I will use the blood results obtained from your routine blood tests. The test results and your answers to the questions will be kept confidential. These results will be used for my study without disclosing your identity.

I invite you to take part in the above study. The participation is voluntarily and you are free to agree or refuse to participate. Your treatment will in no way be prejudiced if you refuse to participate.

I thank you for your participation, as this study would not be possible without your contribution.

Dr KABAHIZI JULES (Principal investigator)

Prof. S NAICKER (Supervisor)

APPENDIX 3. CONSENT FORM

I hereby agree to participate in the study entitled: IMPACT OF DIALYSIS ADEQUACY ON PATIENT OUTCOMES.

I have read and fully understood the contents of the patient information sheet. I understand that the participation in this study is voluntary, and that the results of the study are confidential and they may be used for publication.

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Name of patient	Date	Signature

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Name of researcher	Date	Signature

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Name of witness	Date	Signature

APPENDIX 4. Short form 36 Quality of life scales and dimensions.

ITEMS	SCALES	Dimensions
3. Vigorous activities	Scale 1: Physical Functioning (PF)	Dimension A: PHYSICAL HELTH
4. Moderate activities		
5. Lift, carry groceries		
6. Climb several flights		
7. Climb one flight		
8. Bend, kneel		
9. Walk mile		
10. Walk several blocks		
11. Walk one block		
12. Bathe, dress		
13. Cut down time	Scale 2: Role-Physical (RP)	
14. Accomplished less		
15. Limited in kind		
16. Had difficulty		
21. Pain-magnitude	Scale 3: Bodily Pain (BP)	
22. Pain-interfere		
1. General health rating	Scale 4: General Health (GH)	
36. Excellent		
34. As healthy as anyone		
33. Sick easier		
35. Health worse		
23. Pep/life	Scale 5: Vitality (VT)	
27. Energy		
29. Worn out		
31. Tired		
32 Social-extent	Scale 6: Social Functioning (SF)	
20. Social-time		
17. Cut down time	Scale 7: Role-Emotional (RE)	
18. Accomplished less		
19. Not careful		
24. Nervous	Scale 8: Mental Health (MH)	Dimension B: MENTAL HEALTH
25. Down in dumps		
26. Peaceful		
28. Blue/sad		
30. Happy		
2. Change in reported health		

Note that the vitality and general health scales are overlapping components of both physical health and mental health dimensions. Question 2 does not belong to any score, dimension, or the total SF-36 scores. It is a self-evaluation of change in health during the past year.

APPENDIX 5. Health Survey for Dialysis Patients (SF36)

Today's Date:_____

Name: Last:_____ First: _____ Date of Birth: _____

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer these questions by "check-marking" your choice. Please select only one choice for each item.



1- In general, would you say your health is:

1. Excellent 2. Very good 3. Good 4. Fair 5. Poor





2- Compared to ONE YEAR AGO, how would you rate your health in general NOW?

1. MUCH BETTER than one year ago.
2. Somewhat BETTER now than one year ago.
3. About the SAME as one year ago.
4. Somewhat WORSE now than one year ago.
5. MUCH WORSE now than one year ago.





3- The following items are about activities you might do during a typical day. **Does your health now limit you** in these activities? If so, how much?

Activities	**1. Yes, Limited A Lot**	**2. Yes, Limited A Little**	**3. No, Not Limited At All**
a) **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all
b) **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all
c) Lifting or carrying groceries?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all
d) Climbing **several flights** of stairs?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all
e) Climbing **one** flight of stairs?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all
f) Bending, kneeing or stooping?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all
g) Walking **more than a mile**?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all
h) Walking **several** blocks?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all
i) Walking **one** block?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all
j) Bathing or dressing yourself?	1. Yes, limited a lot	2. Yes, limited a little	3. No, not limited at all

4- During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities *as a result of your physical health*?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	1. yes	2. No
b) **Accomplished less** than you would like?	1. yes	2. No
c) Were limited in the **kind** of work or other activities?	1. yes	2. No
d) Had **difficulty** performing the work or other activities (for example it took extra effort)?	1. yes	2. No

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	1. yes	2. No
b) **Accomplished less** than you would like?	1. yes	2. No
c) Didn't do work or other activities as **carefully** as usual?	1. yes	2. No



6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely

7. How much **bodily pain** have you had during the **past 4 weeks**?

1. None 2. Very mild 3. Mild 4. Moderate 5. Severe 6. Very severe

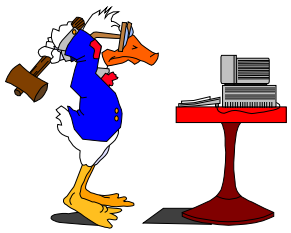


8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question , please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 week** …

	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
a) Did you feel full of pep?	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
b) Have you been a very nervous person?	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
c) Have you felt so down in the dumps that nothing could cheer you up?	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
d) Have you felt calm and peaceful?	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
e) Did you have a lot of energy?	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
f) Have you felt downhearted and blue?	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
g) Do you feel worn out?	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
h) Have you been a happy person?	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
i) Did you feel tired?	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time

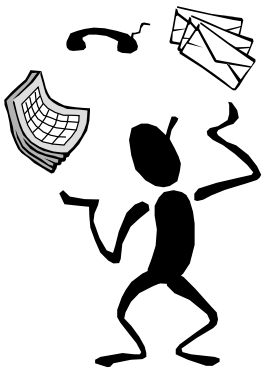


10. During the **past 4 weeks**, how much of the time has your **<u>physical health</u> or <u>emotional problems</u>** interfered with your social activities (like visiting with friends, relatives, etc.)?

1. All of the time
2. Most of the time.
3. Some of the time
4. A little of the time.
5. None of the time.







11. How TRUE or FALSE is **each** of the following statements for you?

	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
a) I seem to get sick a little easier than other people?	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
b) I am as healthy as anybody I know?	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
c) I expect my health to get worse?	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
d) My health is excellent?	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false



Thank you! ❤