



The impact of dialysis therapy on metabolic syndrome traits at the Groote Schuur Hospital

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Marilyn Jacqueline Maree

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Supervisor: Prof. JK Adam

Joint-supervisor: Dr. IG Okpechi

AUTHORS DECLARATION

I, Marilyn Jacqueline Maree, hereby declare that the research described herein was performed by me with the assistance of my supervisors, Professor JK Adam and Dr. IG Okpechi. Neither the whole thesis nor any part thereof has been, is being or will be submitted by me for any other degree at this or any other Tertiary Institution. Where use of the work of others was made, it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Department of Clinical Technology, Faculty of Health Sciences, Durban University of Technology under the supervision of Professor J.K. Adam and in the renal unit, Groote Schuur Hospital, Cape Town, South Africa under the supervision of Dr. IG. Okpechi, Department of Medicine, University of Cape Town.

I hereby certify that the above statement is correct.

SIGNED:.....

Date:.....

Ms M J MAREE

SIGNED:.....

Date:.....

PROF J K ADAM

(M Med Sc, HED, D Tech)

SIGNED:.....

Date:.....

Dr I.G. OKPECHI

(MB;BS, FWACP, PhD, Cert Nephrol (SA) Phys)

DEDICATION

I dedicate this work to:

My heavenly Father, the Lord Jesus Christ who has been my hope and strength through this project and who has proven once again that with Him all things are possible.

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ABSTRACT

Background

The metabolic syndrome (MS) is a clustering of cardiovascular (CV) risk factors and is noted to be increasing globally. Several studies have shown a link between the MS, chronic kidney disease (CKD) and end-stage renal disease (ESRD) possibly through a process of inflammation. Dialysis therapy may increase inflammation and could worsen MS and increase CV risk and diseases in ESRD patients. ESRD has been associated with increased CV disease in dialysis patients. Although there have been several reports on the prevalence of MS from the general population as well as from other specific groups, there are no known studies in South Africa on the prevalence of MS in ESRD patients on chronic dialysis therapy. The prevalence and risk factors for CV diseases are also currently unknown in the dialysis population in Cape Town.

Aim

The aim of this study was to determine the prevalence of MS in the dialysis population at Groote Schuur Hospital in Cape Town, to determine the effect of dialysis on MS and its traits and to evaluate CV risk in this patient group.

Methods

A total of 143 prevalent chronic dialysis patients who consented were used for this study. Demographic and relevant clinical details including systolic and diastolic blood pressures, waist and hip circumference and body mass index were obtained from all patients. Blood was drawn in the fasting state for assessment of full lipogram, glucose, ferritin, iron, calcium and phosphate. The metabolic syndrome was defined using the Adult Treatment Panel III (ATPIII) criteria. To determine the impact of dialysis on MS and its traits in our patients, only incident (new) patients starting dialysis were followed up for assessment of MS traits at timed intervals (at baseline, at 6 months and at 12 months) following initiation of chronic dialysis. To evaluate CV risk in this study, common traditional CV risk factors were assessed and were stratified according to number of risk factors as low (≤ 1), moderate (2 – 4) or high (≥ 4). Relevant statistical methods were used for analysis.

Results

Of the 143 patients in the study, 67.8% were on haemodialysis (HD) and 32.2% were on peritoneal dialysis (PD). The mean age of all the patients was 38.5 ± 10.4 years. The MS was present in 37.1% of all patients (PD – 52.2%, HD 29.9%; $p = 0.015$) and the frequency of increased waist circumference and hypertriglyceridaemia were significantly higher in PD patients than HD patients ($p < 0.0001$ and $p = 0.006$ respectively). Hypertension was the most prevalent MS trait in all the patients (89.5%) and was also the most prevalent trait in males (92.4%), females (85.9%) and in HD and PD patients (91.3% and 88.7% respectively). The frequency of CV risk was 3.5, 75.5 and 21.0% respectively for low, moderate and high CV risk and there was no difference in CV risk in HD and PD patients. High CV risk correlated with body mass index (BMI), increased waist circumference (WC), hyperphosphataemia, raised calcium – phosphate product, raised parathyroid hormone (PTH) and elevated C-reactive protein ($p < 0.05$). There was no significant change in MS prevalence or prevalence of MS traits in patients who were followed up irrespective of gender or modality of dialysis ($p > 0.05$)

Conclusion

The prevalence of the MS is higher in dialysis patients compared to the general population in South Africa and among dialysis patients, the prevalence is higher in PD than HD patients. Patients with MS have significantly higher CV risk factors than those without MS. Although dialysis therapy appear to have no significant effects on the prevalence of the MS or its traits in this study, the increased prevalence of the MS and CV risk factors may be related to the underlying disease process associated with ESRD. There is therefore an urgent need to identify and treat dialysis patients with the MS in order to reduce CV morbidity and mortality in this group of patients. Further prolonged prospective studies are needed to clarify the impact of dialysis on the MS and its traits in the ESRD population.

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LIST OF ABBREVIATIONS

ADA	American Diabetic Association
ANOVA	Analysis of variance
ARF	Acute renal failure
ATP III	Adult Treatment Panel (III)
BMI	Body mass index
BP	Blood Pressure
CAPD	Continuous ambulatory peritoneal dialysis
CHOICE	Choices for Healthy Outcomes in Caring for ESRD
CKD	Chronic kidney disease
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECM	Extracellular matrix
EGIR	European Group for the Study of Insulin Resistance
EPO	Erythropoietin
ESRD	End stage renal disease
FA	Fatty Acids
FBG	Fasting blood glucose
FFA	Free fatty acids
FSGS	Focal segmental glomerulosclerosis
G3P	Glycerol-3-phosphate
GFR	Glomerular filtration rate
GLUT-1	Glucose Transporter-1
GOD	Glucose oxidase
GSH	Groote Schuur Hospital
HC	Hip circumference
HD	Haemodialysis
HDL	High density lipoprotein
HOMA	Homeostasis model assessment

HREC	Human Research Ethics Committee
hs-CRP	High sensitivity CRP
HTN	Hypertension
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IKK β	I κ B kinase beta
IL-6	Interleukin 6
IR	Insulin resistance
JNK	Jun kinase 1
K/DOQI	Kidney Disease Outcomes Quality Initiative
LAE	Left atrial enlargement
LDL	Low density lipoprotein
LVH	Left ventricular hypertrophy
MCV	Mean cell volume
MS	Metabolic syndrome
NCEP	National cholesterol education program
NEFA	Non-esterified fatty acids
NF- κ B	Nuclear factor kappa B
NHANES	National Health And Nutrition Examination Survey
NHLS	National Health Laboratory Service
NKF	National Kidney Foundation
ORG	Obesity related glomerulopathy
PD	Peritoneal dialysis
PEG	Polyethylene glycol
PKC-theta	Protein kinase C-theta
POD	Peroxidise
PPMP	Patients per million population
PTFE	Polytetrafluoroethylene
PTH	Parathyroid hormone
RAAS	Renin-angiotensin-aldosterone system
RRT	Renal replacement therapy
SADTR	South African Dialysis and Transplant Registry

SANAS	South African national accreditation system
SBP	Systolic blood pressure
SNS	Sympathetic nervous system
SPSS	Statistical Package for the Social Sciences
SSA	Sub-Saharan Africa
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
TGF- β 1	Transforming growth factor- β 1
TIBC	Total iron binding capacity
TNF- α	Tumor necrosis factor - alpha
USRDS	United States Renal Data Systems
VLDL	Very low-density lipoproteins
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-hip ratio

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CHAPTER 1

INTRODUCTION

It is estimated that over 1 billion people worldwide are overweight, more than 300 million of whom are clinically obese (WHO, 2003). In the United States, > 60% of adults are overweight or obese, and the number of obese children and adolescents is dramatically increasing. Given its high and increasing prevalence, obesity is considered to be at pandemic levels (Ginsberg and MacCallum, 2009). Obesity is the major propeller of the global increase in type 2 diabetes mellitus (T2DM), and in the past decade has joined malnutrition and infectious diseases as a major health problem facing developing countries (Haslam and James, 2005). Obesity is also a major risk factor for the development of the metabolic syndrome (MS) which is a clustering of CV risk factors. The increasing worldwide prevalence of obesity has been paralleled by a global increase in the number of people with T2DM and MS.

The magnitude of the problem of CKD is enormous, and the prevalence of kidney failure is rising. According to several reports, CKD has emerged as a worldwide public health problem, with major economic implications to the patient and society (Ulas and Ijoma, 2010). In the US, as many as 26 million adults may have CKD, an increase from approximately 10% of the US adult population between 1988 and 1994 to over 13% just one decade later (Coresh et al., 2003 and Coresh et al., 2007). Similar rates have been seen worldwide, with CKD prevalence of 13% in Beijing, China (Zhang et al., 2008) and 16% in Australia (Chadban et al., 2003). Chronic kidney disease is a major contributor to the huge cost of healthcare provision for patients affected by this disease. The cost of care of CKD patients includes not only the direct cost of dialysis and transplantation services, but also indirect costs such as man hours lost at the workplace (Naicker, 2010). Chronic kidney disease is also a major determinant in the progression of accelerated atherosclerosis, ischaemic vascular disease and CV death. Individuals with even the earliest signs of CKD are at increased risk of cardiovascular disease (CVD) and may die long before they reach ESRD (Murussi et al., 2007). The impact of CKD is, therefore, not limited to an increased demand for renal replacement therapies (RRT).

The prevalence of CKD stages 3 to 5 (Table 1), which has been addressed in several studies, differs from country to country and among ethnic groups worldwide. Chronic kidney disease affects mainly young adults aged 20 – 50 years in Sub-Saharan Africa (SSA) and is primarily due to hypertension and glomerular diseases, unlike in developed countries where CKD presents in middle-aged and elderly patients and is predominantly due to diabetes mellitus and hypertension (Fogazzi *et al.*, 2003).

Table 1: Stages of Chronic Kidney Disease (K/DOQI, 2002).

Stage	Description	GFR (mls/min/1.73m ²)
1	Kidney damage with normal or increased GFR	≥ 90 with the presence of a structural abnormality of the kidney or persistent albuminuria
2	Kidney damage with mild decreased GFR	60 – 89
3	Moderate decrease in GFR	30 – 59
4	Severe decrease in GFR	15 – 29
5	Kidney Failure	≤15 or requires dialysis

Cardiovascular diseases are a major cause of morbidity and mortality in patients with CKD and ESRD (Gosmanova and Le, 2011). Although several CV risk factors have been associated with CKD, those that have been postulated to be particularly relevant to CKD include malnutrition/low serum albumin, anaemia, hyperhomocysteinemia, elevated fibrinogen, dysregulated calcium/phosphorus, oxidative stress and various inflammatory factors. Oxidative stress and inflammation have recently gained considerable support as factors relevant in CV diseases in the setting of CKD (Yamamoto and Kon, 2009). These inflammatory risk factors may be abnormal in patients with the MS. Patients with CKD are also known to be affected by diabetes, hypertension, and obesity which are known as traditional CVD risk factors in the general population. Some of these risk factors interact with each other in the pathogenesis of CVD, i.e. fluid overload worsens hypertension and increased oxidative stress enhances inflammation. These risk factors along with others make up the so called “metabolic syndrome” which is highly prevalent in many affluent

societies and has been associated with an increased risk of CKD and various forms of CVD (Chiu and Mehrotra, 2010).

In patients with ESRD on dialysis, several factors have been shown to cause an inflammatory state. In HD patients these include membrane type, flux, extent of convective transport and frequency of dialysis. In PD these include bio-incompatibility of PD solutions and impurity of PD solutions. In PD patients, peritonitis and exit site infections are common. These factors may result in the possibility of a failed kidney transplant in previously transplanted patients who end up on dialysis (Lonnemann, 2004; Shindler, 2004; Ayus et al., 2005).

A detailed literature search was conducted and according to my knowledge no study was found to have investigated the impact of dialysis on metabolic syndrome and its traits in patients with ESRD. Moreover, the prevalence of the MS has not been described in any dialysis population in South Africa. This study hopes to clarify whether the inflammatory state induced by dialysis in incident ESRD patients will worsen the MS traits which itself has been strongly associated with inflammation.

CHAPTER 2

LITERATURE REVIEW

2.1 History of the metabolic syndrome

The first mention in literature on what is currently described as the MS was reported in the early 20th century by some European physicians who wrote about the relationship between metabolic disorders, blood pressure (BP) and diabetes (Hitzenberger and Richter-Quitter, 1921; Hitzenberger, 1921; Kylin, 1921; Maranon, 1922). Table 2 displays the names of authors and the year in which they reported on findings related to the MS.

Reaven, after several years of research on resistance to insulin-mediated glucose uptake, reported in 1988 that this disorder was present in the majority of subjects with T2DM or IGT, but it was also present in 25% of the individuals with normal glucose tolerance. He thus formed the hypothesis that insulin resistance (IR) is the common aetiological factor for a group of disorders, consisting of IGT, hyperinsulinaemia, high levels of very LDL, TG, low levels of HDL cholesterol and hypertension. He then named this group of disorders “syndrome X” in an attempt to stress its unknown aspects and pointed out that individuals with the syndrome are at increased risk of atherosclerosis (Reaven, 1988). Reaven’s description of syndrome X was the spark that has since ‘lit the fire’ on the research of MS.

2.2 Definition of the metabolic syndrome

There have been different definitions of the MS and the lack of a uniform definition from different expert groups essentially stem from different concepts about its origin and its importance in clinical practice. Opinions have varied as to whether it should be defined to indicate insulin resistance, defined for CVD risk stratification, or should simply reflect a collection of statistically related factors. Therefore, different expert groups have attempted to produce diagnostic criteria to define the MS being that its critical importance lies in identifying individuals at high risk of both T2DM and CVD.

Table 2: Previous mentions of the metabolic syndrome in literature

Terms	Author and Year
Hypertension-Hyperglycaemia- Hyperuricaemia syndrome	Kylin, 1923
Metabolic trisyndrome	Camus, 1966
Pleurimetabolic syndrome	Avogaro and Crepaldi, 1967
Syndrome of affluence	Mehnert and Kuhlmann, 1968
Metabolic syndrome	Hanefeld and Leorhardt, 1981
Syndrome X	Reaven, 1988
Deadly quartet	Kaplan, 1989
Insulin resistance syndrome	DeFronzo and Ferrannini, 1991; Haffner, 1992

The World Health Organisation (WHO) in 1998 first proposed a definition for the MS (Alberti and Zimmet, 1998). The WHO criteria had insulin resistance or its surrogates (impaired glucose tolerance or diabetes) as essential components, together with at least two of any of the following: raised BP, hypertriglyceridaemia and/or low HDL-cholesterol, obesity, as measured by waist-to-hip ratio (WHR) or BMI, and microalbuminuria (Table 2.2). The European Group for the Study of Insulin Resistance (EGIR) then produced another definition which was essentially a modification of the then existing WHO criteria by excluding people with diabetes mellitus (Balkau and Charles, 1999). The EGIR criteria required hyperinsulinaemia to be present, used WC instead of BMI or WHR as measure of adiposity and had different cut-offs for other variables (Table 3).

In 2001, the National Cholesterol Education Program (NCEP) ATP III proposed a definition to facilitate clinical diagnosis and primarily aimed at defining CVD risk (NCEP, 2001). The ATP III definition shifted from the previous two definitions by deemphasizing hyperinsulinaemia and insulin resistance, and required 3 of any 5 of: central obesity (measured as WC), raised BP, raised triglycerides, low HDL-cholesterol, and fasting hyperglycaemia to be present in order to make a diagnosis of the MS (Table 3).

Table 3: Definitions of the metabolic syndrome as proposed by different expert groups.

Clinical index	WHO (1998)	EGIR (1999)	ATP III (2001)	IDF (2005)
Insulin resistance	IGT, IFG, T2DM, or Reduced Insulin sensitivity plus 2 of :	Plasma insulin > 75th percentile plus any 2 of:	None Any ≥ 3 of following 5:	None
Body weight	Men: WHR > 0.90; Women: WHR > 0.85 and/or BMI > 30kg/m ²	Men: WC \geq 94cm Women: WC \geq 80cm	Men: WC \geq 102cm Women: WC \geq 88cm	Increased ethnic specific WC Plus any 2 of following:
Lipids	TG \geq 1.7mmol/L And / or	TG \geq 1.7mmol/L And / or	TG \geq 1.7mmo/L	TG \geq 1.7 mmol/L or on treatment for elevated TG
	HDL: Men: < 0.9 mmol/L Women: < 1.0 mmol/L	HDL: Men: < 1.0mmol/L Women: < 1.0 mmol/L	HDL: Men: 1.0mmol/L Women: 1.3 mmol/L	HDL: Men: 1.0 mmol/L Women: 1.3 mmol/L Or on HDL treatment
Blood pressure	$\geq 140/90$ mmHg	$\geq 140/90$ mmHg or on treatment for hypertension	$\geq 130/85$ mmHg	≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or on treatment for hypertension
Glucose	IGT, IFG, or T2DM	IGT, or IFG (Diabetes excluded)	> 6.1 mmol/L (includes diabetes)	≥ 5.6 mmol/L (diabetes included)
Others	Microalbuminuria	Nil	Nil	Nil

WHO – World Health Organization; EGIR - European Group for the Study of Insulin Resistance; ATPIII – Adult Treatment Panel III; IDF – International Diabetic Federation; IGT - Impaired glucose tolerance; IFG - Impaired fasting glucose; T2DM – Type 2 diabetes mellitus; WHR – waist-to-hip ratio; WC – waist circumference; TG – triglycerides, HDL – High density lipoprotein cholesterol

Due to these differences in definition, the confusion created from lack of specificity of the previous definitions, the inability to compare between studies carried out into the MS using these different definitions, and the view of the international diabetes federation (IDF) on the MS as the major driver of the worldwide epidemic of T2DM and CVD, a new worldwide definition was then proposed in 2005 (IDF, 2005).

This new definition recommended the use of the diagnostic glucose level of the American Diabetic Association (ADA) for impaired fasting glucose (5.6mmol/L) to be used rather than the measurement of insulin resistance which was thought to be unrealistic. Waist circumference which had previously been linked to CVDs was the preferred measure of obesity with ethnic specific WC cut-offs proposed for different populations (Tan et al., 2004). The ethnic specific WC recommended reference to

the individual's ethnic group, and not country of residence. The cut-offs for other variables of the MS were the same as those in the ATP III definition.

Finally, the IDF recommended some criteria to be used for research into the MS, including: measurement of insulin resistance, oral glucose-tolerance test, tests for endothelial dysfunction, imaging of visceral adiposity and liver fat, measurement of adipocytokines and inflammatory markers (adiponectin, leptin, interleukin 6 (IL-6), tumor necrosis factor - alpha (TNF- α), urinary albumin, and prothrombotic factors (plasminogen activator inhibitor type 1, fibrinogen) (IDF, 2005). Since these recommendations were made, no groups have proposed any other definition for the MS rather, the search now is for mechanisms causing it and leading to associated CVDs.

2.3 Prevalence of the metabolic syndrome

There are few national surveys reporting the prevalence of the MS, however, available data suggest a wide variation from one population to another depending on the criteria used (Lakka et al., 2002; Ford et al., 2004; Illanne-Parikka et al., 2004; Gu et al., 2005;). In the United States, data from the third national health and nutrition education survey (NHANES) of 1999-2000 using the ATP III criteria reported a prevalence of 27% (Ford et al., 2004) while the Kuopio study in Finland, carried out in non-diabetic middle aged men, free of CVD reported a prevalence of 8.8% by the ATP III criteria and 14.2% by the WHO criteria (Lakka et al., 2002).

Reported prevalence tends to be dependent on the group studied within a given population (diabetics, specific gender, ethnicity/race, age groups). For instance, in a population based study of diabetic subjects in Italy, a prevalence of 75.6% was reported (Bruno et al., 2004), while from the same country, when the study was carried out in subjects with diabetic complications; the prevalence had increased to 92.3% (Bonora et al., 2004).

Gender differences in prevalence have been reported from several studies carried out in different populations (Illane-Parikka et al., 2004; Ford et al., 2004; Oh et al., 2004). However, prevalence usually increases with age in men and women

irrespective of race or ethnicity. The Inter ASIA study of 15,540 adults in China (Gu et al., 2005) reported higher prevalence in women than in men in every age group, rising from 8.4% in men aged 35 to 44 years to 28.6% in women aged 65 to 74 years.

Significant variation in MS prevalence has also been reported among the different ethnic groups in the United States (Park et al., 2003; Ford et al., 2002). The age-adjusted prevalence of the MS from the NHANES (NHANES III 1988-1994) was 31.9% among Mexican Americans, 23.8% among non-Hispanic whites, and 21.6% among African Americans (Ford et al., 2002).

There have been far fewer studies reporting prevalence of the MS from Africa compared to studies from Europe, North America and South East Asia. However, available reports have also had differences in reported prevalence, depending on which definition is used and the specific population studied. Two studies from Nigeria using T2DM reported prevalence of 25.2% (Alebiosu and Odunsan, 2004) and 59.1% (Isezuo and Ezunu, 2005) even though the WHO criteria were used in defining the condition. The discrepant prevalence rates obtained from the two studies from Nigeria could be related to differences in ethnicity of the studied populations. A study of 947 subjects (758 women) by Motala et al. (2011), of rural black South Africans in Kwazulu Natal has reported the age-adjusted prevalence of MS to be 22.1%, with a higher prevalence in women (25.0%) than in men (10.5%). In another study of 334 predominantly hypertensive Xhosa speaking South Africans in Cape Town, MS was found to be present in 19.1% of the population (Okpechi et al., 2007). Schutte and Olckers (2007), have similarly reported a prevalence of 24.8% MS in black African women in the North-West province compared to 30.4% in Caucasian women. There are no known studies of the MS in dialysis patients that has been reported from SSA.

2.4 Pathogenesis of the metabolic syndrome

The aetiology of the MS is still not clear yet and is of complex nature. Poor nutrition, physical inactivity, and subsequent increases in body weight have often been blamed as causes of the MS (Okpechi et al. 2007). What precisely causes the MS

and how it comes about will remain important research questions until definitive answers are found. At present, mechanisms leading to the MS include different theories including insulin resistance, obesity, dyslipidaemia, hypertension and proinflammatory cytokines.

2.4.1 Metabolic syndrome and insulin resistance

Metabolic syndrome and insulin resistance are often used interchangeably and there is a strong case for insulin resistance being the primary cause of MS. Although there is lack of clinical evidence to show that reduction in insulin resistance in people with the MS will prevent CVD, insulin resistance is still thought to be at the core of the MS.

Evidence for the central role of insulin resistance in the development of the MS is supported by the Bruneck Study in Italy which examined the prevalence of insulin resistance among 919 subjects aged 40 – 79 using the homeostasis model assessment (HOMA) method. In this study, the degree of insulin resistance correlated with the number of metabolic abnormalities ($p < 0.05$), and when several abnormalities were clustered together, insulin resistance was almost always present (Bonora et al. 2007).

2.4.2 The metabolic syndrome and obesity

The purpose of adipose tissue throughout the body is energy storage. Calories are stored as triglycerides and released as fatty acids when energy is needed. It is safest for the body to store triglyceride in small peripheral adipocytes and if the capacity of these adipocytes to store triglyceride is exceeded, triglyceride accumulates in liver cells, skeletal muscle cells and visceral fat cells. This abnormal triglyceride deposition may lead to the development of hepatic and muscular resistance to insulin action. Excess triglyceride in myocytes and in abnormally large peripheral adipocytes appears to cause insulin resistance in these cells (Kelley and Mandarino, 2000).

The lipotoxic effect of elevated free fatty acids (FFA) is thought to be the major mechanism through which obesity brings about features of the MS. However, this can occur through any or a combination of these processes: oxidative stress, proinflammatory signalling or through the actions of ceramide. Firstly, studies using magnetic resonance spectroscopy in humans have shown that increased fatty acid levels directly inhibit glucose transport by causing mitochondrial dysfunction (Lowell and Shulman, 2005; Savage et al., 2005) and stimulating certain protein kinases like PKC- θ , that then promote insulin resistance (Lowell and Shulman, 2005).

Secondly, increased reactive oxygen species in response to fatty acids activates nuclear factor kappa B (NF- κ B), which further stimulates the production of other proinflammatory cytokines, including TNF- α and IL-6 (Boden et al., 2005; Jove et al., 2005). Tumor necrosis factor - α activates signalling intermediates namely, I κ B kinase beta (IKK β) and Jun kinase 1 (JNK) which play a central role in cross-talk between inflammatory signalling and insulin signalling, leading to insulin resistance by phosphorylating IRS-1/2 on serine residues (Hirosumi et al., 2002; Gao et al., 2004). In other words, the process of inflammation triggered off by excess fat may be the cause of organ damage that results in the MS phenotypes.

2.4.3. Metabolic syndrome and dyslipidaemia

In general, with increases in free fatty acid flux to the liver, increased production of apo B-containing triglyceride-rich very low-density lipoproteins (VLDL) occurs (Lewis et al., 1995). The effect of insulin on this process is somewhat complex. In the setting of insulin resistance, increased flux of free fatty acids to the liver increases hepatic triglyceride synthesis; however, under physiological conditions, insulin inhibits rather than increases the secretion of VLDL into the systemic circulation (Nielsen and Karpe, 2012). This response in part is an effect of insulin on the degradation of apo B (Taghibiglou et al., 2002). Yet, insulin is also lipogenic, increasing the transcription and enzyme activity of many genes that relate to triglyceride biosynthesis (Foufelle and Ferre, 2002). Whether or not this pathway remains operational in the setting of systemic insulin resistance has not been completely addressed.

Additionally, insulin resistance could also reduce the concentrations of lipoprotein lipase in peripheral tissues (ie, in adipose tissue more than muscle) (Sumner et al., 2005; Wang and Eckel, 2009). This alteration in lipoprotein lipase, however, seems to contribute less to the hypertriglyceridaemia than does the overproduction of VLDL. Nevertheless, hypertriglyceridaemia is an excellent reflection of the insulin resistant condition and is one of the important criteria for diagnosis of the metabolic syndrome.

The other major lipoprotein disturbance in the metabolic syndrome is a reduction in HDL cholesterol. This reduction is a consequence of changes in HDL composition and metabolism. In the presence of hypertriglyceridaemia, a decrease in the cholesterol content of HDL results from decreases in the cholesterol ester content of the lipoprotein core with variable increases in triglyceride making the particle small and dense, a function in part of cholesteryl ester transfer protein (Murakami et al., 1995; Kleber et al., 2010). This change in lipoprotein composition also results in an increased clearance of HDL from the circulation (Brinton et al., 1991; Chatterjee and Sparks, 2011). The relation of these changes in HDL to insulin resistance is probably indirect, arising in concert with the changes in triglyceride-rich lipoprotein metabolism.

In addition to HDL, the composition of LDL is also modified in a similar way. In fact, with a fasting serum triglyceride of ± 2.0 mmol/L, almost all patients have a predominance of small dense LDL (De Graaf et al., 1993; Manzato et al., 1993; Stahlman et al., 2012). This change in LDL composition is attributable to relative depletion of unesterified cholesterol, esterified cholesterol, and phospholipid with either no change or an increase in LDL triglyceride (Halle et al., 1999; Kwiterovich, 2002). Small dense LDL might be more atherogenic than buoyant LDL because (1) it is more toxic to the endothelium; (2) it is more able to transit through the endothelial basement membrane; (3) it adheres well to glycosaminoglycans; (4) it has increased susceptibility to oxidation; and/or (5) it is more selectively bound to scavenger receptors on monocyte derived macrophages; (Packard, 1996; Noto et al., 2006; Singh et al., 2013) however, this contention is not entirely accepted (Lada, 2004). In some studies, this alteration in LDL composition is an independent risk factor for cardiovascular disease (Zambon et al., 1999; Rizzo and Berneis, 2007). However,

more often this association is not independent, but related to the concomitant changes in other lipoproteins and other risk factors (Sacks and Campos, 2003).

2.4.4 Metabolic syndrome and Hypertension

The relationship between insulin resistance and hypertension is well established, (Bonora et al., 2001) and relates to several different mechanisms. First, it is important to note that insulin is a vasodilator when given intravenously to people of normal weight with secondary effects on sodium reabsorption in the kidney (DeFronzo et al., 1975; Steinberg et al., 1994; Timmerman et al., 2010). Evidence indicates that sodium reabsorption is increased in white people but not Africans or Asians with the metabolic syndrome (Barbato et al., 2004). In the setting of insulin resistance, the vasodilatory effect of insulin can be lost, (Tooke et al., 2000) but the renal effect on sodium reabsorption preserved (Kuroda et al., 1999). Fatty acids themselves can mediate relative vasoconstriction (Tripathy et al., 2003). Insulin also increases the activity of the sympathetic nervous system, an effect that might also be preserved in the setting of the insulin resistance (Egan, 2003). However, when assessed by concentrations of fasting insulin, HOMA or the HOMA insulin resistance index, insulin resistance contributes only modestly to the increased prevalence of hypertension in the metabolic syndrome (Hanley et al., 2002).

2.4.5 Metabolic syndrome and proinflammatory cytokines

The association of the metabolic syndrome with inflammation is well documented (Fernandez-Real and Ricart, 2003, Sutherland et al., 2004). The increases in proinflammatory cytokines including interleukin 6, tumour necrosis factor-alpha and C-reactive protein (CRP) (Fernandez-Real and Ricart, 2003) reflect overproduction by the expanded adipose tissue mass (Trayhurn and Wood, 2004). Evidence suggests that monocyte-derived macrophages reside in adipose tissue and might be at least in part the source of the generation of proinflammatory cytokines locally and in the systemic circulation (Weisberg et al., 2003; Xu et al., 2003). There is increasing evidence that insulin resistance in the liver, muscle, and adipose tissue is not only associated with the abundance of proinflammatory cytokines (and relative deficiency of the anti-inflammatory cytokine adiponectin), but is a direct result of this

burden (Neuschwander-Tetri and Caldwell, 2003.) It remains unclear however, how much of the insulin resistance related to the adipose tissue content of macrophages is paracrine versus endocrine. As a general index of inflammation, CRP concentrations vary by ethnic origin and within ethnic groups by fitness (Chambers et al., 2001 and LaMonte et al., 2002). For instance, concentrations of CRP were higher in healthy Indian Asians than in European white people and were related to greater central obesity and insulin resistance in Indian Asians (Chambers et al., 2001). Presently, it is still not clear whether these differences when adjusted for other covariates will relate to different rates of development of diabetes and/or cardiovascular disease.

2.5 Chronic kidney disease

2.5.1 Introduction

Chronic kidney disease is defined by the presence of sustained abnormalities of renal function and results from different causes of renal injury. Chronic kidney disease can lead to progressive loss of renal function, and may terminate in ESRD after a variable period of time following the initiating injury (NKF 2002). The public health impact of ESRD has led to increased interest in clinical and public health interventions that can delay or prevent the occurrence of ESRD in individual patients and in high-risk populations with CKD.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease recommend that CKD be adopted to define the presence of kidney injury and impaired kidney function (NKF 2002). The NKF criteria includes the presence for 3 or more months of impaired renal function across a continuum of renal injury from isolated anatomic, radiographic, biomarker, and urinary abnormalities to decreased glomerular filtration rate (GFR), irrespective of the primary cause of the renal injury (NKF 2002). Classification of CKD requires the establishment of presence or absence of renal injury, estimate of GFR, and determination that kidney disease has persisted for 3 or more months. Equations that convert the serum creatinine into an estimated GFR or creatinine clearance are available and are used to avoid misinterpretation of serum

creatinine values. An estimated GFR above 60 mL/min/1.73m², in the absence of other anatomic, radiographic, or urinary abnormalities, is not classified as CKD. The NKF classification defines five stages of CKD by increasing degree of impaired kidney function (Table1), and as kidney damage progresses the remaining nephrons compensate for the reduction in nephron mass by increasing the single nephron filtration rate with this hyperfiltration promoting further injury (Brenner and Mackenzie, 1997). At each stage, therefore, patients can benefit from measures that delay or prevent the progressive loss of renal function such as modification of medications with renal clearance, avoidance of nephrotoxins, and reduction of cardiovascular risk factors (St Peter et al., 2003).

Patients with CKD need to be monitored for progression to kidney failure, and patients who advance to CKD stage 3 require increased monitoring and control of hypertension, anaemia, renal bone disease, and nutrition. Recognition and early referral of patients who advance to stage 4 and 5 CKD is important if the transition to ESRD treatment is to be successful. It is thought that for patients in these early stages of CKD, early recognition and administration of appropriate treatment may delay the onset of ESRD. For example, delayed referral for ESRD treatment has been associated with less than optimal vascular access placement, failure to manage renal bone disease and nutrition, poor anaemia control, impaired quality of life, and increased risk of severe hypertension, uraemic symptoms, pulmonary oedema, and emergent dialysis (Arora et al., 1999; Joshi et al., 2013; Selim et al., 2013).

2.5.2 Prevalence of chronic kidney disease and end stage renal disease

An estimate of the global burden of ESRD was provided in a survey which included 122 countries. It reported that the approximate number of patients on RRT is over 1.4 million and that more than 80% of these patients live in Europe, North America, and Japan (Moeller et al., 2002). Reported prevalence rates of patients on RRT are generally used to assess the prevalence of ESRD.

There is a wide variation in prevalence rate, expressed as number of patients per million population (pmp), among countries and several factors may be responsible

for these differences. Firstly, there is a strong relationship between prevalence rate and per capita income, and governmental infrastructure, as these can influence both the availability and quality of dialysis and transplantation services. The prevalence rate of RRT is 644 pmp in the 15 countries of the European Union (Berthoux et al., 1999), compared with a prevalence rate of 166 patients pmp in Central and Eastern European countries (Rutkowski, 2002).

Secondly, the reported prevalence rates in poorer countries like those of Africa and Asia being far less than those of developed economies is generally related to poor infrastructure. In West Africa for instance, the prevalence of ESRD ranges from 1.6 pmp in Ghana to 20 pmp in Mauritania (Fogazzi et al. 2003) and in the countries of North Africa that have better established renal replacement programs, it ranges from 30 pmp in Libya to 186.5 pmp in Egypt (Naicker, 2003). Data from the South African Dialysis and Transplant Registry (SADTR) of 1994 revealed that 3399 patients (99 pmp) were alive and on treatment for ESRD (SADTR 1994).

Thirdly, the maintenance and updating of renal registries is not standardised. Renal registries offer an important source of information on several aspects of CKD and are very useful in gaining insight on the burden of kidney diseases and allowing comparisons of incidence and prevalence of ESRD, mortality and morbidity, patient demographics and treatment modalities among countries (Stengel et al., 2003). Also, renal registries often record data of patients who are at the last stage of kidney disease with very little known about the prevalence of earlier stages of CKD and it has been acknowledged that the majority of individuals at early stage of CKD have gone undiagnosed and under-treated. However, several countries do not have registries and the content of national registries is often uneven, for example, some registries are updated yearly, whereas other registries are updated less frequently.

Fourthly, there are striking racial and ethnic differences in the incidence and prevalence rates of CKD and ESRD. In 1999, the incidence rates for ESRD in the US were 237 pmp in Caucasians, 953 pmp in African Americans, 386 pmp in Asian Americans and native Hawaiians and other Pacific Islanders, and 652 pmp in American Indians and Alaska Natives. Furthermore, 10 percent of all new ESRD patients were Hispanic (USRDS 2001).

There is also significant variability in the causes of ESRD among the various racial and ethnic groups. As an example, whereas diabetic nephropathy is the most common cause of ESRD in all racial/ethnic groups, hypertensive nephropathy is the cause of ESRD in 33 percent of African Americans, compared to less than 25 percent in all other racial/ethnic groups. The age and gender adjusted ratio (African American to Caucasian) of hypertensive ESRD is 6 to 1. African Americans, and to a lesser extent other racial and ethnic minorities, also have a disproportionately higher incidence rate of ESRD due to diabetes and glomerulonephritis compared to Caucasians, and these minority groups in the US tend to reach ESRD at a younger age than Caucasians (mean age 57 and 58 years, compared to 63 years) (USRDS 2001).

2.5.3. Risk factors of chronic kidney disease and end stage renal disease

There are several risk factors, including those that are components of the MS, which are associated with CKD and ESRD.

2.5.3.1 Diabetes mellitus

Diabetes mellitus is the most common cause of ESRD reported by the United States Renal Data Systems (USRDS) for the United States population and it accounted for nearly 45% of all new cases of ESRD starting renal replacement therapy between 1996 and 2000 (USRDS 2002). High blood glucose level is the common factor in the initiation and progression of renal injury among diabetic patients. Renal cells are stimulated by hyperglycaemia to produce humoral mediators, cytokines, and growth factors that are responsible for the structural alterations such as increased deposition of extracellular matrix (ECM) and the functional alterations such as increased permeability of glomerular basement membrane or shear stress (Schena and Gesualdo, 2005).

Hyperglycaemia additionally induces an abnormal activation of protein kinase C- θ (PKC- θ), which is involved in the development of diabetic nephropathy. Upregulation of PKC- θ has been observed in the kidneys of rats with diabetic

nephropathy (Koya et al., 1997) and associated with transforming growth factor- β 1 (TGF- β 1), fibronectin, and collagen type IV up regulation.

Glucose Transporter-1 (GLUT-1), a surface receptor of resident renal cells, modulates the influx of glucose into renal cells. Mesangial cells have been shown to overexpress GLUT-1 mRNA when exposed to high glucose concentrations leading to overproduction of GLUT-1 protein and increased glucose transport into the cells (Heilig et al., 1997; Lu et al., 2012). Chronic hyperglycaemia can also result in glycosylation of serum and tissue proteins leading to the formation of advanced glycosylation end products. In this process, some of the excess glucose combines with free amino acids on serum or tissue proteins (Makita et al., 1991; Thomas et al., 2005; Titov and Shiriaeva, 2011).

2.5.3.2 Hypertension

Hypertension is ranked as the second most common cause of ESRD in the United States, accounting for 23% of incident ESRD patients between 1996 and 2000 (USRDS, 2002). The higher US incidence of hypertension-associated ESRD may relate to its higher incidence in African Americans. When compared with Caucasians, African Americans show a disproportionate increase in the incidence of hypertensive ESRD in all age groups (USRDS 1999). In South Africa, hypertension accounted for 45.6% of all ESRD, second only to glomerulonephritis (52.1%) from the 1994 SADTR data (SADTR 1994).

Approximately 70% to 80% of individuals with CKD have hypertension, and its prevalence increases as glomerular filtration rate declines (Coresh et al., 2001). Even mild-to-moderate hypertension is an important risk factor for progression of CKD toward irreversible renal failure (Coresh et al., 2001). Typically, significant hypertension initially affects the renal vasculature, resulting in hyaline thickening of small arteries and arterioles. Eventually, the vascular lesions progress to vessel wall necrosis (fibrinoid necrosis, necrotizing arteriolitis and hyperplastic arteriolosclerosis), which may extend to the glomerulus as well (necrotizing glomerulitis) (Kumar et al., 2003).

Mule and colleagues (2005), have analysed the influence of MS on target organ damage (cardiac, renal and retinal) in a group of non-diabetic patients with essential hypertension. They found that the presence of the MS may amplify hypertension-related cardiac and renal changes, over and above the potential contribution of each single component of this syndrome (Mule et al., 2006). Cuspidi et al. (2004), in a study of hypertensive subjects, reported equal values of ambulatory blood pressures in patients with and without the MS but found increased cardiac and extra-cardiac involvement including microalbuminuria in patients with the MS.

In the MS, hypertension is often related to obesity and is accompanied by impaired pressure natriuresis, renal vasodilation and glomerular hyperfiltration, neurohumoral activation, and metabolic changes all of which may cause glomerular injury and further impairment of renal-pressure natriuresis, resulting in more severe hypertension and a gradual loss of kidney function (Hall, 1997; Hall et al., 2002; Redon et al., 2009).

2.5.3.3 Dyslipidemia

Lipid abnormalities are independent risk factors for the incidence and progression of CKD. Hunsicker et al. (1997) described a systematic analysis to determine baseline factors that predict the decline in GFR, or which alter the efficacy of the diet or blood pressure interventions. They found six factors including low serum HDL cholesterol to independently predict a faster decline in GFR (Hunsicker et al., 1997; Obermayr et al., 2008).

Lipotoxicity, mediated via long chain non-esterified fatty acids (NEFA), has been linked to many of the manifestations of the MS. High-circulating NEFA from abdominal fat mass drives the cellular uptake of more fatty acids (FA), which inhibits the secretion of adiponectin and reduces the mitochondrial uptake and oxidation of FA. The excess intracellular FA is shunted toward the production of reactive intermediates, such as ceramide, diacylglycerol, and fatty acyl- CoA. These reactive compounds are cytotoxic and capable of inducing cell apoptosis and organ damage (Bagby, 2004; Kamijo et al., 2002).

In the kidney, filtered NEFA can aggravate the chronic tubule damage and inflammatory phenotype that develop during proteinuric states. Lipid loading of both glomerular and tubular cells is a common response to renal injury that contributes to the progression of nephropathy (Weinberg, 2006).

2.5.3.4 Obesity

There is growing evidence that obesity may be a risk factor for progressive renal injury (Stengel et al., 2003; Fox et al., 2004). The risk of either incident ESRD or kidney disease–related death among NHANES III participants was independently associated with a BMI greater than or equal to 35 kg/m² (Stengel et al., 2003). Obese participants in the Framingham study who were initially free of kidney disease at baseline were more likely to have a decrease in estimated GFR (Fox et al., 2004). Obesity-associated renal dysfunction including proteinuria, nephrotic syndrome, and CKD are frequently seen in clinical practice (USRDS 2003). In a review of over 6800 renal biopsies carried out in a study on obesity related glomerulopathy (ORG) – defined as focal segmental glomerulosclerosis (FSGS) and glomerulomegaly or glomerulomegaly occurring alone), Kambham et al (2001) reported a progressive, 10-fold increase in biopsy frequency of ORG from 0.2% in 1986 to 1990 to 2.0% in 1996 to 2000 (Kambham et al., 2001).

The first cases of obesity related FSGS in the paediatric population were reported in 2001 (Adelman et al., 2001). Seven African- American adolescents with severe obesity were followed up over a 12 year period and had renal biopsies for the diagnosis of unexplained heavy proteinuria. Calculated creatinine clearance was normal in six patients and decreased in one. Observed histologic features included glomerular hypertrophy, FSGS, increased mesangial matrix and cellularity, relative preservation of foot process morphology, and absence of evidence of inflammatory or immune-mediated pathogenesis. Compared with lean subjects, obese subjects have reduced renal vascular resistance and increased renal blood flow, elevated GFR, and abnormal pressure natriuresis that shifts toward a higher BP, often referred to as impaired pressure natriuresis (Reisin et al., 1995; Reisin, 2001; Lohmeier and Iliescu, 2013). The increased activity of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), the blunted

activity of the natriuretic peptides, accompanied with hyperleptinemia, and hyperinsulinemia, all contribute to renal sodium retention and a hyper-hemodynamic state in cases of obesity (Reisin, 2001; Zoccali, 2009). Physical compression of the kidneys by adipose tissue is also thought to contribute to this complex interaction that ultimately gives rise to glomerular hyperfiltration, glomerular cell proliferation, matrix accumulation, and, finally, glomerulosclerosis and the loss of nephrons (Halle et al., 1999).

2.5.3.5 Cardiovascular Disease

Patients with CVD and CKD are at increased risk of developing ESRD. Autopsy studies have found a correlation between extent of atherosclerosis and degree of glomerular scarring (Kasiske, 1987; Smith et al., 1989). In one such study, it was observed that the prevalence of glomerulosclerosis was substantially greater among individuals with moderate to severe atherosclerosis (15%) compared with individuals with mild disease (8%). Further, comparison of the mean glomerular area of nonsclerotic glomeruli suggested that there were compensatory increases in glomerular size in individuals with moderate to severe atherosclerotic disease and glomerular area was independently associated with increasing coronary artery atherosclerosis (Kasiske, 1987).

2.6 Treatment of CKD and ESRD associated with MS

Lifestyle modifications are beneficial in patients with MS. Weight reduction has been shown to be effective for reducing proteinuria in obese patients (Morales et al., 2003; Praga and Morales, 2006). There is a protective effect of weight loss on CKD progression prior to progression to ESRD, but weight reduction may no longer be indicated once a patient progresses to ESRD, as renal replacement therapy has a paradoxical effect on survival (Kalantar-Zadeh et al., 2003). A higher BMI has a beneficial effect on survival in ESRD patients. Bariatric surgery is often performed in cases of extreme obesity ($\text{BMI} > 40 \text{ kg/m}^2$). Navarro-Diaz et al. (2006), reported a remarkable improvement in glomerular hyperfiltration following recovery from renal alterations.

Renin-angiotensin system inhibitors prevent the progression of CKD and the development of microalbuminuria in diabetes patients. Effective treatment of dyslipidemia decreases proteinuria and retards the progression of CKD to ESRD, as shown by a meta-analysis completed by Fried et al (Fried et al., 2001).

Patients with ESRD have a poorer quality of life and a shorter life expectancy compared with individuals of the same age in the general population (K/DOQI, 2002). Many patients with ESRD will require renal replacement therapy when they reach stage 5 and their GFR drops below 15 ml/min.

A substantial number of patients with ESRD on dialysis present with the state of chronic low-grade inflammation. The potential causes of inflammation may be related to the loss of kidney function, reduced clearance of inflammatory cytokines, uraemia per se or its consequences (increased oxidative or carbonyl stress, accumulation of advanced glycation end products, secondary hyperparathyroidism, vitamin D deficiency and fluid overload) (Kautzky-Willer et al., 1995; Mak, 1998). Extracorporeal circulation of blood during HD may also act as a stimulus for an inflammatory response, as well the usage of polytetrafluoroethylene (PTFE) grafts and tunneled cuffed catheters or non-biocompatible dialyzer membranes (Zoui and Hakim, 1994).

Absolute or functional iron deficiency in ESRD results from the presence of uraemia and chronic inflammation (Means and Krantz, 1992; Nangaku and Eckardt, 2006). Furthermore, iron requirements are increased in patients treated with recombinant human erythropoietin, due to enhanced erythropoiesis, that often necessitates therapy with intravenous iron. It was shown that the degree of anaemia associated with deteriorated tissue oxygenation, could predispose such patients to the development of IR and consequently hyperinsulinemia (Igaki et al., 2004). On the other hand, iron overload, which can be registered in HD patients, synergistically acts with other factors committed to protein catabolism (Feldman et al., 2002).

In ESRD patients on continuous ambulatory peritoneal dialysis (CAPD) the MS occurs in about 50% of patients (Li PK et al., 2009). Patients on CAPD often tend to gain a lot of weight from absorption of glucose in the peritoneal dialysate fluid. This

often predisposes patients to various CV risk factors such as diabetes, hyperlipidaemia and obesity. The proinflammatory effects of the increased adipose tissue in CAPD patients put them at high risk for CV diseases. Lifestyle modification, including appropriate dietary restriction and exercise, especially reduction of fat mass in obese patients, has been one of the major areas proposed for managing patients with MS. (Li PK et al., 2003).

In CAPD patients, MS seems to predict poor survival. Increased CV risk in the PD population is likely a result of the interaction between traditional and non-traditional CV risk factors and inflammation (Li PK et al., 2009). Evidence in PD patients that interventions targeting the individual elements of MS can improve outcomes is still lacking.

In PD patients, avoiding or minimizing peritoneal dialysate glucose by using icodextrin (a glucose polymer that is not absorbed) and amino-acid solutions may aid weight control. A trial using icodextrin as compared with 2.5% dextrose PD fluid showed that patients receiving icodextrin had no increase in weight after 52 weeks, in contrast to a weight gain of almost 2 kg in the dextrose group (Li PK et al., 2009). As in managing obesity, lifestyle modification works through diet, exercise, and body weight control. Many of the PD patients at Groote Schuur Hospital tend to have hypertension that usually requires treatment with antihypertensive agents. Elevation of BP in PD patients is obviously multifactorial, but is partly related to fluid status and salt intake. Restriction in salt and fluid intake is important. We still aim to achieve a BP of 130/85 mmHg in our PD patients. Multidrug treatment is usually required to manage BP, and not uncommonly, many PD patients require 3 or more antihypertensive medications to control BP (Li PK et al., 2009).

The impact of dialysis therapy on metabolic syndrome components, i.e. whether these components get better or worse with dialysis therapy is presently unknown. This project is therefore designed to study the effect that dialysis (both HD and CAPD) has on the metabolic syndrome and cardiovascular risk factors in dialysis patients.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Study design and study population

The study was designed to assess the prevalence of metabolic syndrome and to prospectively evaluate the impact of dialysis therapy (HD and PD) on the metabolic syndrome and its various components in patients attending the renal unit at Groote Schuur Hospital (GSH). Groote Schuur Hospital is a South African state hospital situated in Cape Town. The chronic dialysis program at GSH is limited by the number of patients that it can accommodate on dialysis at any given time. Incident ESRD patients are assessed weekly by a team of nephrologists, nurses, social workers and members of the GSH administrative team according to certain selection criteria (Appendix A). Only patients who meet the selection criteria are accepted for dialysis. At GSH, approximately, 50 patients are annually transplanted with another 50 incident ESRD patients accepted to join the dialysis programme. All the prevalent ESRD patients on dialysis (HD and PD) were selected to participate in this study. Only incident ESRD patients accepted for dialysis therapy in the unit were selected to be followed up in order to determine the impact of dialysis on their metabolic factors. The sample size for this study was therefore limited by the unit patient population.

3.2 Ethics

The study was approved by The Human Research Ethics Committee (HREC) of the University of Cape Town [REC REF: 379/2009] (Appendix B) as well as by The Durban University of Technology Faculty Research Committee (Appendix C). All dialysis patients (HD and PD) attending the GSH dialysis unit and accepted for chronic dialysis were included in the study. Patients unwilling to sign the consent form and all patients under the age of 18 years were excluded. Patients were also excluded if they were receiving dialysis for acute renal failure (ARF).

3.3 Data Collection

All patients received a copy of the patient information and consent form (Appendix D) to enable them to understand the details of the study before signing the consent form. The patient information and informed consent, originally in English were translated into Xhosa as this is the other major home language common to most of the patients. Patients who signed the consent forms were requested to come on their next dialysis visit fasting, to ensure collection of fasting blood for the assessment of fasting lipids and glucose. On the day of assessment of the patients, demographic and clinical details including age, gender, cause of ESRD, history of CVD, number of anti-hypertensive's etc. were recorded (Appendix E). Duration on dialysis was calculated by subtracting the date of commencement of dialysis from the date of the patient's assessment and was recorded in months.

In prevalent dialysis patients, (i.e. stable treatment for ≥ 3 months), clinical and biochemical assessment were performed only once in order to determine the prevalence of the metabolic syndrome in the population. However, for incident patients, clinical and biochemical assessment were done at the time of initiation of dialysis (Time 0), and at 6 months and 12 months after commencement of dialysis in order to determine how dialysis therapy had impacted on the metabolic and cardiovascular profiles of the patients. This was done in incident PD and HD patients.

3.4 Clinical assessment of subjects

The following clinical assessments were performed in all the patients:

3.4.1 Anthropometric measurements

3.4.1.1 Weight

With each patient wearing light indoor clothing without shoes, weight was measured to the nearest 0.1 kg on an electronic scale placed on a firm, level surface. The

Weylux Model 824/890 (Made in the UK) scale was used. This scale has a weighing capacity of 200 kg.

3.4.1.2 Height

A wall-mounted stadiometer was used to measure height, without shoes, to the nearest 0.1 cm.

3.4.1.3 Waist and Hip circumference

To measure WC, a measuring tape was placed snugly in a horizontal plane around the abdomen at the level of the iliac crest. The measuring tape was parallel to the floor and the measurement was taken at the end of a normal expiration to the nearest 0.1 cm. Hip circumference (HC) was measured at the level of the greater trochanters. This position is generally taken as the widest circumference below the WC. It was also measured using the tape measure and was reported to the nearest 0.1 cm. The waist to hip ratio was determined. All measurements were done by a trained research nurse, using the same tape measure throughout the period of the study.

3.4.1.4 Body Mass Index

Body mass index was calculated by dividing as body weight (kg) by height squared (m^2). The BMI was categorized following conventional methods as shown in Table 4.

3.4.2 Blood Pressure

In Groote Schuur Hospital, BP is routinely measured and recorded in the patients' charts by trained and qualified dialysis nurses using the Dynamap BP apparatus (Dynamap ProCare, GE Medical Systems, Germany). However, for this study, patients were made to sit comfortably for a period of no less than five minutes with BP taken in both arms and the arm with the greater reading was used for assessment. Two BP measurements were taken from this arm two minutes apart

Table 4: BMI Categories

BMI Range	Category
< 16.4	Severely underweight
16.5 – 18.4	Underweight
18.5 – 24.9	Normal
25 – 29.9	Overweight
30 – 34.9	Obesity class 1
35 – 39.9	Obesity class 2
> 40	Obesity class 3 (morbid obesity)

and the average of the two readings was recorded as the patient's BP. Blood pressure was measured this way throughout the study.

3.5 Laboratory Measurements

Blood was drawn and sent to the National Health Laboratory Service (NHLS) for biochemical analysis. The NHLS laboratory is accredited with the South African National Accreditation System (SANAS). The South African government recognise SANAS as the single national accreditation body that gives formal recognition to laboratories. The biochemical analyses were performed on the day of blood collection using the Roche Hitachi Modular Chemistry Auto Analyzer from Roche diagnostics, Mannheim, Germany.

3.5.1 Biochemical tests

3.5.1.1 Calcium (Ca^{2+})

An automated colorimetric assay method was used to determine the Ca^{2+} levels in the blood. The serum mixed with the reagents formed a purple complex. The colour intensity of the purple complex formed is directly proportional to the Ca^{2+} concentrations and was measured photometrically (Gindler and King, 1972).

3.5.1.2 Inorganic Phosphate (Pi)

The endpoint method with sample blanking was used to determine the Pi levels in the blood. This is an automated process. The inorganic phosphate forms an ammonium phosphomolybdate complex with ammonium molybdate in the presence of sulphuric acid. The complex is determined photometrically in the ultraviolet region (340 nm) (Gindler and King, 1972).

3.5.1.3 C-reactive protein

The measurement of C-reactive protein was vital to this study as it was used as an inflammatory marker. The test principle is the particle-enhanced immunoturbidimetric assay. Human CRP agglutinates with the latex particles coated with monoclonal anti-CRP antibodies. The aggregates are determined turbidimetrically (Price et al., 1987 and Eda et al., 1998). High CRP was then defined as being > 5 mg/l [Ref ranges: 0.0 mg/l – 0.5 mg/l].

3.5.2 Haematological Tests

These tests were done on the Advia[®] 120I Haematology system supplied by Siemens (Siemens Healthcare Diagnostics, Deerfield, IL, USA)

3.5.2.1 Haemoglobin

Chemical Reactions: The sample and the Advia[®] 120 HGB reagent were mixed in the haemoglobin reactor chamber. The haemoglobin chemical reactions consist of two steps:

1. Red blood cells are lysed to release haemoglobin.
2. The heme iron in the haemoglobin is oxidized from the ferrous to the ferric state, and is then combined with cyanide in the Advia[®] 120 HGB reagent to form the reaction product.

Measurement: Optical density readings were obtained calorimetrically at 546 nm. After processing, the optical density data were plotted on the haemoglobin rate curve where time in seconds was plotted along the x-axis and the present light

transmission was plotted along the y-axis. The haemoglobin transmission histogram was divided into 5 parts:

1. Advia[®] 120 sheath/rinse reading from previous cycle
2. Draining of the Advia[®] 120 sheath/rinse, and refilling with reaction solution consisting of sample and Advia[®] 120 HGB reagent.
3. Reaction solution readings (15.5s to 18.0s)- Sample mean.
4. Draining of the reaction solution and refilling with Advia[®] 120 sheath/rinse.

Advia[®] 120 sheath/rinse readings (baseline transmittance) for the current sample (baseline mean value was between 2.5 and 4.1).

3.5.2.2 White Blood Cell Count

The whole blood sample was mixed with Advia[®] 120I BASO reagent that contained acid and surfactant. The red cells were haemolysed, and the white blood cells were analysed by two- angle laser light scattering detection using a laser diode.

3.5.2.3 Platelet Count

The platelets were analysed by a single optical cytometer after appropriate dilution of the blood sample with Advia[®] 120 platelet reagent. The platelets were counted from the signals from the detector with two different gain settings.

3.5.3: Iron Studies

3.5.3.1 Iron (Fe)

There are numerous photometric methods that have been described for the determination of Fe (Roche/Hitachi, 2008-03. Code: 11965239001V11). All have the following in common:

- Liberation of Fe³⁺ ions from the transferrin complex using acids or detergents.
- Reduction of Fe³⁺ ions to Fe²⁺ ions.
- Reaction of the Fe²⁺ ions to give a coloured complex.

The method used in this study was the FerroZine method without deproteinization. Under acidic conditions, iron was liberated from transferrin. Lipemic samples were clarified by the detergent. Ascorbate reduced the released Fe^{3+} ions to Fe^{2+} ions which then reacted with FerroZine to form a coloured complex. The colour intensity is directly proportional to the iron concentration and was measured photometrically (Packet insert from the Roche/Hitachi analyser, 2008-03. Fe. Code: 11965239001V11).

3.5.3.2 Ferritin

Ferritin is a macromolecule with a molecular weight of at least 440 kD. Ferritin was measured by the use of two monoclonal mouse antibodies (M4.184 and M-3.170) to form a sandwich complex. During the first incubation, 10 μL of sample, a biotinylated monoclonal ferritin-specific antibody and a monoclonal ferritin-specific antibody labelled with a ruthenium complex^a formed the sandwich complex. During the second incubation, after the addition of streptavidin-coated micro particles, the complex becomes bound to solid phase via interaction of biotin and streptavidin. The reaction mixture was aspirated into the measuring cell where the micro particles were magnetically captured onto the surface of the electrode. Unbound substances were then removed with ProCell. Application of a voltage to the electrode then induced chemiluminescent emission which was measured by a photomultiplier. Results were determined via a calibration curve which was instrument- specifically generated by 2-point calibration and a master curve provided via the reagent barcode (Roche/Hitachi analyser, 2010-05. Ferritin. Code: 04366522001V10).

3.5.3.3 Percentage Saturation of Transferrin (Tf)

The main utility of measuring the total iron binding capacity (TIBC) in addition to serum Fe is to calculate the percentage saturation of transferrin.

Formula used: % Saturation of Tf = (serum Iron divided by TIBC) x 100.

3.5.4 Lipogram

3.5.4.1 Triglycerides (TG)

In this enzymatic method, free glycerol was converted to glycerol-3-phosphate (G3P) by glycerol kinase. Glycerol-3-phosphate was acted upon by glycerol phosphate oxidase to produce dihydroxyacetone phosphate and hydrogen peroxide. The hydrogen peroxide combined with 4-chlorophenol under the action of peroxidase to produce an oxidation product that does not react with the colorimetric component of reagent 2. After this initial reaction sequence was completed, the Mod P records a blank absorbance reading. Then reagent 2 was added. The second reaction was driven by the reagents from bottle 1, with lipase added in reagent 2 to convert triglycerides to glycerol, and 4-aminophenzone were added to react with the hydrogen peroxide produced in the last reaction. The reaction is measured at 505 nm (secondary wavelength = 700 nm). This method is a two-reagent, endpoint reaction that is specific for triglycerides (Roche/Hitachi analyser, 2008-03. TG Code: 11921428001V12).

3.5.4.2 High density Lipoproteins-cholesterol (HDL-c)

In this study the automated method for direct determination of HDL-c in serum and plasma was employed by way of the homogeneous enzymatic colorimetric test principle with the use of polyethylene glycol (PEG)-modified enzymes and dextran sulphate.

In this method a magnesium/dextran sulphate solution was added to the specimen to form water-soluble complexes with non-HDL-c fractions. These complexes were not reactive with the measuring reagents added in the second step. With the addition of reagent 2, HDL-c esters were converted to HDL-c by PEG-cholesterol esterase. The HDL-c was acted upon by PEG-cholesterol oxidase, and the hydrogen peroxide produced from this reaction combines with 4-amino-antipyrine and HSDA under the action of peroxidase to form a purple/blue pigment that is measured photometrically at 600 nm (secondary wavelength = 700 nm). When the cholesterol measuring enzymes were modified with PEG, they were preferentially more reactive with HDL-c than the other cholesterol fractions. This endpoint reaction is specific for HDL-c (Roche/Hitachi analyser, 2008-03. TG. Code: 11921428001V12).

3.5.5 Endocrine Tests: PTH

3.5.5.1 Parathyroid hormone

Detection of the subfunctioning of the parathyroid glands (hypoparathyroidism) requires the use of a highly sensitive test in order to be able to measure PTH levels well under normal concentration. Hyperfunctioning of the parathyroid glands results in an increased secretion of PTH (hyperparathyroidism).

The Elecsys assay for determining intact PTH was used. It employs a sandwich test principle in which a biotinylated monoclonal antibody reacts with the N-terminal fragment (1 - 37) and a monoclonal antibody labelled with a ruthenium complex^a reacts with a C-terminal fragment (38 - 84). The antibodies used in this assay were reactive with the epitopes in the amino acid regions 26 - 32 and 37 - 42. The duration of the assay was approximately 18 minutes (Roche/Hitachi analyser, 2010 - 06. PTH. Code: VS - 11972103122V25).

Procedure:

First incubation: 50 µL of sample, a biotinylated monoclonal PTH-specific antibody and monoclonal PTH-specific antibody with a ruthenium complex form a sandwich complex.

Second incubation: After addition of streptavidin-coated micro particles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture was aspirated into the measuring cell where the micro particles were magnetically captured onto the surface of the electrode. Unbound substances were then removed from the ProCell. Application of a voltage to the electrode then induced chemiluminescent emission which was measured by a photomultiplier.

Results were determined by a calibration curve which was instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode (Roche/Hitachi analyser, 2010 - 06. PTH Code: VS - 11972103122V25).

3.5.5.2 Glucose

The enzymatic colorimetric assay test principle was employed to measure glucose. In this method glucose was oxidised by glucose oxidase (GOD) to gluconolactone in the presence of atmospheric oxygen. The resultant hydrogen peroxide oxidised 4 - aminophenazone and phenol to 4 - (p - benzoquinone-monoimino) - phenazone in the presence of peroxidase (POD). The colour intensity of the red dye was directly proportional to the glucose concentration and was measured photometrically (Roche/Hitachi analyser, 2008 - 09. Glucose Code: 11972804001V10).

3.6 Definitions

3.6.1. Diabetes

Although diabetes mellitus is defined by the IDF as fasting glucose of ≥ 5.6 mmol/L, the NCEP ATP III criteria of ≥ 6.1 mmol/L was used to define diabetes for this study as this criterion has been widely used in several studies and as such provides us with basis (rationale) for comparison with those studies. Hence, diabetes mellitus was defined as a fasting blood glucose (FBG) level ≥ 6.1 mmol/L or self-reported current treatment with any antidiabetic medication (insulin or oral hypoglycaemic agents) (NCEP, 2001).

3.6.2 Hypertension

Hypertension (HTN) was defined as an average (calculated from 2 measurements) systolic blood pressure (SBP) ≥ 135 mmHg, an average diastolic blood pressure (DBP) ≥ 85 mmHg, or self-reported current treatment with antihypertensive medication for hypertension (NCEP, 2001).

3.6.3 Dyslipidaemia

Dyslipidaemia was defined as self-reported current treatment with a cholesterol-lowering medication or meeting at least 1 of the following criteria: triglycerides ≥ 1.7 mmol/L, HDL cholesterol < 1.1 mmol/L for men and < 1.3 for women (NCEP, 2001)

3.6.4 Prevalence of MS

The NCEP ATP III definition and criteria was used to determine the prevalence of the MS. The metabolic syndrome was defined as the presence of 3 or more of the following risk factors: abdominal obesity: waist circumference > 102 cm in men and > 88 cm in women; serum triglyceride concentration ≥ 1.7 mmol/L or HDL cholesterol concentration < 1.1 mmol/L in men or < 1.3 mmol/L in women; blood pressure $\geq 135/85$ mmHg or treatment of hypertension; and serum glucose concentration ≥ 6.1 mmol/L or treatment of diabetes (NCEP, 2001).

3.6.5 Cardiovascular risk

Cardiovascular risk was assessed as “high”, “medium” or “low” depending on the number of these risk factors that were present. Patients with ≤ 1 risk factor were classified as having low CV risk, those with 2 - 4 were classified as having moderate CV risk and those with > 4 were classified as high CV risk (Seedat et al., 2006 and De Backer et al., 2003). In this study, cardiovascular risk was computed by using the following variables: Age > 60 years, male, smoking, presence of diabetes, presence of hypertension, increased WC (obesity), increased triglycerides (dyslipidaemia), raised CRP and increased calcium phosphate product.

3.7 Statistical Analysis

All data was entered into Microsoft excel. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 19 statistical software (SPSS Inc., 444N. Michigan Ave, Chicago, Illinois, 60611, USA). Student t-test and analysis of variance (ANOVA) was used for comparing continuous variables and chi-square (χ^2) test was used for categorical variables with appropriate control of differing variables. Pearson’s correlation coefficient was used for identifying association between metabolic syndrome and various variables. Difference in duration of dialysis between PD and HD patients was taken into consideration during analysis to avoid bias. Level of statistical significance was taken at $p < 0.05$.

CHAPTER 4

RESULTS

4.1 Prevalence of MS in patients

4.1.1 Baseline demographics of patients

A total of 143 dialysis patients were included in the study of which 97 (67.8%) were on HD and 46 (32.2%) were on PD (Figure 1).

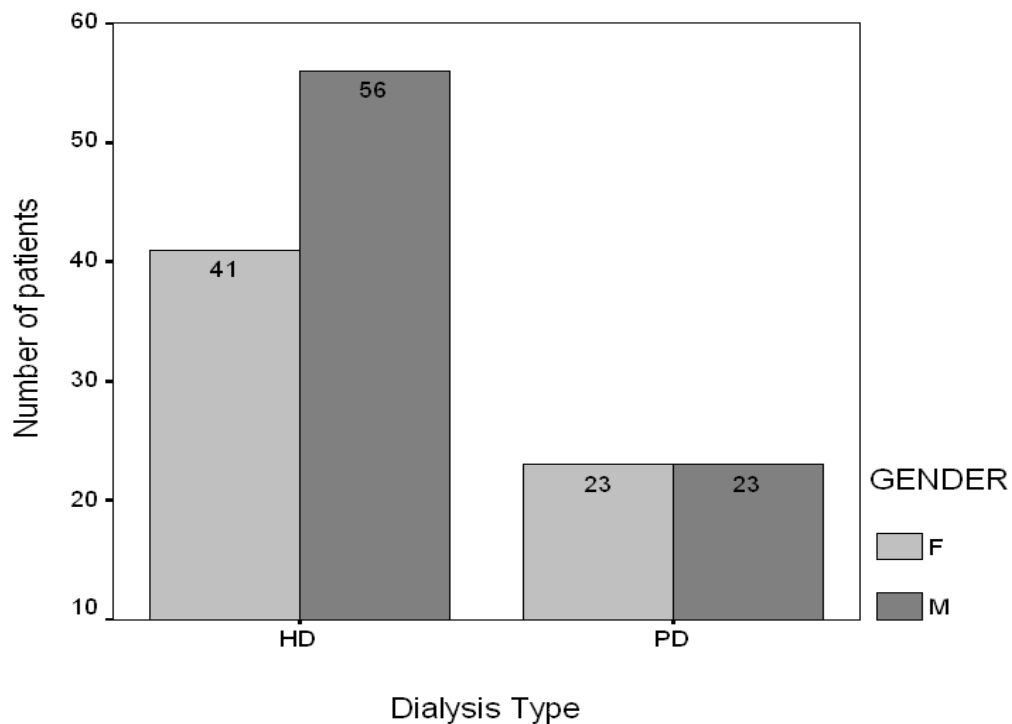


Figure 1: Patient numbers on dialysis by gender

The baseline demographic features of the study participants are as shown in Table 5. The mean duration on dialysis was 22.1 ± 49 months (min – 3 mths; max – 308.06 mths). Male subjects made up 55.2% of the entire study population and the mean age of all participants was 38.5 ± 10.4 years. There was a low level of literacy with 67.1% receiving no formal education as well as low level of employment (37.8%).

The main cause of end stage renal failure was hypertension (58.7%) and 8.4% had a previous history of CVD.

Table 5: Baseline demographic features of study patients

Factor	Value (mean or percentage)
Age (years)	38.5 ± 10.4
Gender (%)	F - 44.8 M - 55.2
Smoking (current %)	13.3
Alcohol (%)	9.1
Duration on dialysis (mnths)	22.1 ± 49
Level of education (%)	
None	67.1
Matric	29.4
Post Matric	3.5
Employed (%)	37.8
Cause of ESRD (%)	
HTN	58.7
DM	3.5
GN	8.4
Other	29.4
Previous Tx (%)	23.1
History of CVD (%)	8.4

ESRD – End stage renal disease, HTN – Hypertension, DM – Diabetes mellitus, GN – Glomerulonephritis, CVD – Cardiovascular disease, Tx - Transplant.

4.1.2 Baseline clinical features of patients

The baseline clinical features, including blood pressures (SBP and DBP), BMI, waist circumference and waist-hip-ratio are as shown in Table 6.

4.1.3 Baseline laboratory results of study patients

Baseline laboratory (biochemical and haematological) profiles of the patients are represented in Table 7.

Table 6: Baseline clinical features of study patients

Variable	Mean
SBP (mmHg)	148 ± 26
DBP (mmHg)	81.8 ± 16.3
BMI (kg/m ²)	24.8 ± 4.5
WC (cm)	75.8 ± 27.7
HC (cm)	84.3 ± 29.2
WHR	0.90 ± 0.08

SBP – Systolic Blood Pressure, DBP – Diastolic Blood pressure, BMI – Body mass index, WC – Waist circumference, HC – Hip circumference, WHR – Waist –to-hip ratio.

Table 7: Baseline laboratory results of study patients

Variable	Mean
Iron (µmol/l)	10.9 ± 8.7
Iron Sats (%)	22.4 ± 13.6
Haemoglobin (g/dl)	8.4 ± 2.3
WBC (per/l)	7.8 ± 3.2
PLT (per/l)	271.38 ± 119.1
MCV (fl)	84.5 ± 7.1
URR*	64.5 ± 15.5
KtV*	1.3 ± 0.75
Calcium (mmol/l)	2.0 ± 0.3
In. Phos. (mmol/l)	1.8 ± 0.6
CXP	3.7 ± 1.5
PTH (pmol)	60.7 ± 48.4
CRP(mg/l)	11.8 ± 22.1
Ferritin (µmol/l)	516.7 ± 553.1

WBC – White blood cells, PLT – Platelets, MCV – Mean cell volume, URR – Urea reduction ratio, Kt/v – K = Clearance, t = time, v = distribution volume, CXP – Calcium phosphate product, PTH – Parathyroid hormone, CRP – C - reactive protein.

Haematological indices were generally low with mean haemoglobin of 8.4 ± 2.3 g/dl, Iron (10.9 ± 8.7 µmol/l), iron saturation (22.4 ± 13.6%) and mean cell volume (MCV) which was in the lower limit of normal (84.5 ± 7.1fl). Indices of mineral bone disease (i.e. serum calcium, phosphate and PTH) at baseline were deranged in all the patients. Also, the factors associated with inflammation that were assayed for were

elevated (CRP - 11.8 ± 22.1 mg/l [Ref range 0 - 5]; Ferritin – 516.7 ± 553.1 [Ref range 30 - 400]) (Table 7).

4.1.4 Metabolic syndrome traits at baseline

Although the MS was present in 37.1% of all patients at baseline, several patients (42.7%) had two MS traits. The distribution of MS traits in all the patients is illustrated in Figure 2.

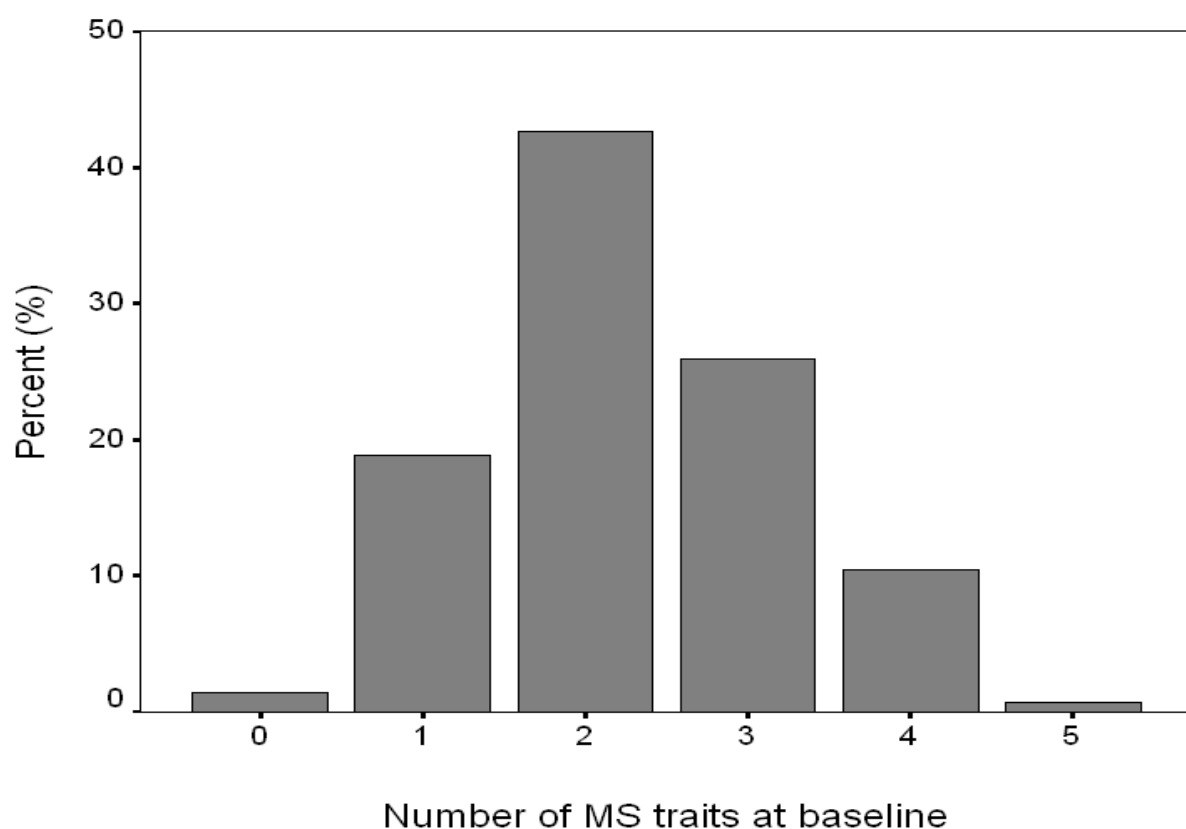


Figure 2: This figure shows the number of MS traits present in all the patients assessed at the time of their assessment. The number of patients with 2 MS traits had the highest frequency.

Hypertension was the most prevalent MS trait as 128/143 dialysis patients (89.5%) were hypertensive. On the other hand, abnormal glucose (diabetes or impaired glucose tolerance) was seen in 37/143 patients (25.9%) making it the least prevalent trait in the dialysis patients (Table 8).

Table 8: Overall prevalence of metabolic syndrome and its various traits

Variable	Percentage (%)
WC (cm)	28.7
DM	25.9
TG (mmol/l)	28
l-HDL(mmol/l)	55.2
HTN	89.5
MS present	37.1

WC – Waist circumference, DM – Diabetes Mellitus, TG – Triglycerides, l-HDL-c – High Density Lipoproteins, HTN – Hypertension, MS – Metabolic syndrome.

4.2 Baseline features between male and female dialysis patients

4.2.1 Comparison of baseline features between male and female dialysis patients

When comparison was made between gender for all dialysis patients, females were slightly older than the males, however this was not significantly different ($p = 0.082$) (Table 9).

Table 9: Baseline features between male and female

Variable	Male (n = 79)	Female (n = 64)	p - value
Age (years)	37.1 ± 11	40.2 ± 9.6	0.082
Duration (mnths)	14.2 ± 35.3	31.9 ± 60.8	0.042
SBP (mmHg)	152 ± 27	143 ± 24.4	0.041
DBP (mmHg)	83.7 ± 17.1	79.4 ± 15	0.118
BMI (kg/m ²)	24 ± 4	25.8 ± 5	0.020
WC (cm)	77.5 ± 27.5	73.7 ± 28.1	0.414
HC (cm)	84.2 ± 28	84.4 ± 31	0.975
WHR	0.91 ± 0.07	0.87 ± 0.08	0.001

SBP – Systolic Blood Pressure, DBP – Diastolic Blood pressure, BMI – Body mass index, WC – Waist circumference, HC – Hip circumference, WHR – Waist –to-hip ratio.

Females also had a significantly longer duration on dialysis compared to males ($p = 0.042$). Assessment of blood pressures between the genders showed a significantly higher SBP in males than in females (152.0 ± 27.0 mmHg vs 143.0 ± 24.4 mmHg; $p = 0.041$). Diastolic BP was, however, not significantly different between males and females ($p = 0.118$).

4.2.2 Comparison of baseline laboratory results between male and female

Haematological parameters were generally lower in females than in males, but the MCV was significantly lower in males than in females ($p = 0.002$). The BMI and HDL-c was also significantly lower in males than in females with p - values at 0.020 and 0.041 respectively (Table 10).

Table 10: Comparison of laboratory results at baseline between males and females

Variable	Male (n = 79)	Female (n = 64)	p - value
FBG (mmol/l)	5.6 ± 2	5.3 ± 1.7	0.367
TG (mmol/l)	1.3 ± 0.8	1.6 ± 2.2	0.278
HDL-c (mmol/l)	1.12 ± 0.33	1.31 ± 0.67	0.041
Iron ($\mu\text{mol/l}$)	12 ± 11	9.7 ± 4.5	0.094
Iron Sats (%)	22.8 ± 13.4	22 ± 14.04	0.734
HB (g/dl)	8.6 ± 2.25	8.2 ± 2.3	0.289
WBC ($10^9/\text{l}$)	8.0 ± 3.44	7.6 ± 2.8	0.513
PLT ($10^9/\text{l}$)	272 ± 137.8	270.6 ± 92.0	0.943
MCV (fl)	82.9 ± 5.81	86.5 ± 8.0	0.002
URR*	62.3 ± 11.5	66.8 ± 18.6	0.243
Kt/v*	1.2 ± 0.49	1.6 ± 0.93	0.06
Calcium (mmol/l)	2.02 ± 0.27	2.1 ± 0.33	0.494
In. Phosphate (mmol/l)	1.8 ± 0.63	1.8 ± 0.614	0.635
CXP	3.71 ± 1.37	3.8 ± 1.64	0.852

* Only done on HD patients

FBG – Fasting blood glucose, TG – Triglycerides, HDL-c– Low High density lipoprotein-cholesterol, HB – Haemoglobin, WBC – White blood cells, PLT – Platelets, MCV – Mean cell volume, URR – Urea reduction ratio, Kt/v – K = Clearance, t = time v = distribution volume, CXP – Calcium phosphate product.

4.2.3 Comparison of baseline metabolic syndrome traits between male and female

When comparison was made for differences of the different MS traits between all males and females on dialysis, WC was found to be significantly lower ($p = 0.016$) in males than in females. Although the difference in frequency of abnormal glucose approached significance between males and females, it did not reach statistical levels of significance ($p = 0.088$). Other MS traits as well as the prevalence of MS did not show significant difference between males and females (Table 11).

Table 11: Baseline MS traits between male and female

	Overall Percentage (%)		p - value
	Male (n = 79)	Female (n = 64)	
WC (cm))	20.3	39.1	0.016
DM	31.6	18.8	0.088
TG (mmol/l)	27.8	28.1	1.000
HDL-c (mmol/l)	55.7	54.7	1.000
HTN	92.4	85.9	0.280
MS present	33.9	24.4	0.373

WC – Waist circumference, DM – Diabetes Mellitus, TG – Triglycerides, HDL-c - High Density Lipoproteins-cholesterol, HTN – Hypertension.

4.3 Analysis of baseline features in HD & PD patients

4.3.1 Comparison of baseline demographic and clinical features between PD and HD patients

When comparison was made between HD and PD patients, the results showed no significant difference in the age of these two groups ,but the duration on dialysis was significantly different ($p = 0.007$). SBP was not significantly different in both groups but DBP showed a significant difference, being higher in PD patients than in HD patients ($p = 0.048$). Also, when indices of obesity were assessed, BMI, WC and HC were significantly higher in PD patients than in HD patients with $p < 0.05$ (Table 12).

Table 12: Baseline demographic and clinical features of PD and HD patients

Variable	PD (n = 46)	HD (n = 97)	p - value
Age (years)	39.3 ± 10.9	38.1 ± 10.3	0.508
Duration (mnths)	10.4 ± 13.9	27.7 ± 58.03	0.007
SBP (mmHg)	148.2 ± 23.7	147.9 ± 27.4	0.944
DBP (mmHg)	85.7 ± 15.3	79.9 ± 16.4	0.048
BMI (kg/m ²)	26.3 ± 4.5	24 ± 4.3	0.004
WC (cm)	93.5 ± 16.2	67.4 ± 28.2	p < 0.0001
HC (cm)	100.8 ± 15.1	76.5 ± 31.0	p < 0.0001
WHR	0.93 ± 0.08	0.88 ± 0.07	0.001

SBP – Systolic Blood Pressure, DBP – Diastolic Blood pressure, BMI – Body mass index, WC – Waist circumference, HC – Hip circumference, WHR – Waist –to-hip ratio.

4.3.2 Comparison of MS traits between HD & PD patients at baseline

Hypertension occurred frequently in HD (88.7%) and PD (91.3%) patients but the frequency was not significantly different between the two groups ($p = 0.774$). A significantly higher frequency of PD patients had increased waist circumference and increased serum triglycerides compared to HD patients (50% vs 18.6%; $p < 0.0001$ and 43.5% vs 20.6%; $p = 0.006$ respectively). The prevalence of MS was significantly higher in PD patients than HD patients with $p = 0.015$ (Table 13).

Table 13: Baseline MS traits between HD & PD patients

	Overall percentage (%)		p-value
	PD (n = 46)	HD (n = 97)	
WC (cm)	50	18.6	<0.0001
DM	21.7	27.8	0.541
TG (mmol/l)	43.5	20.6	0.006
HDL-c (mmol/l)	45.7	59.8	0.15
HTN	91.3	88.7	0.774
MS present	52.2	29.9	0.015

WC – Waist circumference, DM – Diabetes Mellitus, TG – Triglycerides, HDL-c – High Density Lipoprotein cholesterol, HTN – Hypertension.

4.3.3 Comparison of baseline laboratory results between PD and HD

Table 14 shows the comparison of the baseline laboratory (biochemical and haematological) results between PD and HD patients. Haemoglobin (PD – 9 ± 2.7 g/dl vs HD 8.1 ± 2.0 g/dl; $p = 0.044$) and Platelets (PD - 305.4 ± 148.2 vs HD - 255.3 ± 99.4 ; $p = 0.018$) were significantly lower in the HD patients than in PD patients. The WBC and the MCV was also lower in HD than in PD, but it was not significant. The factors associated with inflammation that were assayed for were elevated with a CRP of 13.4 ± 29.2 mg/l in PD patients and 10 ± 11.1 mg/l in HD patients and a Ferritin of 495.5 ± 373.3 mg/l in PD patients and 526.7 ± 621.9 mg/l in HD patients (Table 14).

Table 14: Baseline laboratory results between PD and HD patients

Variable	PD (n = 46)	HD (n = 97)	p-value
FBG (mmol/l)	5.2 ± 1.8	5.6 ± 1.9	0.159
TG (mmol/l)	1.7 ± 1.1	1.3 ± 1.8	0.119
HDL-c (mmol/l)	1.2 ± 0.3	1.2 ± 0.6	0.464
Iron (μ mol/l)	10.7 ± 4.8	11.0 ± 10.1	0.844
Iron sats. (%)	22.2 ± 9.1	22.5 ± 15.4	0.897
HB (g/dl)	9.0 ± 2.7	8.1 ± 2.0	0.044
WBC (10^9 /l)	8.3 ± 3.2	7.6 ± 3.1	0.182
PLT (10^9 /l)	305.4 ± 148.2	255.3 ± 99.4	0.018
MCV (fl)	85.2 ± 7.5	84.2 ± 6.9	0.411
URR	-	64.5 ± 15.5	-
Kt/V	-	1.4 ± 0.8	-
Calcium (mmol/l)	2.1 ± 0.3	2.0 ± 0.3	0.004
In. Phosphate (mmol/l)	2.0 ± 0.7	1.7 ± 0.6	0.020
CXP	4.3 ± 1.7	3.5 ± 1.3	0.004
PTH (pmol/l)	54.2 ± 49.8	67.6 ± 46.7	0.282
CRP (mg/l)	13.4 ± 29.2	10 ± 11.1	0.576
Ferritin (μ g/l)	495.5 ± 373.3	526.7 ± 621.9	0.756

FBG – Fasting blood glucose, TG – Triglycerides, HDL-c– Low High density lipoprotein, HB – Haemoglobin, WBC – White blood cells, PLT – Platelets, MCV – Mean cell volume, URR – Urea reduction ratio, Kt/v – K = Clearance, t = time, v = distribution volume, CXP – Calcium phosphate product, PTH – Parathyroid hormone, CRP – C - reactive protein.

4.4 Analysis of data of patients with MS compared to patients with no MS

4.4.1 Comparison of the demographic features of patients with MS and without MS

The MS was present in a higher percentage of males than females. However, there was no gender difference between patients with or without the MS. Smoking and the use of alcohol was not significantly different between both groups. Patients with ESRD due to HTN were more likely to have MS than patients with other causes for ESRD. The MS was present in a significantly lower percentage (13.2% in patients with MS and 28.9% in patients with no MS) of patients with previous transplants ($p = 0.040$). The percentage of PD patients with MS (45.3%) was more than the PD patients with no MS (24.4%) (Table 15).

Table 15: Characteristics of patients with no MS verses patients with MS

Variable	Overall percentage (%)		p - value
	No MS (n = 90)	MS (n = 53)	
Gender (female)	47.8	39.6	0.387
Smoking (yes)	11.1	17.0	0.466
Alcohol (yes)	7.8	11.3	0.552
Level of education(none)	67.8	66.0	0.168
Cause of ESRD:			0.094
HTN	54.4	66.0	
Other	45.5	34.0	
Previous Tx (yes)	28.9	13.2	0.040
Steroids (yes)	8.9	1.9	0.154
History of CVD (yes)	7.8	9.4	0.909

ESRD – End stage renal disease, HTN – Hypertension, CVD – Cardiovascular disease, Tx - Transplant., HD – Haemodialysis, PD – Peritoneal dialysis.

4.4.2 Comparison of baseline features of patients with MS verses patients with no MS

Comparing demographic and clinical features between patients with MS and those without MS, no significant difference was found for age and blood pressure (SBP

and DBP). However, patients with no MS had been on dialysis for a significantly longer duration than those without MS ($p = 0.009$). Also, BMI ($p < 0.0001$), WC ($p < 0.0001$) and HC ($p < 0.0001$) were significantly lower in patients with no MS than in patients with MS (Table 16).

Table 16: Baseline features between patients with MS and patients with no MS

Variable	No MS (n = 90)	MS (n = 53)	p - value
Age (years)	37.73 \pm 10.8	39.8 \pm 9.7	0.265
Duration (mnths)	28.6 \pm 60.1	11.1 \pm 13.4	0.009
SBP (mmHg)	148 \pm 26.2	147.8 \pm 26.3	0.977
DBP (mmHg)	81 \pm 16	83.1 \pm 16.8	0.474
BMI	23.7 \pm 3.9	26.5 \pm 4.8	< 0.0001
WC (cm)	68 \pm 26.2	89.1 \pm 25.3	< 0.0001
HC (cm)	77.1 \pm 28.7	96.6 \pm 26	< 0.0001
WHR	0.88 \pm 0.07	0.92 \pm 0.08	0.001

SBP – Systolic Blood Pressure, DBP – Diastolic Blood pressure, BMI – Body mass index, WC – Waist circumference, HC – Hip circumference, WHR – Waist –to-hip ratio.

4.4.3 Comparison of baseline laboratory results between patients with MS and patients with no MS

Comparing the laboratory features of patients with MS and those without MS, only fasting blood glucose, fasting triglycerides and HDL-c were significantly different between the groups ($p < 0.05$). CRP and Ferritin was higher in subjects with MS compared to subjects without MS, but there was no significant difference ($p = 0.260$ and $p = 0.559$ respectively) (Table 17).

4.5 Cardiovascular risk assessment at baseline

Out of a total of 143 dialysis patients, 3.5% had low risk of CVD, 75.5% had medium risk and 21% had high risk as shown in Figure 3.

4.5.1 Cardiovascular risk at baseline between HD and PD

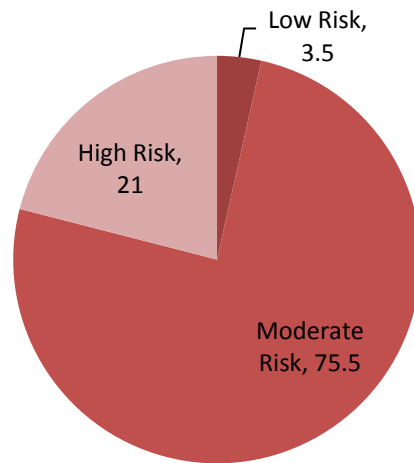


Figure 3: Overall cardiovascular risk at baseline

Table 17: Baseline laboratory results between patients with MS and patients with no MS

Variable	No MS (n = 90)	MS (n = 53)	p-value
FBG (mmol/l)	4.9 ± 0.9	6.5 ± 2.6	< 0.0001
TG (mmol/l)	1.2 ± 1.8	1.7 ± 0.9	0.042
HDL-c (mmol/l)	1.3 ± 0.6	1.1 ± 0.3	0.045
Ferritin (µg/l)	495.9 ± 582.1	553 ± 501.9	0.559
Iron (µmol/l)	11.4 ± 10.3	10.2 ± 5.2	0.434
Iron sats. (%)	22.6 ± 13.0	22.2 ± 14.8	0.890
HB (g/dl)	8.2 ± 2.3	8.8 ± 2.4	0.112
WBC (10 ⁹ /l)	7.8 ± 3.3	7.8 ± 2.9	0.905
PLT (10 ⁹ /l)	266 ± 117.8	280.6 ± 121.9	0.480
MCV (fl)	84.8 ± 6.8	84 ± 7.5	0.540
URR	66.2 ± 16.4	59.7 ± 11.5	0.138
Kt/v	1.5 ± 0.8	1.1 ± 0.4	0.112
Calcium (mmol/l)	2.0 ± 0.3	2.1 ± 0.3	0.484
In. Phos. (mmol/l)	1.8 ± 0.6	1.8 ± 0.7	0.901
CXP	3.7 ± 1.5	3.8 ± 1.6	0.787
PTH (pmol/l)	61.5 ± 44.9	59.8 ± 52.9	0.891
CRP (mg/l)	8.4 ± 10.3	15.3 ± 29.7	0.260

FBG – Fasting blood glucose, TG – Triglycerides, HDL-c– Low High density lipoprotein, HB – Haemoglobin, WBC – White ,
lood cells, PLT – Platelets, MCV – Mean cell volume, URR – Urea reduction ratio, Kt/v – K = Clearance, t = time, v =
distribution volume, CXP – Calcium phosphate product, PTH – Parathyroid hormone, CRP – C - reactive protein.

medium risk and 20.6% high risk. PD patients presented with 4.3% low risk, 73.9% medium risk and 21.7% high risk as shown in Figure 4.

4.5.2 Cardiovascular risk between male and female at baseline

Figure 5 illustrates that 26.6% of males were at high cardiovascular risk compared with 14.1% of females.

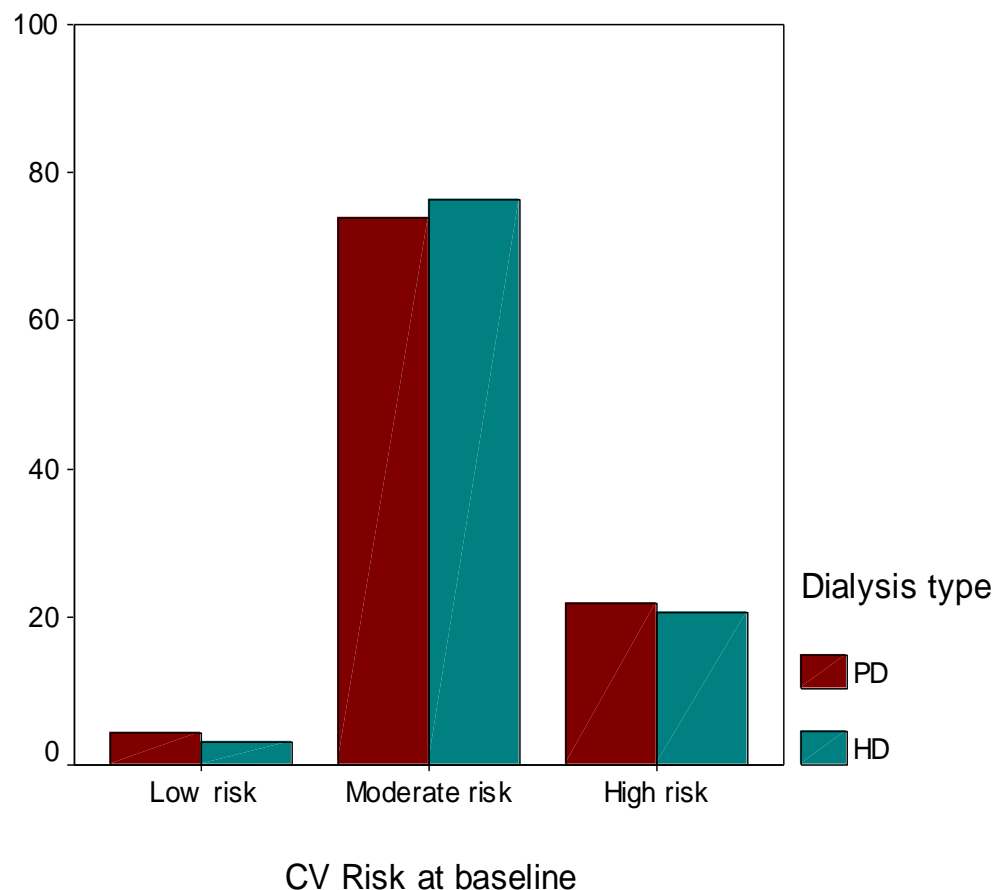


Figure 4: Cardiovascular risk at baseline between HD and PD

4.5.3 Cardiovascular risk in patients with MS compared with patients with no MS at baseline

In the group of patients with metabolic syndrome 80% presented with high risk of cardiovascular disease compared with 20% in the group of patients with no metabolic syndrome (Figure 6).

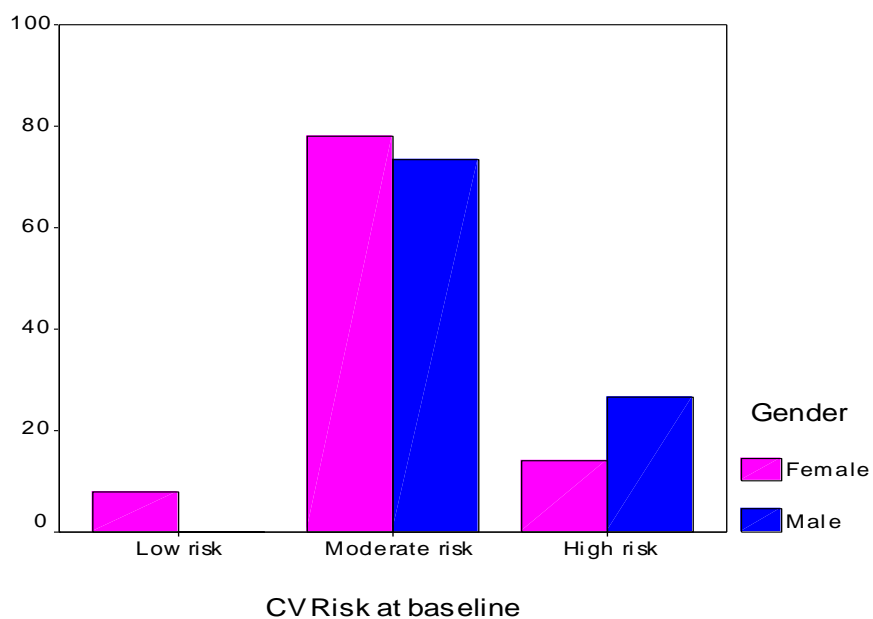


Figure 5: Cardiovascular risk between Male and Female at baseline

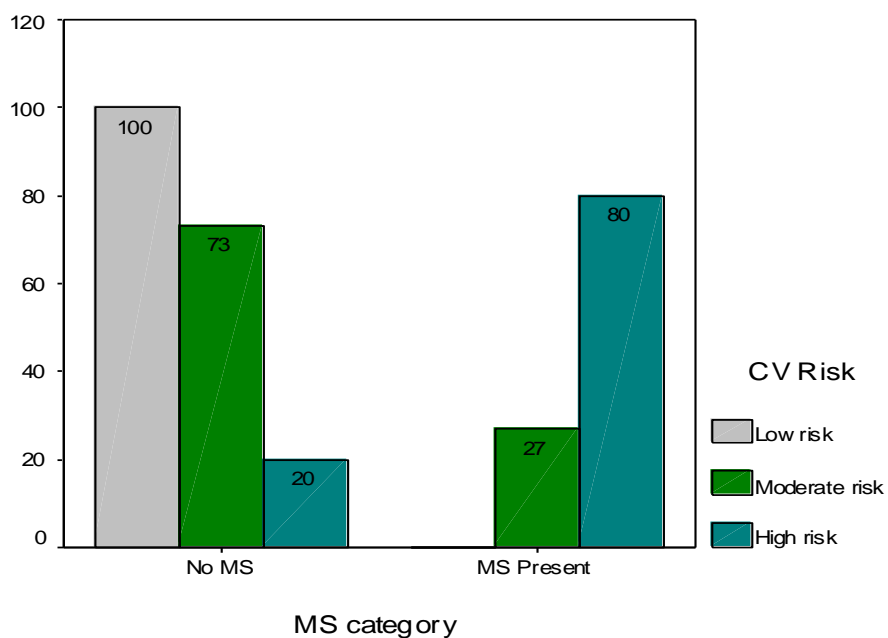


Figure 6: Cardiovascular risk in patients with MS compared with patients with no MS at baseline

4.6 Assessment of impact of dialysis on metabolic syndrome and its traits in dialysis patients at GSH

4.6.1 Comparison of baseline demographics of all patients followed up

There were 52 incident patients identified throughout the study. These patients formed part of those assessed at baseline but were followed up for a period of 12 months to ascertain the effect of dialysis (HD or PD) on MS and its traits. Of these patients, 29 (55.8%) were on HD and 23 (44.2%) were on PD. The baseline demographic features of these patients are as shown in Table 18.

Table 18: Baseline demographic features of all follow-up patients

Factor	Value (Mean or percentage) (n=52)
Age (years)	37 ± 9.85
Duration (mnths)	1.8 ± 2.0
Gender (%)	F – 38.5; M – 61.5
Dialysis type (%)	HD – 55.8; PD – 44.2
Smoking (current)	17.3
Alcohol (%)	7.7
Level of education (%)	
None	59.6
Matric	36.5
Post Matric	3.8
Employed (%)	61.5
Cause of ESRD (%)	
HTN	63.5
GN	7.7
DM	1.9
Other	26.9
Previous Tx (%)	7.7
History of CVD (%)	3.8

ESRD – End stage renal disease, HTN – Hypertension, GN – Glomerulonephritis, DM – Diabetes mellitus, CVD – , Cardiovascular disease, Tx – Transplant.

4.6.2 Comparison of clinical features (at baseline, 6 months and 12 months) of patients who were followed up

On assessment of clinical features of the patients at baseline, 6 months and 12 months, there was no significant difference in the variables assessed ($p > 0.05$) (Table 20). The prevalence of MS at baseline, 6 months and 12 months of follow-up was 46.2, 36.5 and 39.5% respectively ($p = 0.412$).

Many of the patients were male subjects (61.5%) and the mean age of all participants was 37.0 ± 9.85 years. Although the main cause of ESRD was hypertension (63.5%), 92.3% of the patients were on at least one anti-hypertensive agent and only 30.8% were on recombinant human erythropoietin (EPO) therapy (Table 19).

Table 19: Medication

Factor	Value (%)
Steroids	5.8
Anti – Diabetic	11.5
EPO	30.8
Anti - Hypertensives	92.3

EPO – Erythropoietin

Table 20: Comparison of clinical features of follow – up patients

Variable	Baseline	6 Months	12 Months	p-value
SBP (mmHg)	153 ± 23	154.9 ± 25.2	159.6 ± 30.8	0.229
DBP (mmHg)	87.2 ± 15.2	90.6 ± 15.6	89.4 ± 20.1	0.566
BMI	24.6 ± 4.2	25 ± 4.3	25.4 ± 4.4	0.215
WC (cm)	87.1 ± 18.2	91.3 ± 10.8	92.3 ± 11.3	0.056
HC (cm)	97.7 ± 19.1	102.3 ± 9.4	99.3 ± 16	0.383
WHR	0.89 ± 0.07	0.89 ± 0.08	1.12 ± 1.41	0.305
MS present (%)	46.2	36.5	39.5	0.412

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, BMI – Body Mass Index, WC – Waist Circumference, HC – Hip Circumference, MS – Metabolic syndrome.

4.6.3 Comparison of laboratory results of patients who were followed – up

Baseline laboratory (biochemical and haematological) profiles of the patients are as shown in Table 21. There were no significant differences observed over the period

of follow up in these patients even though haemoglobin and factors associated with mineral bone metabolism approached significant levels. C-reactive protein reduced in these patients but was not significantly different from baseline values.

4.6.4 Comparison of clinical features of the follow-up patients (baseline, 6 months and 12 months) according to their MS status

Table 22 shows comparison of the clinical features of all patients who were followed up according to their MS status at baseline (time 0), 6 months and 12 months. Systolic and diastolic BP's were similar in patients with and without the MS at all times. Obesity phenotypes (BMI, WC, and HC) were significantly higher in patients with MS compared to those without MS at baseline, 6 months and 12 months ($p < 0.05$).

4.6.5 Comparison of laboratory features of the follow-up patients at baseline, 6 months and 12 months

Comparison of laboratory features between patients with MS and those without MS are shown in Table 23. Although factors that were used to assay for inflammation

Table 21: Comparison of laboratory results of follow – up patients

Variable	Baseline	6 Months	12 Months	p-value
FBG (mmol/l)	5.8 ± 2.2	5.5 ± 1.2	6.1 ± 4.6	0.086
TG (mmol/l)	1.6 ± 1.0	1.5 ± 1.0	1.5 ± 1.1	0.580
HDL-c (mmol/l)	1.1 ± 0.3	1.2 ± 0.4	1.2 ± 0.4	0.239
Ferritin (µg/l)	339.3 ± 278.2	328.1 ± 266.4	358.9 ± 284.5	0.771
Iron (µmol/l)	11.8 ± 11.3	9.2 ± 4.1	11.0 ± 4.9	0.409
Iron Sats (%)	20.7 ± 9.5	18.6 ± 8.7	22.7 ± 11.8	0.269
HB (g/dl)	8.3 ± 2.4	8.9 ± 2.4	9.4 ± 2.2	0.086
Calcium (mmol/l)	2.1 ± 0.3	2.1 ± 0.3	2.1 ± 0.3	0.819
In.Phos. (mmol/l)	1.8 ± 0.6	1.8 ± 0.7	2.0 ± 0.8	0.134
CxP	3.7 ± 1.4	3.8 ± 1.5	4.1 ± 1.8	0.090
PTH (pmol/l)	58 ± 45.9	-	67 ± 46.7	0.089
CRP (mg/l)	12.6 ± 23.2	-	7.1 ± 11.7	0.122

FBG – Fasting blood glucose, TG – Triglycerides, HDL – High density lipoproteins, HB – Haemoglobin , CXP – Calcium , phosphate product, , PTH – Parathyroid hormone, CRP – C-reactive protein.

Table 22: Comparison of clinical features of follow-up patients at baseline, 6 months and 12months

Variable	Baseline			6 Months			12 Months		
	No MS (n = 28)	MS (n = 24)	p	No MS (n = 33)	MS (n = 19)	p	No MS (n = 26)	MS (n = 17)	p
SBP (mmHg)	153 ± 25	152.9 ± 20.8	NS	151.2 ± 23.1	161.3 ± 27.9	NS	156.9 ± 30.7	163.7 ± 31.4	NS
DBP (mmHg)	87.3 ± 15.8	87 ± 14.9	NS	89.9 ± 14.6	91.8 ± 17.6	NS	88.9 ± 21.4	90.4 ± 18.5	NS
BMI (Kg/m ²)	23.2 ± 4.0	26.3 ± 3.8	0.006	23.5 ± 3.9	27.5 ± 3.9	0.001	24.3 ± 4.0	27.1 ± 4.5	0.043
WC (cm)	81.5 ± 18.1	93.7 ± 16.3	0.015	87.6 ± 9.3	97.6 ± 10.6	0.001	88.7 ± 9.3	97.8 ± 12	0.008
HC (cm)	93.1 ± 20.1	103 ± 16.7	0.060	99.1 ± 8.5	108 ± 8.4	0.001	100.7 ± 8.6	97.2 ± 23.4	0.492
WHR	0.88 ± 0.07	0.92 ± 0.08	0.001	0.89 ± 0.09	0.90 ± 0.05	0.439	0.88 ± 0.09	1.48 ± 2.34	0.281

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, BMI – Body Mass Index, WC – Waist Circumference, HC – Hip Circumference, NS = not significant P value.

4.6.6 Metabolic Syndrome traits at baseline, 6 months and 12months

Figure 7 shows the changes in prevalence of MS and its traits with time in all dialysis patients who were followed up. No significant differences were seen over time for MS and all MS traits.

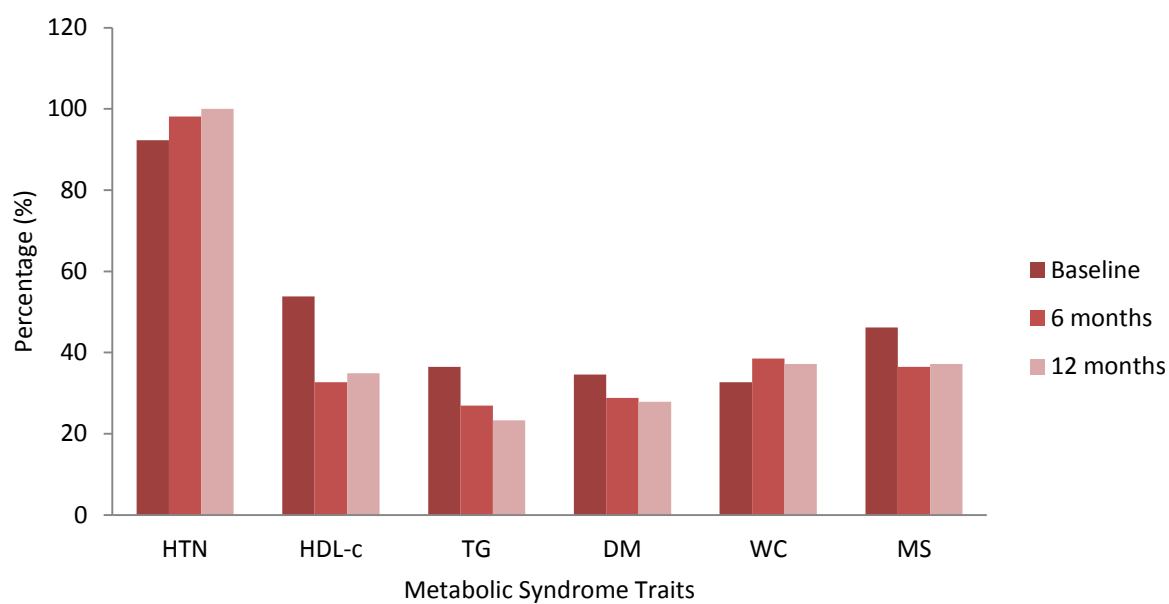


Figure 7: Frequency of MS traits at baseline, 6 months and 12 months. Only the frequency of patients with hypertension and increased waist circumference increased with time on dialysis. HTN – hypertension, HDL-c – high density lipoprotein cholesterol, TG – Triglycerides, DM – diabetes mellitus, WC – waist circumference, MS – metabolic syndrome.

Table 23: Comparison of laboratory features of the follow-up patients at baseline, 6 months and 12 months.

Variable	Baseline			6 Months			12 Months		
	No MS (n = 28)	MS (n = 24)	p	No MS (n = 33)	MS (n = 19)	p	No MS (n = 26)	MS (n = 17)	p
FBG (mmol/l)	5.0 ± 1.2	6.8 ± 2.6*	0.002	5.1 ± 1.0	6.2 ± 1.1	0.001	5.2 ± 1.1	7.6 ± 7.0	NS
TG (mmol/l)	1.1 ± 0.4	2.1 ± 1.1	< 0.0001	1.1 ± 0.4	2.2 ± 1.3	< 0.0001	1.0 ± 0.3	2.4 ± 1.4	< 0.0001
HDL-c(mmol/l)	1.2 ± 0.3	1.1 ± 0.3	NS	1.2 ± 0.4	1.1 ± 0.3	0.008	1.4 ± 0.4	0.9 ± 0.2	< 0.0001
Ferritin (µg/l)	281.6 ± 286.3	409.5 ± 256	NS	319.3 ± 261.4	343.2 ± 281.6	NS	309.4 ± 254.6	434.4 ± 317.9	NS
HB (g/dl)	7.8 ± 2.4	9.0 ± 2.2	NS	8.9 ± 2.4	8.9 ± 2.5	NS	8.9 ± 2.3	10.0 ± 1.9	NS
Ca (mmol/l)	2.0 ± 0.3	2.1 ± 0.3	NS	2.0 ± 0.3	2.2 ± 0.2	NS	2.0 ± 0.3	2.1 ± 0.2	NS
IP (mmol/l)	1.8 ± 0.6	1.9 ± 0.6	NS	1.8 ± 0.7	1.8 ± 0.6	NS	1.9 ± 0.8	2.1 ± 0.8	NS
CXP	3.6 ± 1.3	3.8 ± 1.4	NS	3.7 ± 1.7	3.9 ± 1.3	NS	3.8 ± 1.8	4.5 ± 1.9	NS
PTH (pmol/l)	63.7 ± 44.9	51.5 ± 47.2	NS	-	-	NS	66.8 ± 50.9	67.3 ± 40.7	NS
CRP (mg/l)	9.0 ± 10.4	16.7 ± 32	NS	-	-	NS	5.1 ± 4.4	9.9 ± 17.8	NS

FBG – Fasting blood glucose, TG – Triglycerides, HDL – High density lipoproteins, HB – Haemoglobin, CXP – Calcium phosphate product, PTH – Parathyroid hormone, CRP – C-reactive protein

4.6.7 Comparison of clinical features of the follow-up patients at baseline, 6 months and 12 months between HD and PD

Table 24 shows a comparison of the clinical features of all the patients on HD and PD who were followed up in this study, at baseline (time 0), 6 months and 12 months. There was no significant difference in systolic and diastolic BP's in patients on HD and PD. Obesity phenotypes (BMI, WC, and HC) were higher in patients on PD compared to those on HD at baseline, 6 months and 12 months, but it was not significant.

Table 24: Comparison of clinical features of the follow-up patients at baseline, 6 months and 12 months between HD and PD

Variable	Baseline		6 Mths		12 Mths	
	HD (n = 29)	PD (n = 23)	HD (n = 29)	PD (n = 23)	HD (n = 22)	PD (n = 21)
SBP (mmHg)	154.6 ± 21.8	151 ± 24.7	152.6 ± 22.2	157.9 ± 28.7	155.3 ± 26.4	164.1 ± 34.9
DBP (mmHg)	88.7 ± 16.1	85.3 ± 14.2	88.6 ± 14.1	93.0 ± 17.3	86.4 ± 20.9	92.7 ± 19.0
BMI	24.4 ± 4.3	24.9 ± 4.2	24.6 ± 4.5	25.5 ± 4.0	25.4 ± 4.5	25.4 ± 4.4
WC (cm)	85.3 ± 20.1	89.4 ± 15.7	89.8 ± 11.6	93.2 ± 9.8	92.2 ± 11.9	92.4 ± 10.9
HC (cm)	97.2 ± 22.4	98.3 ± 14.5	103.0 ± 10.9	101.5 ± 7.4	97.7 ± 21.6	101.0 ± 6.5

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, BMI – Body Mass Index, WC – Waist Circumference, HC – Hip Circumference.

4.6.8 Comparison of laboratory features of the follow-up patients at baseline, 6 months and 12 months between HD and PD

Although factors that were used to assay for inflammation (i.e. serum ferritin and CRP) were not significantly different between patients on HD and PD, they were much higher in the PD patients than in HD patients. For instance, CRP for HD and PD at baseline and 12 months were 10 ± 11.1 mg/l vs 15.8 ± 32.6 mg/l and 5.8 ± 4.1 mg/l vs 8.4 ± 16.4 mg/l respectively. Haemoglobin was significantly higher in PD (9.4 ± 2.7 g/dl) than in HD (7.5 ± 1.8 g/dl) at baseline, but there was no significant difference after 12 months (Table 25).

4.6.9 Analysis for correlation (Pearson's Correlation) for MS at baseline, 6 months and 12 months

When analysis was performed to determine factors that correlated with MS at baseline, 6 months and 12 months, there was a significant difference in the BMI at baseline ($p = 0.006$) and at 6months ($p = 0.001$), but no significant difference at 12 months ($p = 0.310$). A significant difference was seen in the WC at baseline ($p = 0.015$), 6months ($p = 0.001$) and at 12 months ($p = 0.008$). Blood pressure (SBP and DBP) did not correlate

Table 25: Comparison of laboratory features of the follow-up patients at baseline, 6 months and 12 months between HD and PD

Variable	Baseline		6Mnths		12Mnths	
	HD (n = 29)	PD (n = 23)	HD (n = 29)	PD (n = 23)	HD (n = 29)	PD (n = 23)
FBG (mmol/l)	6.1 ± 2	5.5 ± 2.3	5.5 ± 1.0	5.5 ± 1.4	7.3 ± 6.2	4.9 ± 0.8
TG (mmol/l)	1.2 ± 0.5	2.0 ± 1.2	1.3 ± 0.6	1.8 ± 1.2	1.1 ± 0.4	2.0 ± 1.5
HDL-c (mmol/l)	1.1 ± 0.3	1.1 ± 0.2	1.2 ± 0.3	1.1 ± 0.4	1.1 ± 0.3	1.3 ± 0.4
Ferritin (µg/l)	337.8 ± 328.9	341.3 ± 200.1	317.1 ± 297.5	341.9 ± 227.0	323.1 ± 283.7	396.3 ± 287.3
HB (g/dl)	7.5 ± 1.8	9.4 ± 2.7*	8.6 ± 2.5	9.2 ± 2.3	9.4 ± 2.2	9.3 ± 2.2
Calcium (mmol/l)	2.0 ± 0.3	2.1 ± 0.2	2.0 ± 0.3	2.1 ± 0.3	2.0 ± 0.3	2.1 ± 0.2
In. Phos (mmol/l).	1.8 ± 0.6	1.8 ± 0.6	1.9 ± 0.7	1.7 ± 0.6	1.8 ± 0.6	2.1 ± 0.9
CXP	3.6 ± 1.3	3.9 ± 1.4	3.9 ± 1.7	3.7 ± 1.4	3.7 ± 1.6	4.5 ± 2
PTH (pmol/l)	69.8 ± 45.9	43.2 ± 42.3	-	-	67.9 ± 50.4	66.0 ± 43.6
CRP (mg/l)	10.0 ± 11.1	15.8 ± 32.6	-	-	5.8 ± 4.1	8.4 ± 16.4

*p < 0.05. FBG – Fasting blood glucose, TG – Triglycerides, HDL – High density lipoproteins, HB – Haemoglobin, CXP – Calcium , phosphate product, PTH – Parathyroid hormone, CRP – C-reactive protein.

with MS at any time (Table 4.23). There was also significant correlation with FBG (baseline p = 0.002, 6months p = 0.001 and 12 months p = 0.090) and TG (baseline p < 0.0001, 6months p < 0.0001 and 12 months p < 0.0001). With reference to the inflammatory markers, ferritin and CRP, there was no significant correlation with MS (Table 26).

4.7 Cardiovascular risk assessment of follow-up patients

4.7.1 Analysis of the demographic and clinical features of the follow-up patients at baseline according to their CV risk assessment

Age increased with severity of CV risk assessment but was not significantly different (p = 0.842) (Table 27). Similarly, SBP (low risk 147.0 ± 19.5, moderate risk 152 ± 21.5 and high risk 156.5 ± 30.5) and DBP (low risk 74.3 ± 5.1, moderate risk 85.9 ± 14.1 and high risk 92.3 ± 19.7) increased with severity of CV risk but were also not significant. There

Table 26: Pearson's Correlation Coefficient for MS at baseline, 6months and 12months

Variable	Baseline (n = 24)		6 months(n = 19)		12months(n = 17)	
	Coef.	p	Coef.	p	Coef.	p
SBP (mmHg)	- 0.003	NS	0.194	NS	0.108	NS
DBP (mmHg)	- 0.009	NS	0.060	NS	0.037	NS
BMI	0.373	0.006	0.445	0.001	0.310	NS
WC (cm)	0.337	0.015	0.447	0.001	0.400	0.008
FBG (mmol/l)	0.424	0.002	0.441	0.001	0.262	0.090
TG (mmol/l)	0.543	< 0.0001	0.495	< 0.0001	0.588	< 0.0001
HDL-c (mmol/l)	- 0.078	NS	- 0.362	0.008	- 0.545	< 0.0001
Ferritin (µg/l)	0.231	NS	0.044	NS	0.217	NS
Calcium (mmol/l)	0.058	NS	0.271	NS	0.206	NS
In. Phos. (mmol/l)	0.069	NS	- 0.038	NS	0.159	NS
CXP	0.080	NS	0.049	NS	0.193	NS
PTH (pmol/l)	- 0.134	NS	-	-	0.005	NS
CRP (mg/l)	0.169	NS	-	-	0.205	NS

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, BMI – Body Mass Index, WC – Waist Circumference, FBG – Fasting blood glucose, TG – Triglycerides, HDL – High density lipoprotein, CXP – Calcium phosphate product, PTH – Parathyroid hormone, CRP – C - reactive protein.

Table 27: Demographic and clinical features of the follow-up patients at baseline according to their CV risk assessment.

Variable	Low Risk (n = 3)	Moderate Risk (n = 39)	High Risk (n = 10)	p - value
Age (years)	35.7 ± 7.2	36.7 ± 10.7	38.6 ± 7.1	0.842
Duration (mnths)	2.1 ± 1.2	1.9 ± 2.3	1.7 ± 0.6	0.954
SBP (mmHg)	147.0 ± 19.5	152 ± 21.5	156.5 ± 30.5	0.803
DBP (mmHg)	74.3 ± 5.1	85.9 ± 14.1	92.3 ± 19.7	0.196
BMI	20.5 ± 2.6	24.2 ± 3.9	27.4 ± 4.1	0.018
WC (cm)	79.3 ± 4.9	84.1 ± 18.9	101.3 ± 9.1	0.018
HC (cm)	96.7 ± 4.6	95.2 ± 21.1	107.4 ± 7.6	0.201

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, BMI – Body Mass Index, WC – Waist Circumference, HC – Hip Circumference.

was a significant increase in BMI (p = 0.018) and in WC (p = 0.018) with an increase in CV risk.

4.7.2 Analysis of the laboratory results of the follow-up patients at baseline according to their CV risk assessment

Table 28 shows the analysis of the laboratory results of the follow-up patients with a significant increase in FBG ($p = 0.011$) with an increase in severity of CV risk. There is a significant decrease in Kt/v ($p < 0.0001$) with an increase in severity of CV risk. Similarly, the URR decreased as severity of CV risk increased, this however only approached significant level ($p = 0.089$).

Table 28: Laboratory results of the follow-up patients at baseline according to their CV risk assessment

Variable	Low Risk (n = 3)	Moderate Risk (n = 39)	High Risk (n = 10)	p - value
FBG (mmol/l)	4.6 ± 1.4	5.5±1.4	7.9±3.7	0.011
TG (mmol/l)	1.0 ± 0.2	1.5±1.0	2.0±0.8	0.183
HDL-c (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	1.0 ± 2.3	0.447
Ferritin (µg/l)	131.0 ± 52.0	322.7 ± 277.7	480.6 ± 277.1	0.126
Iron (µmol/l)	8.4 ± 4.3	12.8 ± 12.6	8.8 ± 4.8	0.536
Iron Sats (%)	19.7 ± 10.1	21.4 ± 9.5	18.6 ± 10.0	0.707
HB (g/dl)	6.8 ± 3.2	8.4 ± 2.5	8.4 ± 1.9	0.528
MCV (fl)	81.8 ± 3.0	82.4 ± 6.0	80.4 ± 5.4	0.630
URR	93	55.4 ± 18.1	55.2 ± 5.7	0.089
Kt/v	3.2	1.1 ± 0.3	0.9 ± 0.2	< 0.0001
Calcium (mmol/l)	2.0 ± 0.0	2.0 ± 0.3	2.2 ± 0.2	0.192
In. Phos. (mmol/l)	1.6 ± 0.5	1.7 ± 0.6	2.1 ± 0.7	0.217
CXP	3.4 ± 1.0	3.5 ± 1.3	4.6 ± 1.2	0.083
PTH (pmol/l)	74.2 ± 67.4	54.1 ± 39.4	68.5 ± 64.1	0.565
CRP (mg/l)	2.3 ± 1.9	10.3 ± 14.8	23.6 ± 41.9	0.206

FBG – Fasting blood glucose, TG – Triglycerides, HDL-c– High density lipoprotein- cholesterol, HB – Haemoglobin, WBC – White blood cells, PLT – Platelets, MCV – Mean cell volume, URR – Urea reduction ratio, Kt/v – K = Clearance, t = time, v - distribution volume, CXP – Calcium phosphate product, PTH – Parathyroid hormone, CRP – c - reactive protein.

With reference to the inflammatory markers, ferritin ($p = 0.126$) and CRP ($p = 0.206$), there was an increase, but it was not significant.

4.7.3 Analysis of the demographic and clinical features of the follow-up patients at 12 months according to their CV risk assessment profile

Cardiovascular risk increased with an increase in age, but it was not significant ($p = 0.413$). There was a significant increase in BMI ($p = 0.026$) and in WC ($p = 0.001$) with an increase in severity of CV risk (Table 29).

Table 29: Demographic and clinical features of the follow-up patients at 12 months according to their CV risk assessment

Variable	Low Risk (n = 2)	Moderate Risk (n = 31)	High Risk (n = 10)	p - value
Age (years)	33.5 \pm 2.1	36.5 \pm 10.0	40.8 \pm 9.3	0.413
Duration (mnths)	1.7 \pm 1.1	1.7 \pm 0.8	1.6 \pm 0.7	0.925
SBP (mmHg)	143.5 \pm 51.6	155.7 \pm 29.2	174.9 \pm 30.4	0.174
DBP (mmHg)	85.0 \pm 21.2	87.4 \pm 21.3	96.6 \pm 15.4	0.441
BMI	23.4 \pm 2.7	24.5 \pm 4.2	28.6 \pm 4.0	0.026
WC (cm)	80.0 \pm 2.8	89.7 \pm 9.8	103.00 \pm 9.4	0.001
HC (cm)	99.5 \pm 0.7	100.7 \pm 8.8	94.9 \pm 30.0	0.611

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, BMI – Body Mass Index, WC – Waist Circumference, HC – Hip Circumference.

4.7.4 Analysis of laboratory results of the follow-up patients at 12 months according to their CV risk assessment

There was a significant increase in TG ($p = 0.016$) and HDL-c ($p = 0.028$) as severity of CV risk increased. There is a significant decrease ($p = 0.027$) in URR (moderate risk 67.0 \pm 5.8 and high risk 58.0 \pm 7.2, but no significant decrease ($p = 0.072$) in Kt/v (moderate risk 1.1 \pm 0.2 and high risk 0.9 \pm 0.2). The inflammatory markers (CRP and Ferritin) increased with an increase in CV risk, but it was not significant ($p = 0.861$ and $p = 0.616$ respectively) (Table 30).

Table 30: Laboratory results of the follow-up patients at 12 months according to their CV risk assessment

Variable	Low risk (n = 2)	Moderate Risk (n = 31)	High Risk (n = 10)	p-value
FBG (mmol/l)	4.6 ± 0.9	6.5 ± 5.3	5.4 ± 1.1	0.724
TG (mmol/l)	0.9 ± 0.1	1.3 ± 0.9	2.4 ± 1.5	0.016
HDL-c (mmol/l)	1.2 ± 0.6	1.3 ± 0.4	0.9 ± 2.0	0.028
Ferritin (µg/l)	177.0 ± 67.9	358.0 ± 291.8	397.8 ± 290.3	0.616
Iron (µmol/l)	8.0 ± 0.1	10.9 ± 5.3	11.8 ± 4.3	0.604
Iron Sats (%)	18.0 ± 0.0	23.0 ± 13.2	22.8 ± 8.3	0.852
MCV (fl)	89.7 ± 10.0	88.6 ± 6.4	86.6 ± 6.4	0.510
URR	...	67.0 ± 5.8	58.0 ± 7.2	0.027
Kt/v	...	1.1 ± 0.2	0.9 ± 0.2	0.072
Calcium (mmol/l)	2.3 ± 0.1	2.0 ± 0.3	2.1 ± 0.3	0.178
In. Phos. (mmol/l)	1.5 ± 0.6	1.8 ± 0.7	2.4 ± 0.8	0.042
CXP	3.4 ± 1.2	3.7 ± 1.7	5.4 ± 2.0	0.034
PTH (pmol/l)	92.6 ± 83.9	61.9 ± 45.9	77.5 ± 44.6	0.491
CRP (mg/l)	2.6 ± 1.6	7.2 ± 13.7	7.6 ± 3.3	0.861

FBG – Fasting blood glucose, TG – Triglycerides, HDL-c– Low High density lipoprotein, HB – Haemoglobin, WBC – White , blood cells, PLT – Platelets, MCV – Mean cell volume , URR – Urea reduction ratio, Kt/v – K = Clearance, t = time, v= distribution volume, CXP – Calcium phosphate product, PTH – Parathyroid hormone, CRP – C - reactive protein.

CHAPTER 5

DISCUSSION

The metabolic syndrome is associated with increased CV risk and is thought to be globally driven by the increasing prevalence of obesity and diabetes mellitus. Although several studies have reported on MS prevalence in different populations in sub-Saharan Africa; there are no studies that have specifically focused on patients with ESRD on dialysis. Dialysis patients have traditionally been known to have a high risk for CV diseases related to anaemia, high calcium-phosphate product, prevalent hypertension, atherosclerosis and inflammation. The prevalence of the MS in dialysis patients or whether the presence of MS worsens CV risk in chronic dialysis patients have not previously been evaluated in South Africa. This study is therefore very important in South Africa as it attempts to identify the impact of dialysis therapy on MS prevalence and prevalence of MS traits in chronic dialysis patients attending the renal unit at Groote Schuur Hospital in Cape Town giving that dialysis therapy may induce inflammation that could worsen the MS. Other important aspects of this study is related to the objectives of this study: (i) to identify the overall prevalence of the MS in dialysis patients (haemodialysis and peritoneal dialysis); (ii) to compare the frequency of MS and MS traits in HD and PD patients at GSH; (iii) to document the frequency of CV risk in dialysis patients and (iv) to identify factors that correlate with MS in our dialysis population.

5.1 Prevalence of the MS and MS traits in dialysis patients

Results of the present study indicated that MS, as defined by the NCEP ATP III criteria, was present in 37.1% of all dialysis patients (PD - 52.2%; HD - 29.9%; $p = 0.015$) (Table 8 and 13). These values indicate higher prevalence of the MS in dialysis patients in South Africa compared to the non-dialysis South African population as previously described by other authors. Motala et al, Schutte and Olckers and Okpechi et al have all previously reported lower prevalence rates of the MS in non-dialysis populations in Kwazulu Natal, the North-West province and in Cape Town of 22.1, 24.8 and 19.1% respectively (Motala et al, 2011, Schutte and Olckers, 2007 and Okpechi et al, 2007). This clearly indicates a higher clustering of risk factors for CV diseases in dialysis patients. The prevalence of the MS in one study reported from United States showed an overall prevalence of 69.3% in a study comprising 202 incident dialysis patients (Young et al). The reason for the extremely high prevalence reported by Young et al may be related to a higher frequency of patients with diabetes mellitus in their study (44.6% compared to 29.5% in this study) as the prevalence from their study was also dependent on cause of ESRD. Regardless, a high prevalence of MS in any population significantly increases the risk of death from CV diseases. This is more so in the dialysis population where there are numerous risk factors for CV disease (Table 31). In a Korean study of 106 stable non-diabetic patients on PD that assessed mortality, technical failure and hospitalization during a five-year follow-up period, the MS was found to be present in 50 patients (47.2%), who experienced significantly lower 5-year survival rates than patients without (90% versus 67%, $p = 0.02$). Univariate Cox regression analysis revealed increases in mortality risk with older age (RR: 1.15; 95%

CI: 1.07 – 1.23; $p < 0.001$), hypoalbuminaemia (RR: 0.06; 95% CI: 0.01 – 0.30; $p = 0.001$), elevated hsCRP levels (RR: 1.14; 95% CI: 1.07 – 1.22; $p < 0.001$) and the presence of MS (RR: 3.39; 95% CI: 1.16 – 9.94; $p = 0.02$). Cardiovascular diseases, malignancy and infections were found to be the major causes of death in 40.0%, 23.1% and 23.1% respectively (Jung et al, 2010). The acceptance of younger patients to dialysis and the exclusion of middle aged diabetic patients may be a major reason to explain some of the differences between this South African data and results from other parts of the world (Moosa et al, 2006; Okpechi et al, 2012).

Table 31: Risk factors for CV disease in dialysis patients

Traditional Risk Factors	“Uraemia-specific” risk factors	Novel Risk Factors
Hypertension	Anaemia	Carbamylation products
Diabetes Mellitus	Phosphate retention	Endothelial dysfunction
Dyslipidaemia	Hyperparathyroidism	Sympathetic system activation
Male Gender	Uraemic toxins	Inflammation
Left ventricular hypertrophy	Hyperhomocystinaemia	Oxidative stress
Smoking	Volume overload	Wasting
Sedentary lifestyle		
Insulin resistance		

Adapted from Johnson et al Comprehensive Clinical Nephrology 2007

Hypertension was the most common individual MS trait in our study, being present in 89.5% of all the study patients (Table 8). Increased waist circumference, diabetes

mellitus, hypertriglyceridaemia and low-HDL cholesterol were present in 28.7%, 25.95, 28.0% and 55.2% respectively. In the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study, Longenecker et al found hypertension to be present in 96% of their entire study population of 1041 dialysis patients (Longenecker et al, 2002). Other studies have equally reported hypertension to be very common in the dialysis population. Young et al found hypertension to be present in 99.0% of their patients and Jalalzadeh et al found it to be present in 68.8% of their patients. The high prevalence of hypertension in dialysis patients may be due to the presence of renal disease (as this is a known and common cause of hypertension), abnormal or inadequate fluid removal in these patients or due to presence and worsening of vascular disease in the patients. It has been reported that about 30% of all deaths worldwide may be directly or indirectly attributable to hypertension (Kearney et al, 2005). One meta-analysis of placebo-controlled studies of hypertension has shown that for every 12/6 mmHg reduction in BP, there is a 35% – 40% reduction in stroke, 20% – 25% reduction in myocardial infarction, and > 50% reduction in heart failure and prevention of CV disease-related death rates (Mancia et al, 2007).

The high prevalence of hypertension in this study could therefore represent an increased risk for CV morbidity and mortality in our dialysis population. The overall frequencies of other MS traits are shown in Table 8, but are fewer in comparison to similar published studies. Whether this is related to differences in socio-economic status, diet or genetic factors was not assessed in our study as it was not part of the aims of this study. Interestingly, the prevalence of MS did not significantly differ between males and females. However, there were more female patients with a higher waist

circumference compared to males (Table 11). Motala et al observed that in subjects with metabolic syndrome, the most frequent individual component was a high waist circumference in both men (90.9%) and women (96.9%) while the least frequent component was elevated fasting plasma glucose in men (50.0%) and women (27.1%) and low serum HDL cholesterol in men (50.0%). A higher hip circumference and waist-to-hip ratios in South African women than in men in the general population was also reported by Motala et al. In this study, and as would be expected, factors that define the MS strongly and significantly correlated with MS at baseline, 6 months and 12 months in those patients who were followed up (Table 26).

5.2 Metabolic syndrome in the HD and PD cohorts

The significantly higher prevalence of MS observed in patients on PD than in those on HD is remarkable and has been described by others. Fortes et al reported a prevalence of MS in 54% PD patients compared to 30% HD patients in Brazil ($p < 0.005$) (Fortes et al, 2007). In an Australian study involving 200 stages 4 (pre-dialysis) and 5 (dialysis – HD and PD) CKD patients, Johnson et al reported prevalence of the MS to be significantly higher in PD patients than in HD patients (38% vs 26%; $p < 0.05$) (Johnson et al, 2007). There are several metabolic complications associated with the use of conventional PD fluids that contain glucose as the osmotic agent. Delarue et al have shown that 60% – 80% of the glucose delivered into the peritoneal cavity during a session of PD is absorbed through the peritoneum. Increased availability (absorption) of glucose may therefore lead to obesity and hyperglycemia as well as dyslipidemia, all components of MS (Delarue et al, 1994).

The increased abnormal metabolism (due to a persistently high delivery of glucose load) in PD has often led to requests for use of substitute non-glucose containing fluids (such as Icodextrin) in PD. In an evaluation of 209 patients, the carbohydrate absorption during an 8-hour overnight exchange was significantly lower with Icodextrin (29 ± 5 g, or 20%) than with 4.25% dextrose (62 ± 5 g, or 86%; $p < 0.01$) (Mistry et al, 1994). Also, the use of Icodextrin solutions may also result in lower serum levels of insulin (28.6 ± 6.0 μ U/ml vs 36.1 ± 10.2 μ U/ml) and an increase in insulin sensitivity (hence lower risk of diabetes) compared to patients receiving standard dextrose solutions (Amici et al, 2001). All PD patients in our hospital (unit), hence in this study, use different concentrations of glucose based PD fluids (1.25%, 2.5% or 4.25%) for dialysis.

Although the proportion of patients with diabetes and the mean blood glucose was similar in PD and HD patients in our study, it was observed that significantly more PD patients than HD patients had hypertriglyceridaemia (43.5% vs 20.65; $p = 0.006$) and increased waist circumference (50.0% vs 18.6%; $p < 0.0001$) both of which may be indirectly attributed to increased glucose loading in the PD patients (Tables 13 and 14).

5.3 Metabolic syndrome in males and females

This study found that the MS was present in 33.9% males and 24.4% females ($p = 0.373$). Jalalzadeh et al reported a male prevalence of 60.9% compared to 39.1% prevalence in females in those on haemodialysis. In PD patients, Park et al found the prevalence to be slightly more in males than females (53.6% vs 46.4%). In non-CKD/ESRD patients, prevalence of the MS has often been shown to be higher in females. For instance, Morales et al, in a study comprising 4,753 adults aged 20 years

or older from 2,636 households in 790 enumeration areas in the Philippines reported an overall prevalence of 11.9% (13.4% in females and 10.5% in males) (Morales et al, 2008). Similarly, one data from South Africa, although showing an overall prevalence of 22.1%, the prevalence in women was over twice that in males (25.0% vs 10.5%)(Motala et al, 2011). The reason for this gender reversal in ESRD patients may be related to differences in gender prevalence of ESRD. Data from the USRDS show that from 1980 to 2009, incidence and point prevalent rates of ESRD are higher in males (Collins et al, 2011). Recent data from our center also show a higher prevalence of ESRD in males (Okpechi et al, 2012). Hence, the higher prevalence of the MS seen in males may just be a reflection of the higher prevalence of ESRD seen in males. It is however unknown if there are other factors that may account this observation.

5.4 Cardiovascular risk in dialysis patients at Groote Schuur Hospital Cape Town

This study is the first, to our knowledge, in sub-Saharan Africa that has attempted to stratify CV risk in dialysis patients. Traditional CV risk factors are often prevalent in dialysis patients as these could be related to the aetiology of kidney disease in the patients; for instance, hypertension and diabetes mellitus are common causes of CKD and would thus be more prevalent in the CKD population than in the general population. The CHOICE study demonstrated that many dialysis patients have high prevalence rates of traditional risk factors for cardiovascular disease (Longenecker et al, 2002). One study from Nigeria in non-dialysis CKD patients found at least one form of ECG abnormality in 86% of the patients in their study, with left ventricular hypertrophy, left atrial enlargement and combination of left ventricular hypertrophy (LVH) and left atrial

enlargement (LAE) found in 27.6%, 21.6% and 17.2% respectively (Chijioke et al, 2012). In our unit, Freercks et al recently reported that coronary calcification (a surrogate of CV risk) was present in 38.6% of HD patients and that this was associated with age and prior CV disease (Freercks et al, 2012). In our study, the frequency of patients on HD and PD with low, moderate or high CV risk was similar and not statistically significantly different (Figure 4). This might just be a pointer to the fact that CV risk is similar in all dialysis patients independent of modality. However, there were significantly more male patients with high CV risk compared with females (26.6% vs 14.1%; $p = 0.012$) (Figure 5). Male gender is known to be a non-modifiable risk factor for CV disease (NCEP 2002). Given the high prevalence of CV risk in our dialysis population, it can therefore be argued that there is a need to pay more attention to the treatment of these risk factors in order to reduce CV morbidity and mortality.

5.5 Impact of dialysis on MS

In this study, to assess the impact of dialysis on MS, incident ESRD patients starting dialysis therapy were followed up over a 12-month period. Clinical and laboratory parameters were assessed in these patients at baseline (onset of dialysis), at 6 months and at 12 months. Of the 52 patients followed-up, MS was present in 46.2% at baseline, 36.5% at 6 months and 37.2% after 12 months ($p = 0.412$; Table 20 and Figure 7). Although one may look at this and want to conclude that dialysis reduces the proportion of patients with MS, a closer look at our data will show the opposite. The mean SBP, DBP, BMI, triglycerides and waist circumference of patients who were followed up in this study increased from baseline to 12 months (Tables 20, 4.21 and 4.22). However,

due to exclusion of some patients during follow up either due to death (n = 2) or getting a renal transplant (n = 7), the changes in these MS parameters were not significant and the prevalence of MS over time appeared to reduce. Seven of the patients who did not complete follow up at 12 months had MS at baseline (Table 23).

Many studies indicate that the procedure of dialysis may contribute to inflammation in ESRD patients (Docci et al,1990; Ayus et al, 2005; Lai and Leung 2010) . The adipose tissue is known to secrete many inflammatory hormones (adipokines) such as TNF- α and IL-6 (Xu et al, 2003) which worsen insulin resistance, hence the MS. In this study, we sought to identify if inflammatory markers (CRP and ferritin) were made worse by dialysis, especially in patients with MS given that dialysis and the MS can contribute to inflammation.

The results of this study did not find a significant change in the levels of these inflammatory markers over the period of follow up in all the patients or specifically in those with the MS from baseline (Table 21). However, those with the MS had higher values of these markers at baseline and at 12 months (Tables 4.21 and 4.23). Although persistent infections is a common cause of raised inflammatory markers in ESRD patients, it could be that at the time of assessment of our patients, there were none who had any active infections accounting for the absence of elevated inflammatory markers. Another reason why the levels of inflammatory markers were not significantly elevated as expected could be the relatively short duration of follow-up (12 months) in this study. Factors such as heart failure and atherosclerosis which also commonly account for elevated inflammatory markers in ESRD often happen over extended durations on

dialysis and therefore could partly explain why in our patients' markers of inflammation did not increase with time.

Finally, as CRP and ferritin are acute phase reactants, they may not be optimal markers in the assessment of inflammation in dialysis ESRD patients. Indeed, some studies have prospectively compared the predictive value on mortality of different inflammatory markers in dialysis patients and shown that that IL-6 is a better prognostic marker than other molecules including CRP or TNF- α (Honda et al, 2006). Also, among dialysis patients, high sensitivity CRP (hs-CRP) and IL-6 have been associated with twice the risk of sudden cardiac death (Parekh et al, 2008) and 1.43 - fold higher risk of cardiovascular mortality (Rao et al 2005). Although CRP was used as marker of inflammation in this study, hs-CRP and IL-6 were not assessed. Despite the inability of our study results to show that inflammation is increased in dialysis patients, it is important to identify, treat and reduce CV risk factors in dialysis patients as this will go a long way in reducing the morbidity and mortality associated with increased CV risk in this population.

CHAPTER 6

CONCLUSION

This study is about the only one known to us from South Africa describing the prevalence of the MS and CV risk in both HD and PD patients and reporting on factors observed to be correlated with the MS and CV risk in this population. This is the main strength of this study. Moreover, there are not many studies worldwide that have assessed the prevalence of the MS in an overall dialysis population. This study has therefore shown that MS occurs at a higher frequency than in comparative studies in the general population and that among all dialysis patients, PD patients have a higher burden of MS compared to HD patients.

Although we did not follow-up patients long enough to assess hard end-points like the occurrence of a CV disease like stroke, myocardial infarction or death occurring from a cardiovascular cause, our results suggest that our dialysis patients are at greater risk of these complications than non-dialysis age and gender matched controls in the general population.

Thus, this study uncovers the need for early identification of these risk factors and urgent initiation of therapy. For example, hypertension was the most common MS risk factor observed overall (89.5%, see Table 8) and was also the most common MS trait observed in HD (88.7%) and PD (91.3%) patients (Table 13). As hypertension is known to be a common contributor to CV morbidity and mortality worldwide, there is therefore need: (i) to increase awareness of hypertension amongst dialysis patients, (ii) to ensure

that all dialysis patients are receiving correct and adequate anti-hypertensives and (iii) to ensure adequate control of BP in dialysis patients to recommended targets. In a South Korean study, Jung et al have shown that in patients on chronic maintenance HD, stroke was more frequent in those with history of hypertension and with higher SBP/DBP at the time of admission than the ESRD patients without stroke. This therefore strengthens the argument for adequate treatment to enable reduction of the prevalence of all MS traits in dialysis patients.

In patients who were followed-up for 12 months in order to assess the impact of dialysis on the MS, there was a significant increase in waist circumference ($p = 0.001$), BMI ($p = 0.026$), serum triglycerides ($p = 0.016$), inorganic phosphates ($p = 0.042$) and calcium-phosphate product ($p = 0.034$) (Tables 29 and 30). This thus shows the metabolic nature of ESRD and dialysis in worsening the values of these variables. Markers of inflammation (serum ferritin and CRP) did not significantly increase as was expected over the 12 month period. This could be as a result of the insensitivity of serum ferritin and CRP as markers of inflammation if the degree of inflammation is low. Others have used newer and more sensitive markers for detecting inflammation in their cohort.

6.1 Limitations of this study

This study has a number of weaknesses. Although we were able to find significant changes with time on some MS traits during dialysis, not being able to follow these patients for a longer duration may have blunted our results as the true impact of dialysis on the MS may not have been well studied. Also, we were unable to assess certain

socio-demographic factors such as level of income, type of diet and possibly certain unique cultural practices that could have had influence on the frequency of these MS traits. Our inability, due to financial constraints, to assay for more sensitive markers of inflammation such as interleukin-6, TNF- α and hs-CRP may be some of the reasons for not observing an increased level of inflammation in the dialysis patients with time on dialysis. In terms of prediction of recurrent CV events and death, the strongest association with prognosis has been with hs-CRP which has consistently predicted new coronary events in patients with unstable angina and acute myocardial infarction. Hence, there is need for further research on the usefulness of more sensitive markers of inflammation in dialysis patients. Also, we did not take into consideration the role that lipid lowering agents such as simvastatin could have played with regards to changes in lipid profile and their effects in attenuating inflammation and inflammatory markers. Although many of our patients were prescribed this medication, however, as their compliance cannot be ascertained, we did not assess this factor in the present study. Finally, our study sample size was limited by the number of patients accepted for the long-term renal replacement therapy in our unit. Hence, the relatively small sample size of our study could have limitations on our study results.

6.2 Recommendation

Given the results of this study, it is recommended that modifiable CV risk factors should be routinely looked for and treated in all dialysis patients.

CHAPTER 7

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CHAPTER 8 – APPENDICES

Appendix A: Renal assessment tool for renal replacement therapy rationing in the Western Cape, South Africa

Category 1*	Category 2**	Category 3***
Age < 50 yrs	Age 50 – 60 yrs	Age > 60 years
BMI < 30 kg/m ²	BMI 30 – 35 kg/m ²	BMI > 35kg/m ²
Gainfully employed	Hypertension with TOD	Transplantation contraindicated or associated with unacceptable risk
HIV negative	Diabetes Mellitus	HIV infection other than described in category 2
HBsAg Negative	Smoking	Active substance abuse
South African citizen	HBsAg/HCV positive (no cirrhosis)	HBeAg positive or cirrhosis
	HIV positive (CD4 > 200, undetectable viral load, on HAART)	Diabetes mellitus + age > 50 yrs
	Late presentation needing urgent dialysis	Active uncontrollable malignancy with short life expectancy
	Comorbid disease (e.g. stable IHD)	Non-South African citizen
	Previous renal transplant	Advanced irreversible progressive vital organ disease (cardiac/cerebrovascular/liver/lung/unresponsive infections)
	Poor home circumstances	Mental illness resulting in diminished capacity to take responsibility for actions
	Convicted criminal in serious offence	Habitual non-adherence with any medical treatment
	Not gainfully employed	
	Poor social network/support	
	No proximity to dialysis unit	

BMI – Body mass index; HIV – Human immunodeficiency virus; HBsAg – Hepatitis B surface antigen; HCV – Hepatitis C virus; HAART – Highly active antiretroviral therapy; HBeAg – Hepatitis B e antigen; IHD – Ischaemic heart disease; TOD – Target organ damage

* - Patients in this category must be accepted

** - Patients in this category will be accepted depending on availability of space on the programme and the number of factors in this category

*** - Patients with any one of category 3 factors will be excluded

Appendix B: The Human Research Ethics Committee of the University of Cape Town [REC REF: 379/2009] approval



UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

09 September 2009

REC REF: 379/2009

Dr IG Okpechi
Medicine

Dear Dr Okpechi

PROJECT TITLE: IMPACT OF DIALYSIS THERAPY ON METABOLIC SYNDROME TRAITS AT THE GROOTE SCHUUR HOSPITAL CAPE TOWN.

Thank you for submitting your study to the Research Ethics Committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 16th September 2010.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely,


PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

S Thomas

Appendix C: The Durban University of Technology Faculty Research Committee approval



20 August 2010

Reference: Proposal Ratification: MJ Maree, Student number 21032640

Dear Mrs Maree

MASTER OF TECHNOLOGY DEGREE IN CLINICAL TECHNOLOGY - NEPHROLOGY

This serves to confirm the ratification of your research proposal by the Higher Degrees Committee, at its meeting on **17 August 2010**, as follows:

1. Research proposal and provisional dissertation title:

THE IMPACT OF DIALYSIS THERAPY ON METABOLIC SYNDROME TRAITS AT THE GROOTE SCHUUR HOSPITAL

Supervisor: Prof JK Adam

Co-supervisor/s: Dr IG Okpechi

Please note that any proposed changes in the dissertation title require the approval of your supervisor/s, the Faculty Research Committee, as well as ratification thereof by the Higher Degrees Committee.

2. Research budget to the amount of **R 14 978.00**

Please note that this funding is not a scholarship or bursary and is therefore not paid directly to you, but is controlled by your supervisor. Any proposed changes to use of this funding allocation require the approval of your supervisor and the Faculty Research Committee.

The Institutional Research Committee has stipulated that:

- (a) The funding for the Research budget allocated to you is subject to compliance with the Intellectual Property Rights from Publicly Financed Research and Development Act No. 51, 2008 (including the Regulations) in force from time to time;
- (b) This University retains the ownership of any Intellectual Property (patent, design, etc.) registered in respect of the results of your Masters/Doctors Degree in Technology studies as a result of the award and the provisions of the above Act;
- (c) Should any amounts accrue to you in respect of the disposal of any tangible assets developed or created during the course and scope of your Masters/Doctors Degree in Technology, such amount will first be directed towards repaying the University the funding investment which the University has made in approving your request for funding, with the balance being retained by you;

Postgraduate Development and Support Directorate

P O Box 1334, Durban, 4000, South Africa Tel: +27 (31) 373 2828/2436 - Fax: +27 (31) 331 373 2847
www.dut.ac.za



- (d) If the University provided the equipment/materials for the creation of artefacts, this cost must be refunded to the University if such artefacts are sold;
- (e) Should you find any of the terms above not acceptable then you are given the option to decline the Research budget award to your project in writing.

May we remind you that in terms of Rule G25(2)(b), if you fail to obtain the Masters/Doctors degree within the maximum time period allowed after first registering for the qualification, the Senate may refuse to renew your registration or may impose any conditions it deems fit. You may apply to the Faculty Research Committee for an extension.

Please note that you are required to re-register each year.

You are invited to apply for a Postgraduate Award from the Postgraduate Development and Support Directorate. The forms are available on the DUT website at www.dut.ac.za; please note that conditions apply. You are also invited to contact the PGDS office to enquire about further support for your research studies.

Should you experience any problems relating to your research, your supervisor must be informed of the matter as soon as possible. If the difficulties persist, you should then approach your Head of Department and thereafter the Executive Dean of the Faculty.

Please refer to the 2010 General Rule Book concerning the rules relating to postgraduate studies, which include *inter alia* acceptable minimum and maximum timeframes, submission of thesis/dissertations, etc. You are also advised to read the Postgraduate Students' Guide which is available on the DUT website.

Please do not hesitate to contact this office for any assistance. We wish you success in your studies.

Kind regards,



Prof Annelie Jordaan

Director: Postgraduate Development and Support Directorate

Cc Faculty officer: **Mr Vikesh Singh**

TIP Research Finance: **Ms R Govender**

Head of Department: **Mrs P Pillay**

Supervisor: **Prof JK Adam**

Appendix D: Patient information and consent form



Department of Biomedical and Clinical Technology

Faculty of Health Sciences

P O Box 1334, DURBAN, 4000

Title of the Research Study:

The impact of dialysis therapy on metabolic syndrome traits at the Groote Schuur Hospital in Cape Town

Principal Investigator:

Mrs Marilyn Maree, student enrolled for the Masters Degree: Clinical Technology (Nephrology) at Durban University of Technology.

Brief Introduction and Purpose of the Study:

You are invited to be a volunteer for a research study. The information in this letter will help you understand what the research is about and how it will benefit your quality of life on dialysis. If there are any questions, which are not clearly explained in this letter, do not hesitate to ask the promoter or investigator.

The purpose of this study is to find out the extent of metabolic and cardiovascular risk your body has been exposed to due to end stage renal disease (ESRD) and dialysis. The metabolic syndrome describes a condition in which a person has a combination (three or more) of any of five metabolic disorders (diabetes, hypertension, high triglycerides, low HDL-cholesterol and increased waist circumference). The presence of these disorders is thought to increase the risk for cardiovascular disease.

Outline of the Procedures:

Routine bloods will be taken at the start of the study and the following tests will be requested: Haemoglobin, calcium, phosphates, PTH (parathyroid hormone), lipogram, (Triglycerides, cholesterol, LDL-c, HDL-c), blood glucose (mmol/L) and ferritin. The clinical assessment of the patient will include measurement of blood pressure (average of 3 readings), height (cm), weight (kg), body mass Index (kg/m^2), waist circumference (cm) and hip circumference (cm). The cardiovascular assessment will be computed from the electrocardiogram (ECG). These tests will be repeated at 6 months and 12 months after commencement of dialysis in order to determine how the metabolic and cardiovascular profiles have been altered by dialysis therapy.

Risks or Discomforts to the Subject:

There are no risks or side effects involved. Blood samples will be taken from the dialysis needles, which is routinely inserted to perform dialysis therapy. Therefore you will not endure any added pain.

Benefits:

Early detection of factors that are associated with metabolic and cardiovascular risk is amenable to treatment. If it is found that you have a high risk, aggressive therapy will be initiated to halt or slow down the progression of such risk factors.

Reason/s why the Subject May Be Withdrawn from the Study:

Your participation is entirely voluntary and you can refuse to participate or stop at any time without stating a reason. Your withdrawal will not affect your access to future medical care. The investigator retains the right to withdraw you from the study if it is your best interest.

Remuneration:

There will be no remuneration for the participant.

Costs of the Study: The patient will be liable for the normal costs of dialysis and routine biochemical analysis.

Confidentiality:

All information obtained in this trial will be strictly confidential. Data that may be reported in the scientific journals or published will not include information that will identify you as a patient in this study.

Research-related Injury:

There will not be any research related injuries. Your withdrawal at any time will not affect your medical treatment.

Persons to Contact in the Event of Any Problems or Queries:

Mrs Marilyn Maree	Prof Jamila Adam	Prof. IG Okpechi
Principal Investigator	Promoter	Co/Promoter
0732153171	031 373 5291	0844167793

Statement of Agreement to Participate in the Research Study:

(I,.....subject's full name,
ID number....., have read this document in its
entirety and understand its contents. Where I have had any questions or queries, these
have been explained to me byto my
satisfaction. Furthermore, I fully understand that I may withdraw from this study at any
stage without any adverse consequences and my future health care will not be
compromised. I, therefore, voluntarily agree to participate in this study.

Subject's name **Subject's signature**.....
Date:.....

Researcher's name **Researcher's signature**.....
Date:.....

Witness name **Witness signature**.....
Date:.....

Supervisor's name..... **Supervisors signature**.....
Date:.....

Appendix E: Incwadi yolwazi kwane sivumelwano

Imalunganophandolwezemfundo:

Ingxinano engamandla ye dialysis therapy yesigulo se metabolic syndrome kwane mpawu zaso e G.S.H e Cape Town

Umphandi Omkhulu:

Mrs Marilyn Maree, Umfundi ofundele i M.D Clinical Technology (Nephrology - malunga nezintso) e Durban University of Technology

Ukwazisa kancinci kwane mbangi / isizathu sokuyifundela

Uyamenywa ukuba uzokuzigqatsa kuphando ngezifundo. Ulwazi oluku lencwadi luyakukunceda ukuba uqonde (wazi) uphando lunga ntoni na kwaye ibaluleke kangakanani ukwazi nge dialysis ebomini bakho. Ukuba ikhona nayiphina imibuzo, engacaciswanga kakuhle kule ncwadi, sukulibazisa ungonqeni ukubuza kumkhuthazi okanye kumphandi.

Okufutshane ngale nqubo :

Igazi liyakuthathwa rhoqo xa kuqala ezizi fundo kwaye oluvavanyo liyaku celwa : Haemoglobin, Calcium, Phosphates, Parathyroid Hormone i program, (Triglycerides, Cholesterol, LDC-c, HDL-c) blood glucose (mmol/L) kwane ferritin. Inqubo yase sisibhedlele yesigulane iyafuneka umlinganiselo wonyuko gazi (umlinganiselo wazo zontathu) ubude (cm) ubunzima (kg) ubukhulu bomzimba (kg.m^2) ubukhulu, ukumila kwesinqa (cm) ubukhulu bedywantsi (cm). Inqubo yentliziyo (ubetho) luyakujongwa nge computer yomatshini be ECG. Oluvavanyo luyakuphinda phindwa kwi nyanga ezi 6 kwane 12 emva kokuba beliqaliwe olwe dialysis ukwenzela okokuba kuthathwe izigqibo zokuba kuyakuqhutywa njani ne metabolic ne Cardiovascular iziphumo nezigqibo zakuthathwa yi dialysis therapy.

Iingcipheko okanye ukunga khululeki kulomba

Azikho iingcipheko okanye ezinye ezigulo ezenzekayo or (akubikho zingcipheko okanye zigulo ezizezinye zenzekayo). Uthatho lwegazi / Uvavanyo lwegazi

lakufunyanwa kwi mijovo / iinaliti zedialysis, lthethe ukuthi iyakufakwa nje ngesiqhelo esebenze idialysis therapy.

Izinto eziluncedo

Ukuziqaphela ngethuba izinto ezinxulumane ne metabolic nengcipheko zentliziyo kungakwazeka ukuzizama ukuzinceda. Ukuba kunokufumaneka ukwingcipheko enkulu okanye (egqithisileyo), I therapy engamandla iyakuqalisa ukuyekelela okomzuzwana okanye ihlise inqubo leyo yengcipheko.

Izi / Isizathu sokuba kutheni esisifundo mhlwawumbi singakhutshwa (siyekiswe) ezifundweni

Ukuthatha kwakho inxaxheba ibikuku volontiya kwaye unako ukungaxumi ukungaqhubekiki okanye uyeke nangaliphi ixesha ngaphandle kwesizathu. Ukuyeka kwakho akusoze kukumoshele indlela yoku bonana nogqirha okanye unyango kwixa elizayo. Umphandi uyawagcina (uyawuhlonipha) amalungelo akho okuyeka kwakho kwezizifundo ukuba ibalulekile lonto kuwe.

Ukuhlawula

Akhukho ntlawulo ngokuthatha kwakho inxaxheba.

Lindleko zezifundo

Isigulane sokuqhuba nje ngesiqhelo indleko ze dialysis nendlela ye Biochemical Analysis.

Imfihlelo

Konke ebesithetha ngako koluvavanyo kuya kuba yimfihlelo. Amanqaku ayokuthi aziswe kono nzululwazi bamaphepha okanye kubhalwe ngawe awuzufaka igama lakho okanye athethe ngawe nje ngesigulana ebesikwezizifundo.

Uphando olunxulumene Nokonzakala

Akuzubakho naluphina uphando olunxulumene nokonzakala, Ukuyeka kwakho nangaliphina ixesha akusayi kuphazamisana nonyango lwakho.

Naba abantu onokubatsalela xa unemibuzo okanye ingxaki

Mrs Marilyn Maree

Prof Jamila Adam

Prof. IG Okpechi

Umphandi Omkhulu:	Promoter	Co/Promoter
0732153171	031 373 5291	0844167793

Isivumelwano sokuthatha inxaxheba kuphando lwezizi fundo,

Ndingu(igama ngoku pheleleyo) Inombolo ye ID.....Ndiyifundile yonke ndayiqonda le kuthethwa ngayo kweli phepha nomongo wayo. Apho ndinemibuzo khona, okanye engenye into ibicacisiwe kum ngunanini ngaphandle kwengxaki , kwaye inkathlelo yempilo yam iyakuhlala ijongekile, koko uku volontiya kuyahlala kuvumelekile kwezizi fundo.

Igama lesigulana:.....

Umhla:.....

Igama lomphengululi:.....

Umhla:.....

Igama lengqina:.....

Umhla:.....

Igama lomphathi.....

Umhla:.....

Appendix F: Study Protocol

IMPACT OF DIALYSIS THERAPY ON METABOLIC SYNDROME TRAITS AT THE GROOTE SCHUUR HOSPITAL CAPE TOWN.

Study number				
Age				
Gender	M		F	
Type of dialysis	HD		PD	
Duration on dialysis (months)				
Smoking	NEVER	YES		NO
Alcohol	YES		NO	
Level of Education	NONE	MATRIC		> MATRIC
Occupation	UNEMPLOYED		EMPLOYED	
Cause of ESRD	HTN	DM	GN	OTHERS
Previous renal transplant	YES		NO	
Current steroid treatment	YES		NO	
Past history of CVD	YES		NO	
Anti-Hypertensive medications	YES		NO	
Number of anti-hypertensives				
Anti-diabetic medications	YES		NO	
EPO	YES		NO	
Average SBP (mmHg)				
Average DBP (mmHg)				
Height (cm)				
Weight (kg)				
BMI (kg/m ²)				
Waist Circumference (cm)				
Hip circumference (cm)				
FBG (mmol/L)				
TG (mmol/L)				
HDL-cholesterol (mmol/L)				
Ferritin				
Iron				
Iron SATS				
Calcium (mmol/L)				
Inorganic Phosphates (mmol/L)				
C x P product				
PTH				

SOUTH AFRICAN CONGRESS OF NEPHROLOGY

16-19 April 2010

International Convention Centre • Cape Town • South Africa



TITLE OF PRESENTATION:

CARDIOVASCULAR RISK ASSESSMENT IN HAEMODIALYSIS PATIENTS AT GROOTE SCHUUR HOSPITAL: USING THE METABOLIC SYNDROME PREVALENCE AS A SURROGATE MARKER.

AUTHORS

TITLE	FIRST NAME	SURNAME
Ms	Marilyn	Maree
Prof.	Brian	Rayner
Prof.	Charles	Swanepoel
Dr	Ikechi	Okpechi

ABSTRACT:

Background:

Cardiovascular disease (CVD) disproportionately affects patients with end-stage renal disease (ESRD) and remains the leading cause of death for dialysis patients in the United States. The metabolic syndrome represents a novel approach to traditional CVD risk factors and has been reported to be associated with an increased risk of CVD from several large studies. The prevalence of the metabolic syndrome is presently not known in our dialysis population.

Methods:

Demographic and relevant clinical details including systolic and diastolic blood pressures, waist and hip circumference and body mass index were obtained from consenting haemodialysis patients attending the Groote Schuur Hospital in Cape Town. Blood was drawn in the fasting state for assessment of full lipogram, glucose, ferritin, iron, calcium and phosphate. The metabolic syndrome was defined using the

International Diabetes Federation (IDF) criteria as presence of any 3 out of 5 traits (hypertension, increased waist circumference, impaired fasting glucose, high triglycerides and low HDL cholesterol).

Results

Gender distribution in the study was fairly equal (F = 51.2%) with a mean age of 38.8 ± 1.2 years in all the subjects. Glomerulonephritis accounted for most cases of ESRD in the patients (40.7%). The metabolic syndrome was present in 31.4% of the participants. The prevalence of hypertension, raised fasting glucose, increased waist circumference, high triglycerides and low HDL cholesterol was 87.2%, 34.6%, 24.7%, 17.8% and 38.8% respectively. Analysis of variance (ANOVA) showed significantly increased serum phosphate with the number of metabolic syndrome traits increased ($p = 0.036$).

Conclusion:

The prevalence of the metabolic syndrome is high in our HD population, especially giving the criteria for selection of patients for the chronic RRT program. The impact of this high prevalence on morbidity and mortality in our HD patients still requires further studies.

Appendix H: Abstract – SARS Congress of Nephology 2012

Title: Metabolic syndrome and cardiovascular risk in dialysis patients attending the Groote Schuur Hospital in Cape Town

¹**M Maree**, ² J K Adam ³ IG Okpechi,

^{1,3} - Division of Nephrology and Hypertension, University of Cape Town

² – Durban University of Technology

First author details:

Tel: [(W) 0214043305; (Cell) 0732153171]

E-mail: marilyn.maree@westerncape.gov.za

Introduction: The metabolic syndrome (MS) is a clustering of cardiovascular (CV) risk factors and is noted to be increasing globally. End-stage renal disease (ESRD) is associated with increased morbidity and mortality due to increased CV disease in ESRD patients. The prevalence of MS and CV risk is currently unknown in the dialysis population in Cape Town.

Subjects and methods: Prevalent dialysis patients (haemodialysis – HD, and peritoneal dialysis – PD) who consented were used for this study. Demographic and clinical data were recorded. Fasting blood was used to measure various biochemical indices. The MS was defined using the Adult Treatment Panel III (ATPIII). CV risk was stratified according to number of risk factors as low (≤ 1), moderate (2 – 4) or high (≥ 4). Relevant statistical methods were used for analysis.

Results: Of the 143 patients in the study, 67.8% were on HD and 32.2% were on PD. The mean age of all the patients was 38.5 ± 10.4 years. The MS was present in 37.1% of all patients (PD – 52.2%, HD 29.9%; $P = 0.015$) and the frequency of increased waist circumference and hypertriglyceridaemia were significantly higher in PD patients than HD patients ($p < 0.0001$ and $p = 0.006$ respectively). The frequency of CV risk was 3.5, 75.5 and 21.0% respectively for low, moderate and high CV risk and there was no

difference in CV risk in HD and PD patients. High CV risk correlated with BMI, increased waist circumference, hyperphosphataemia, raised calcium – phosphate product, raised PTH and elevated C-reactive protein ($p<0.05$).

Conclusion: The prevalence of the MS is higher in dialysis patients compared to the general population in South Africa and among dialysis patients, the prevalence is higher in PD than HD patients. Strategies to reduce CV risk in the dialysis population should be targeted.

Appendix I: Abstract – EDTNA Congress of Nephrology 2013

Abstract title:

High prevalence of metabolic syndrome and cardiovascular risk factors in dialysis patients in CapeTown

Marilyn Maree¹, Jamilla Adam², Ikechi Okpechi³.

¹ - Groote Schuur Hospital, Department of Health, Cape Town, South Africa

² - Durban University of Technology, Health Sciences, Durban, South Africa

³ - University of Cape Town, Department of Medicine Division of Nephrology and Hypertension, Cape Town, South Africa

Introduction: The metabolic syndrome (MS) is a clustering of cardiovascular (CV) risk factors and is increasing globally. End-stage renal disease (ESRD) is associated with increased morbidity and mortality due to increased CV disease in ESRD patients. Prevalence of MS and CV risk in ESRD patients in Cape Town is unknown.

Subjects and methods: Prevalent dialysis patients in our centre were used for this study. Demographic and clinical data were recorded. The MS was defined using the Adult Treatment Panel III (ATPIII) criteria. CV risk was stratified according to the number of risk factors into low, moderate and high. Relevant statistical methods were used for analysis.

Results: Of 143 patients in the study, 67.8% were on haemodialysis (HD), overall mean age was 38.5±10.4 years and MS was present in 37.1% of patients [HD: 29.9%, peritoneal dialysis (PD): 52.2%; p=0.015]. Increased waist circumference and hypertriglyceridaemia were significantly higher in PD than HD patients (p <0.0001 and p = 0.006 respectively). The frequency of CV risk was 3.5, 75.5 and 21.0% respectively for low, moderate and high CV risk and there was no difference in CV risk between HD and PD patients. High CV risk correlated with BMI, increased waist circumference, hyperphosphataemia, and elevated C-reactive protein (p<0.05) amongst others.

Conclusion: The prevalence of MS is higher in dialysis patients compared to the general population in South Africa and among dialysis patients, the prevalence is higher in PD than HD patients. Strategies to reduce CV risk in the dialysis population should be targeted.