

The Prevalence of Malnutrition Inflammation Complex Syndrome in
Maintenance Haemodialysis patients at Charlotte Maxeke

Johannesburg Academic Hospital

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Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree,
Master of Internal Medicine in the branch of nephrology.

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DECLARATION

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

SIGNED: -----

DATE: -----

DEDICATION

This research report is dedicated to my loving family for their understanding, encouragement and support. Thanks to almighty God.

ABSTRACT

Background: The malnutrition inflammation complex syndrome in patients on chronic haemodialysis (HD) is an important factor that affects patients' outcome. The malnutrition inflammation score (MIS) measures the severity of this syndrome. The association between age, sex, race, duration on dialysis, hospitalisation frequency, co-morbidities, aetiologies of end stage renal disease (ESRD) and MIS has not been fully studied in the state dialysis sector.

Method: All patients on maintenance HD at Charlotte Maxeke Johannesburg Academic Hospital were studied. MIS as well as the above mentioned variables were obtained. The association between MIS and each of the variables were investigated. **Results:** A total of 68 patients were enrolled into the study. The study showed a significant *p*-value when assessing the association between hospitalisation frequency, hypertension and renal failure associated co-morbidities and MIS, 0.002, 0.02 and 0.03 respectively. These variables have shown to occur in increasing frequency in those with low MIS. A number of biases and pathophysiological concepts are discussed, as possible explanations to these associations. Age, sex, race, dialysis time and Kt/V [marker of dialysis clearance, calculated as the coefficient of K (dialyser clearance of urea) and t (dialysis time) divided by V (volume of distribution of urea, approximately equal to patient's total body water)] were not significant in relation to MIS. **Conclusion:** Despite the number of limitations in the current study, MIS is proven to be a useful tool to assess patients' risk of complications whilst aiding in improving the overall clinical outcome in dialysis patients. More longitudinal studies with a larger study population are needed to make a well grounded understanding of the associations between these variables and MIS.

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LIST OF ABBREVIATIONS

• ADPKD	: Adult dominant polycystic kidney disease
• BBB	: Blood brain barrier
• BMI	: Body mass index
• CKD	: Chronic kidney disease
• CMJAH	: Charlotte Maxeke Johannesburg Academic Hospital
• CRP	: C-reactive protein
• ESRD	: End stage renal disease
• FSGS	: Focal segmental glomerular disease
• GIT	: Gastrointestinal Tract
• GFR	: Glomerular filtration rate
• HD	: Haemodialysis
• HEMO	: Haemodialysis
• HIV	: Human Immunodeficiency virus
• IGF -1	: Insulin-like growth factor
• IHD	: Ischaemic heart disease
• IL	: Interleukin
• KDOQI	: Kidney disease outcomes quality initiative
• MICS	: Malnutrition inflammation complex syndrome
• MIS	: Malnutrition inflammation score
• PEM	: Protein energy malnutrition
• PTH	: Parathyroid hormone
• RPGN	: Rapid progressive glomerulonephritis
• SA	: South Africa
• SGA	: Subjective global assessment

- SLE : Systemic lupus erythematosus
- TIBC : Total iron binding capacity
- TNF : Tumour necrosis factor

CHAPTER ONE

1.1 INTRODUCTION

The prevalence of chronic kidney disease (CKD) is as much as 13.9% in sub-Saharan Africa (1). End stage renal disease (ESRD) is constantly growing and fast becoming a major health burden to many countries. As more and more patients are being placed on maintenance dialysis, investigations into factors that determine good dialysis outcome and better overall health are of utmost importance.

Doctors initially believed that poor dialysis technique and treatment was the cause of poor clinical outcome. However, in the Haemodialysis (HEMO) study (2), increasing the dialysis dose or using high influx dialysis membranes failed to show any significant improvement in mortality and hospitalization. This recent multi-centred randomised clinical trial, was conducted on 1846 haemodialysis patients at 15 clinical centres, comprising 72 dialysis units situated mainly in the United States of America. The primary analysis of the HEMO study showed no statistical significance on the “effect of higher dialysis flux (relative risk (RR) 0.92; 95% confidence interval (CI) 0.81 to 1.06 or higher urea Kt/V (RR 0.96; 95% CI 0.84 to 1.10) as markers of dialysis clearance on all-cause mortality” (2).

The protein energy malnutrition (PEM) and inflammation complex is one of the most considered causes for the high rate of hospitalisation and mortality in maintenance dialysis patients. There are epidemiological studies validating a strong association between malnutrition-inflammation complex and clinical outcomes, in dialysis patients (3). PEM is a state where the body has low reserves of protein and fat partly due to inadequate nutrient intake relative to the body's requirement (4).

Malnutrition and inflammation are two entities that often overlap and co-exist in patients with ESRD or CKD. Furthermore, these two entities often share the same causative factors (5). The term malnutrition-inflammation complex syndrome (MICS) thus denotes the close relationship between the two entities. The importance of this syndrome has been demonstrated in both haemodialysis and peritoneal dialysis patients. MICS is believed to be the main cause of decreased quality of life, high rate of cardiovascular atherosclerotic disease, erythropoietin hyporesponsiveness in addition to increasing mortality and hospitalisation rates in dialysis patients (6).

The following literature review will provide better insight to the factors implicated in the development of MICS. Understanding the aetiology of the syndrome helps the clinician to appreciate the complexity of this condition and its relevance to the patient at a clinical level.

1.2 LITERATURE REVIEW

1.2.1 Malnutrition in renal insufficiency

Malnutrition is an important problem in patients on long term renal replacement therapy. The pathogenesis of malnutrition is multifactorial. The review article by Kalantar et al (6), lists some of the probable causes of PEM syndrome in dialysis patients. These causes include: “inadequate nutrient intake, nutrient losses during dialysis, hypercatabolism due to comorbid illnesses, hypercatabolism associated with dialysis therapy, endocrine disorders of uraemia, acidemia with metabolic acidosis and concurrent nutrient losses with frequent blood loss.” In the following sections, each of these causes will be discussed in detail.

1.2.1.1 Anorexia in haemodialysis

Inadequate nutrient intake is due to anorexia and dietary restrictions that are often placed on haemodialysis patients (7). Anorexia is defined as a loss of desire to eat. Kalantar et al showed that 38% of patients on haemodialysis had diminished appetite and of these, 7% had poor appetite and 31% had fair appetite (7). Pathogenesis of anorexia in haemodialysis (HD) patients is unclear (8). There are however a number of mechanisms which are thought to contribute to the development of anorexia in HD patients. It is postulated that uraemic toxins, increases the level of leptin and ghrelin hormones, which in turn impairs gastric emptying (8-12). This process renders patients to lose their desire to eat. The mechanisms of these hormones are explained below. Another important factor resulting in anorexia is inflammation. Inflammation is associated with increased levels of C-reactive protein (CRP), interleukin 6 (IL-6), tumour necrosis factor alpha (TNF- α), these cytokines and their negative effect on eating habits are discussed later (12). Emotional and psychological disorders are also mediators that are implicated in HD-related anorexia (6).

Uraemia itself seems to be an anorexigenic substrate. In 1996, Anderstan et al (13) showed that by injecting uraemic plasma ultrafiltrate intraperitoneally into normal rats, ingestion behaviour was inhibited. In the control group, the absence of the inhibitory effect on eating behaviour of non-uraemic ultrafiltration supported the conclusion that uraemic intoxication is

indeed a key feature in HD-related anorexia. The study further illustrates that uraemic states affects all nutrient components including carbohydrate and protein metabolism.

In addition to uraemia, there are other hormonal mechanisms which contribute to anorexia. The hypothalamus is responsible for receiving and interpreting peripheral signals related to energy and adiposity states (14). Leptin and ghrelin are the signals that are released from the adipose tissue and gastro-intestinal system respectively. Leptin is an anorexigenic hormone, its metabolic action is mediated through the hypothalamus, where it increases α - melanocyte-stimulating hormone, and counteracts the neuropeptide-y and agouti - related peptide. Both these peptides (neuropeptide-y and agouti – related peptide) are appetite stimulants (15). Thus, through the action of leptin, food intake is suppressed. Leptin is cleared from the hypothalamus by glomerular infiltration and metabolised by renal tubules; this explains why there is an elevation in leptin levels in patients with CKD (16).

Ghrelin is a peptide hormone secreted by the stomach and small intestine; it promotes the secretion of neuropeptide-y and agouti-related peptide in the hypothalamus. This results in increased gastric secretions and motility. In normal subjects, there is a pre-prandial rise and post-prandial fall in plasma ghrelin levels after which it is degraded by the kidneys (17). There are three different gene products of ghrelin: acyl-ghrelin, des-acyl-ghrelin and obestatin. The acyl-ghrelin is an orexigenic hormone whereas the des-acyl-ghrelin and obestatin are anorexigenic (18). A clinical study has recently shown that ghrelin is a predictor of mortality in HD patients, and it is associated with wasting and inflammation (19). HD patients with PEM have low ghrelin and high leptin levels, whereas HD patients with no PEM do not share this association (20). Total plasma ghrelin has a negative correlation with the stages of CKD (21). Patients with ESRD have a three-fold increase in ghrelin as compared to controls (21-23). In patients with ESRD, there is an increase in circulating total ghrelin, obestatin, des-acyl-ghrelin due to decreased renal clearance. There is however no compensatory increase in acyl-ghrelin. All these changes favour the development of cachexia and PEM (22).

Anorexia is indeed an important cause of malnutrition in uraemic patients (24). Traditionally signs of uraemia are indicators of poor dialysis (25, 26). However, uraemic anorexia can occur in patients with adequate dialysis parameters. In order to explain this phenomenon, there have been numerous hypotheses to explain the appetite disorder in dialysis patients. In 1972 Babb et al (26), proposed the middle molecule hypothesis. Middle molecules (between

500 Daltons and 60 kilo Daltons) are uraemic retention solutes. There is a strong school of thought that the unfiltered middle molecules cross the blood brain barrier (BBB) resulting in decreased appetite. These uraemic solutes can be dialysed using 'high flux' dialysers – which remove higher molecular weight solutes (28). It is reported in some observational studies that the use of high flux membranes is related to lower morbidity and mortality (28, 29). However, in the HEMO study there was no survival benefits amongst patients chronically on the high flux vs low flux dialysis membranes (2). In 1984 the peak concentration hypothesis, suggested that patients on intermittent dialysis had variable levels of serum urea and small molecule weight uraemic toxins, which led to anorexia (30-31). Patients on continuous ambulatory peritoneal dialysis had more stable concentrations of uraemic toxins (31). Finally, the tryptophan-serotonin hypothesis suggested that the deranged levels of amino-acid profiles, which exist in patients with ESRD, result in an anorectic response. This can occur in patient on dialysis and in those that are not receiving any form of renal replacement therapy. The low levels of essential amino acids in the plasma and cerebrospinal fluid, permits a high level of tryptophan across the BBB, resulting in serotonin synthesis, which in turn is responsible for appetite inhibition (32).

Dietary restrictions in patients on HD can make food less desirable. Many dieticians and nephrologists impose a highly restrictive diet on dialysis patients, making their day-to-day meal choice a challenge (33). A case control study by Kalantar et al, suggests that dietary restrictions on dialysis patients (including low potassium and phosphate) lead to avoidance of fresh fruits and vegetables. This is named as an atherogenic diet (34). In an effort to reduce phosphate intake, many patients avoid natural phosphate- rich products like meat and poultry, which can contribute to PEM (33).

PEM and wasting can be due to nutrient losses that occur during dialysis. HD itself is a protein catabolic process. Studies have suggested during dialysis there is a marked increase in protein degradation, resulting in a negative net protein balance in the whole body protein pool (35). The negative protein balance is accounted for by dialysate amino acid loss, skeletal muscle catabolism and a compensatory reduction in protein synthesis (36). Fortunately, this problem can be addressed by the use of biocompatible membranes and adequate nutrient intake or supplementation (37).

Another important factor resulting in anorexia is inflammation. Inflammation is associated with increased levels of pro-inflammatory cytokines such as CRP, IL-6 and TNF- α . There is

a strong and consistent association between anorexia and high levels of inflammatory markers in HD patients (38). It is well documented that cytokines can inhibit appetite in not only healthy individuals but also in those with underlying diseases such as cancer, sepsis, chronic pulmonary diseases and cardiac cachexia (40). Inflammation in HD patients, will be discussed in the succeeding sections.

1.2.1.2 Hypercatabolism in haemodialysis

Hypercatabolism is a syndrome characterised by increased catabolic hormones (such as cortisol, catecholamines) and inflammatory cytokines (such as TNF, IL6) as well as decreased anabolic insulin effects. The combination of these processes results in skeletal and cardiac muscle protein breakdown and in turn results in negative protein balance (41). Hypercatabolism occurs in chronic disease such as diabetes, congestive cardiac failure, renal failure and liver failure. The consequence of this syndrome is muscle wasting and metabolic impairment. Management includes appropriate nutrient supplementation, for example amino acid mixtures together with conventional therapy, targeted at treating the underlying disorder (42).

1.2.1.3 Endocrine disorders in haemodialysis

It is postulated but not established, that many endocrine disorders in renal failure may promote protein and energy malnutrition (43). One of the commonly documented findings is the resistance to insulin and insulin-like growth factor 1 (IGF-1), first described by DeFronzo et al in 1979 (44) and Fouque et al in 1995 (45). Insulin resistance in uraemic individuals is brought on by numerous factors i.e.; secondary hyperparathyroidism, hyperleptinaemia, acidosis, inflammation and calcitriol deficiency. Hyperleptinaemia in particular, increases insulin excretion from the pancreatic islet cells (46). Some scientists however are of the opinion that direct activity of uraemic toxins results in insulin resistance (47, 48). Studies by Tuzcu et al, 2005 (49) and Stefanovic, 2003 (50), demonstrated that the treatment for insulin resistance in chronic renal disease (CKD) is in fact adequate and effective haemodialysis.

1.2.1.4 Calcium and phosphate balance disorders occur in all stages of CKD

Severe secondary hyperparathyroidism however occurs in advanced CKD stages and in patients on renal replacement therapy (51). Parathyroid hormone (PTH) is often labelled as a uraemic toxin. Excessive PTH results in bone mass loss and cardiovascular calcification. In advanced CKD there is a progressive decline in calcitriol, which is an active Vitamin D

product. Calcium absorption from the gut is also decreased. These calcium abnormalities are responsible for the exaggerated PTH production resulting in secondary hyperparathyroidism (52). High concentrations of PTH in plasma may promote amino acid catabolism and gluconeogenesis (53). Altered Vitamin D and glucose metabolism (i.e. deficiency of 1.25 dihydroxycholecalciferol) causes PEM resulting in malnutrition (52-54).

1.2.1.5 Acidaemia in renal failure

Toxic metabolites such as acids accumulate during renal failure contributing to malnutrition (55). In humans acidaemia suppresses albumin synthesis, promoting a negative protein balance and inducing protein degradation (56). Total protein turnover and long term nutritional status can be improved with optimal correction of metabolic acidosis in patients on HD (57).

1.2.1.6 Volume overload in renal failure

Volume overload is another factor which is associated with malnutrition (5). A study by Dumler et al (58) has illustrated a significant association between serum albumin concentration and extracellular water content ($R=0.223$; $p<0.0001$). The study illustrates that overhydration is a contributory factor to hypoalbuminaemia in CKD. Improvement of fluid status in dialysis patients is important in maintaining a good long-term nutritional profile (59).

1.2.1.7 Blood loss in renal failure

Finally, patients with CKD may have significant blood losses via GIT bleeding, frequent samplings for laboratory investigations and sequestration of blood in the haemodialyser (60). These frequent blood losses may contribute to malnutrition.

1.2.2 Inflammation in renal insufficiency

Recurrent chronic inflammatory processes occur frequently in those with CKD and ESRD (5). There are numerous mechanisms which increase inflammation in patients with CKD. These mechanisms can significantly contribute towards the development of malnutrition.

1.2.2.1 Decrease in clearance of pro-inflammatory cytokines

Declining renal function results in the decrease in renal clearance of pro-inflammatory cytokines and molecules, i.e. TNF, IL1, IL6 and CRP (61 - 63). This depicts the bi-

directional relationship between inflammation and renal failure. At times inflammation is not the cause for reduced glomerular filtration rate (GFR) but is a consequence of renal failure (5). Inflammation is associated with increased plasma levels of catabolic cytokines, which are found in both non-dialysed and dialysed patients with advanced CKD (64).

1.2.2.2 Volume overload with endotoxaemia

Fluid overload induces vascular congestion of the GIT system, resulting in increased permeability and translocation of bacteria and its endotoxins from the gut into the systemic circulation. This process leads to the production of pro-inflammatory cytokines (65 - 67).

1.2.2.3 Oxidative and carbonyl stress

In patients with advanced renal disease the level of oxygen-free radical species are significantly high. This results in dysregulation of cellular processes and subsequently leads to vascular injury (68). Oxidative stress is therefore an important condition that contributes to the development of atherosclerosis, endothelial dysfunction and inflammation (69).

Carboxyl stress results in advanced glycosylated end products which can initiate inflammation in patients with renal failure (70). Patients with ESRD or CKD are reported to have low levels of anti-oxidants such as vitamin C, vitamin E, selenium and glutathione (71). Dialysis itself may reduce antioxidants such as vitamin C and carotenoids, leading to oxidative stress and inflammation (72). A low level of vitamin C is especially associated with increased cardiovascular morbidity and mortality (73).

1.2.2.4 Comorbid conditions

There is an increased prevalence of comorbid conditions in patients with CKD, which can contribute to the development of inflammation. As mentioned in the section on PEM, comorbid conditions induces a hypercatabolic state. Primary causative disorders of renal dysfunction, for example: systemic lupus erythematosus (SLE) and Human immunodeficiency virus (HIV) infection need to be considered, as these are inflammatory diseases themselves (74). In addition, an inflammatory process can occur even in the absence of other co-morbid illnesses. In this setting, only the acute-phase response proteins will be elevated (75).

1.2.2.5 Haemodialysis dependent factors

There are various HD related factors which can contribute to the inflammatory process.

These include:

- Exposure to dialysis tubing / dialysis membrane: In a retrospective study, Levin and colleagues, illustrated that infection was the major cause of mortality in patients on cellulosic membranes and that with the use of polysulfone membranes (76) the incidence of infection was reduced.
- Poor quality of dialysis water: HD patients are vulnerable to the contaminants in the water used to prepare concentrates and dialysis fluids (77).
- Foreign bodies in the form of dialysis grafts and intravenous catheters, which can harbour biofilms (78).

Having discussed the numerous factors contributing to the development of malnutrition and inflammation, one can appreciate the common links between the two entities. Pro-inflammatory cytokines is the most common link, although oxidative stress, carbonyl stress and uraemic toxins also play important roles (79, 80).

1.2.3 Scoring systems

Numerous scoring systems evaluate for PEM and inflammation. The conventional subjective global assessment (SGA), is a relatively easy tool that has been validated to determine nutritional status and predict the degree of sickness (81). However, its semi quantitative features, poor definition and evaluator dependency makes it a less reliable tool (82).

The malnutrition inflammation score (MIS) is a recent scoring system wherein 70% of components are based on the conventional SGA and 30% are based on three additional components - albumin, transferrin and body mass index (BMI). In the MIS questionnaire, there are 4 sections: patients' related medical history, physical exam, BMI and laboratory parameters. "Patients' related medical history comprises of: change in end dialysis dry weight (overall change in past 3-6 months), dietary intake, gastrointestinal symptoms, functional capacity and comorbidity including number of years on dialysis. Physical exam considers signs of muscle wasting and loss of subcutaneous fat stores. Laboratory parameters include albumin and serum transferrin. Albumin, transferrin and BMI are validated and generally accepted as markers of nutritional status and inflammation in dialysis patients (82). Each component gets a score between 0 (normal) to 3 (severely malnourished) in which a higher score means a more severe degree of malnutrition and inflammation. Please refer to Appendix A. MIS is said to be superior to the conventional SGA. In a longitudinal study, the

MIS score correlated strongly with 12-month hospitalization rates and mortality in maintenance haemodialysis patients (6). The relative risk for death for each 10 unit increase in MIS score was 10.43 (95% confidence interval, 2.28-47.64; $p = 0.002$). The SGA showed a weaker association, for each 1 unit increase, the relative risk of death was 3.90 (95% confidence interval 1.29-11.74; $p = 0.02$) (6). Another study by Sohrabi et al, illustrates the strong correlation between a high MIS score and quality of life in HD patients. The study was able to demonstrate a statistically significant difference in physical status between those with moderate and severe malnutrition. Parameters to assess physical status amongst others were physical functioning, role limitation due to physical health, general health and a physical component summary (83). There were lower physical and mental scores in those with higher MIS. A study from Taiwan, illustrated that MIS could be used as a tool to predict fatal and non-fatal cardiovascular and infectious events amongst those on peritoneal dialysis (84).

At the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), patients are placed on state dialysis programmes depending on their general fitness for transplant. Due to the state's limited resources and the costly nature of organ transplantation, patients with a good social and functional status are chosen for the programme. In order to keep patients optimised in terms of their health status whilst on dialysis, doctors in the dialysis unit regularly assess their patients. Patients are also referred to the appropriate auxiliary professionals, for example: physiotherapists, social workers, dietitians and psychologists to optimise all areas of patients' social, physical and mental wellbeing.

1.2.4 The epidemiology of MICS

Depending on the study method and setting, the prevalence of malnutrition and inflammation, often occurring together as malnutrition inflammation complex, has been reported to be as much as 90% in those on maintenance haemodialysis.

In a study of 62 ESRD patients on maintenance haemodialysis in Karachi, Pakistan, Zehra and colleagues identified over 60 (97%) patients with MICS, out of these 31(50%) patients had mild MICS (MIS score: 1-10) and 29 (47%) patients moderate MIC (MIS score 11-20) (85). Two studies from Africa, conducted on maintenance haemodialysis patients, also showed a high prevalence of malnutrition. In a cross-sectional study of 40 dialysis patients, Aatif et al from Morocco, found the prevalence of malnutrition ranging from 12.5% to 65%

as assessed by a BMI of less than 18.5 kg/m² and serum albumin of less than 35 mg/dl respectively (86).

A study by Gracia-Iguacel and colleagues, found the prevalence of protein energy wasting syndrome in a Spanish Dialysis centre, to be 41% (87). This was similar to the five year prospective study of 809 maintenance haemodialysis patients in the USA where Rambod and colleagues found a baseline prevalence of malnutrition/inflammation of 46% using the MIS (88).

Data from these studies, from four different continents show that malnutrition and inflammation are highly prevalent among those on maintenance HD. The prevalence is higher among the low resource countries compared to developed countries (85-88).

1.3 PURPOSE OF STUDY

Upon reviewing the literature, there are no studies (at present) looking at the prevalence of MICS in our state dialysis units in South Africa. In light of view of our patients' poor economic status and disease burdens, the prevalence of MICS in this vulnerable population is an issue that needs to be addressed appropriately. With the aid of the MIS scoring system, doctors will be able to readily identify those that are at higher risk of developing severe MICS. The different elements of MICS can be studied and the possible causes i.e. patient and dialysis related factors can be addressed. Cardiovascular risk factors can be more closely monitored and optimised. Therefore, interventions that can successfully manage MICS, may ameliorate the cardiovascular epidemic and poor outcome in dialysis patients (5). This may save the hospital and the state as a whole, some of its limited resources.

Kalantar et al (6) conducted a study in California, showing poor correlation between demographics such as age, race, sex, time on dialysis, kt/v and MIS. It has yet to be investigated whether this holds to be true in the South African population with its complex ethnic and economic diversity. Furthermore, there are no studies which look at the association between aetiology of ESRD, underlying comorbidity and MIS. This information may be of value to the clinician, as it may indicate those patients are at risk of developing MICS.

Lopez-Gomez et al had demonstrated a state of chronic inflammation in patients who returned to dialysis after failing kidney transplant, but in whom a transplant nephrectomy was not performed (89, 90). These studies were able to demonstrate that with the removal of the

transplanted kidney, much of the inflammatory markers were abated. Similarly, peritoneal dialysis has its own unique factors, which may produce a state of chronic inflammation. Episodes of latent or overt peritonitis, peritoneal dialysis catheter related infections, constant exposure to peritoneal dialysis solution (which may contain bioincompatible substances or endotoxins) and finally loss of residual renal function were the causative factors for chronic inflammation (91, 92). For these reasons, patients often fail peritoneal dialysis and have to be switched to HD. In our study, those who failed kidney transplant and failed peritoneal dialysis were specifically assessed in terms of their MICS risk.

Finally, over the last decade there have been a number of studies focusing on the potential link between hypertension and inflammation. The idea emerged after cross-sectional and prospective studies showed that circulating inflammatory markers are elevated in those with hypertension, and their levels predict the onset of hypertension (93, 94). More recently there are systemic review articles which have focused on the relationship between novel inflammatory mechanisms and hypertension (95, 96).

For the purpose of this study, the MIS scoring was used to assess the degree and prevalence of MICS in haemodialysis patients at the CMJAH. The adequacy of dialysis was measured mainly by using the Kt/V value. K stands for the dialyser clearance (the rate at which the blood passes through the dialyser, expressed as millilitres per min), t stands for time and V is the volume of distribution of urea. The kidney disease outcomes quality initiative (KDOQI) group has adopted the Kt/V of 1.2 as the standard dialysis adequacy. In this study, a correlation between adequacy of dialysis and MIS was investigated.

CHAPTER 2

2.1 METHODOLOGY

2.1.1 Study sample(s)

All patients on chronic HD (more than 3 months) at CMJAH from the period of January 2015 to December 2015 were recruited into the study. The study protocol conformed to the ethical guidelines of the Human Research Ethics Committee of the University of the Witwatersrand (Appendix B). Informed consent was obtained from each participant. The following patients were excluded from the study: patients on HD for less than three months, those with a recent documented acute infection or involvement in major trauma in the past three months and those with documented ongoing infection or sepsis. All patients' age, gender, race, kt/v value,

number of years on dialysis, annual hospitalization frequency, aetiology of ESRD and co-morbidities were recorded (Appendix C). The number of years on HD was defined as the duration of time (in years) from first month of HD treatment until December 2015. The MIS of each patient was recorded.

2.1.2 Data collection

All enrolled patients' hospital files and notes were studied. In addition to interviewing the patients, the hospital files assisted in confirming the hospitalization frequency and reasons thereof. As many of the admissions were related to vascular access problems, the indication for admission was specifically enquired about. Hospitalization was defined as any admission that included an overnight stay. Annual hospitalisation frequency was the total number of hospital admission during the 12 month retrospective study, regardless of the length of each admission. All hospital admissions (including those needing vascular access) versus admissions for specific renal related complications (anaemia, uncontrolled BP, fluid overload, bleeding diathesis, and electrolyte imbalances) were compared. All laboratory measurements were recorded from the patients' file or National Health Laboratory Service systems. The averages of three months of Kt/V values were recorded.

The MIS was calculated on each patient. The MIS consisted of four main parts, the medical history, physical examination, BMI and laboratory parameters. The medical history included changes in weight, dietary history, gastro-intestinal symptoms, functional capacity, number of years on dialysis and co-morbidities. The physical examination involved detection of loss of subcutaneous fat and signs of muscle wasting. Laboratory parameters such as serum albumin and total iron binding capacity (TIBC) are usually utilised to complete the MIS, but TIBC is not routinely measured. An evidence based alternative to TIBC is ferritin and this was used for our study (97). The average of three months of albumin and ferritin was calculated. Each of the four components had a severity score of 0 (normal) to 3 (very severe). The total MIS for each patient was calculated and recorded individually. The data collection sheet and MIS scoring sheet is provided in Appendix C and A, respectively.

2.1.3 Statistical analysis

All data that was collected was entered onto an electronic spreadsheet (Microsoft Excel, Microsoft Office 2007, Microsoft Corporation). Categorical data was summarised using proportions. The relationship between categorical variables was analysed using chi-squared

test. Continuous data was assessed for normality and where applicable summarised as mean $\pm$ SD (standard deviation).

Two-sided t-tests and analysis of variance (Anova) were used to assess differences in continuous variables. If however the data was not normally distributed, medians and interquartile ranges were used to describe the dispersion. In order to compare the medians, a nonparametric measure, Mann-Whitney test was used. All data was analysed at 95% confidence intervals and a *p* value below 0.05 was considered as being statistically significant.

CHAPTER 3

3.1 RESULTS

Amongst 70 patients who received chronic HD at CMJAH, only 2 were excluded, as they were on dialysis for a period of less than 3 months. Thus, a total of 68 patients were enrolled into the study. For the purpose of comparison, the MIS was divided into those with low MIS (0 to 10) and high MIS (11 to 20). There were no patients with MIS above 20. The characteristics of the patients and comparison between patients with high and low MIS are shown in table 3.1. Statistical significance was reported as a *p*-value below 0.05.

Table 3.1 – Characteristics and comparison of patients at CMJAH receiving HD with low and high MIS

Characteristics	Overall	LOW MIS	HIGH MIS	P-values
	(N=68)	(n=53)	(n=15)	
	Mean (SD) or n%	Mean (SD) or n%	Mean (SD) or n%	
Age (years)				
Mean(SD)	41(12.5)	42(11)	39(18.8)	0.41
Sex				
Male (%)	33(49)	28(49)	5(45)	0.8
Female (%)	35(51)	29(51)	6(55)	
Race				
Black (%)	63(93)	54(95)	9(82)	0.12
White (%)	2(3)	2(3)	—	
Indian (%)	1(1)	—	1(9)	
Coloured (%)	2(3)	1(2)	1(9)	
Annual Hospital Admissions				
None (%)	29(43)	29(51)	—	0.003
Admitted once (%)	28(41)	21(37)	7(64)	
Admitted Twice (%)	6(9)	4(7)	2(18)	

Admitted Thrice (%)	4(6)	2(3)	2(18)	
Admitted Four times (%)	1(1)	1(2)	–	
Annual Hospital Admissions(real)				
None (%)	50(74)	46(81)	4(36.4)	0.002
Admitted once (%)	14(21)	10(17)	4(36.4)	
Admitted Twice (%)	3(4)	1(2)	2(18.2)	
Admitted Thrice (%)	1(1)	–	1(9)	
Dialysis Adequacy (Kt/V)				
Mean(SD)	1.5(0.5)	1.5(0.5)	1.48(0.2)	0.8
Time on Dialysis (Years)				
Mean(SD)	6(5.2)	6(5.2)	8(4.9)	0.08
Aetiology				
Hypertension (%)	50(74)	44(77)	6(55)	0.14
Kidney related conditions (%)	18(26)	13(23)	5(45)	
Co-morbidities				
1. Hypertension				
Yes (%)	41(60)	38(67)	3(27)	0.02
No (%)	27(40)	19(33)	8(73)	
2. Peritoneal				
Yes (%)	15(22)	14(25)	1(10)	0.43
No (%)	53(78)	43(75)	10(91)	
3. Failed Renal Transplant				
Yes (%)	10(15)	8(14)	2(18)	0.66
No (%)	58(85)	49(86)	9(82)	
All Kidney related Diseases				
Yes (%)	46(68)	42(74)	4(36)	0.03
No (%)	22(32)	15(26)	7(64)	

There were a total of 15 patients with high MIS and 53 patients with low MIS. The average age of patients was 41 ± 12.5 years. The average age of patients with a high MIS was 39 years and low MIS was 42 years. The Mann Whitney test revealed that there is no statistical significance between age and MIS.

The male to female ratio was 0.96 and this was equally distributed amongst the high MIS and low MIS group. (Figure 3.1).

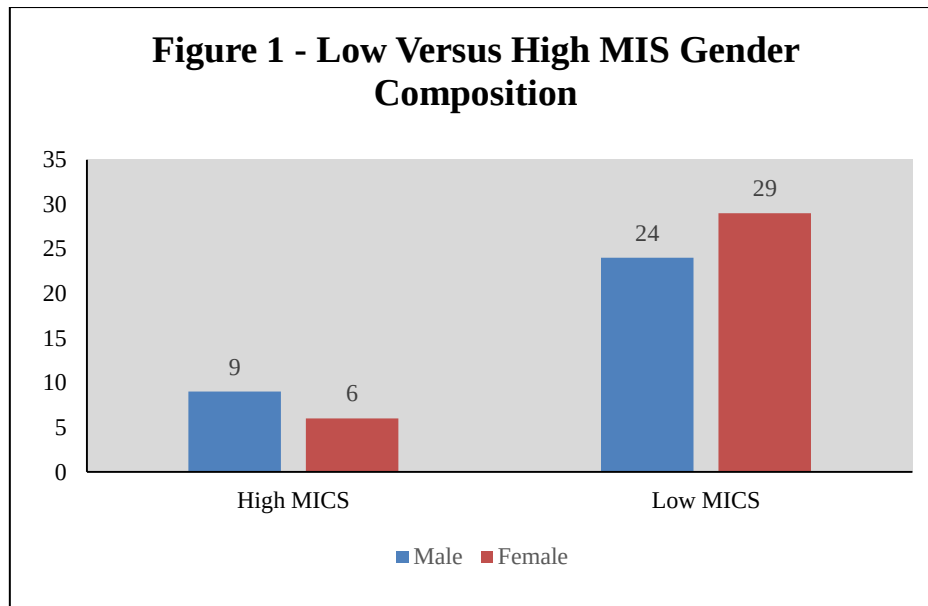


Figure 3.1: Low versus high gender composition of patients presenting at CMJAH on HD.

There were a total of 63 black, 2 coloured, 1 Indian and 2 white patients enrolled in the study. The association between the races and severity of MIS was statistically not significant. Both race and sex were categorical variables, and thus the chi-square test was used to compare these with the MIS.

The average time on dialysis was 6 ($\pm$ 5.2) years. Patients with a high MIS, had on average 8 years on HD, whereas patients with low MIS had on average 6 years on HD.

The average Kt/V value in patients with a high MIS was 1.48 and those with a low MIS was 1.50. The Mann Whitney test revealed that there was no statistical significance between MIS and Kt/V value. There was no statistically significant difference in age, gender or ethnic distribution between the low MIS and high MIS groups.

The hospitalisation frequency was compared with MIS. Since the data was not normally distributed the Mann Whitney test was used. Comparing all annual hospital admissions (including those needing vascular access) with their MIS, a *p* value of 0.003 was attained. Whilst comparing admissions with renal- related complications and their MIS, there was a

significant p value of 0.002. Although it may seem that there may be a significant association between hospitalisation and MIS, it is important to note that only 26 of the 56 admissions were related to renal failure associated complications that needed treatment. The rest of the admissions were related to vascular access related issues. The commonest indications for admission apart from vascular access were anaemia, fluid overload and uncontrolled blood pressures, all of which are related to chronic kidney disease itself.

Co-morbidities were defined as those that are a consequence of kidney disease i.e. hypertension, erectile dysfunction, IHD and neuropathy, anaemia, tertiary hyperparathyroidism and those that are not a consequence of kidney diseases i.e. epilepsy, diabetes, hypothyroidism and hepatitis, prostate cancer. Failed transplant and failed peritoneal dialysis were also included under co-morbidities. There was an association between co-morbidities related kidney disease and MIS with a p -value of 0.03.

Amongst the patients with a low MIS, 67% had hypertension and amongst those with a high MIS, 27% had hypertension. There was a statistically significant relation between MIS and hypertension with a p -value of 0.02.

No statistical significance existed between MIS and those that failed peritoneal dialysis or failed renal transplant, p -values 0.43 and 0.66, respectively. In the data there was only 1 patient with diabetes, therefore assessing the association between diabetes and MIS would not have provided any valuable results (Figure 3.2).

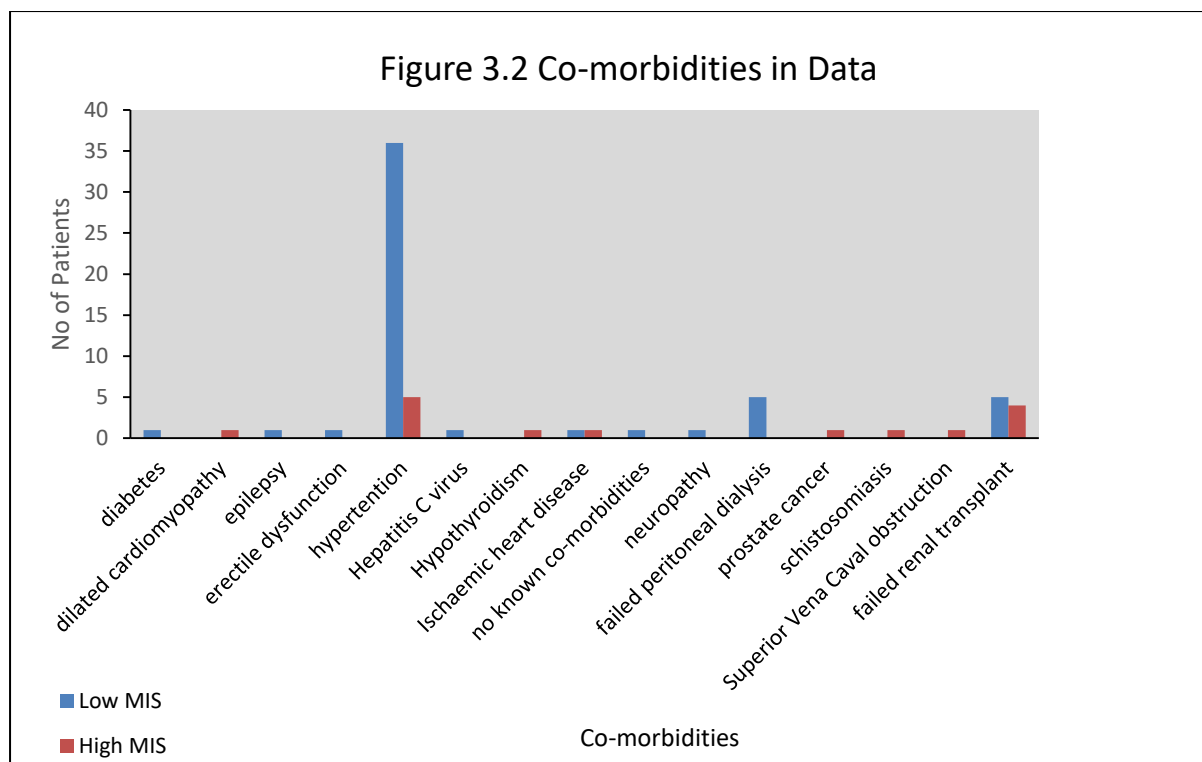


Figure 3.2: Co-morbidities recorded amongst 68 patients on HD at CMJAH.

Hypertension was the commonest documented aetiology of ESRD. Hypertension was recorded as the cause in 74% of patients with ESRD. The Chi-square test revealed a p value of 0.14 indicating poor relationship between hypertension and MIS. Causes of ESRD were recorded as unknown in 6 patients, 3 had urethral strictures, 1 was diabetic and 2 had adult dominant polycystic kidney disease (ADPKD). There was only one patient with each of the following documented aetiologies: focal segmental glomerulonephritis (FSGS), immunoglobulin A nephropathy, reflux nephropathy, renal dysplasia, schistosomiasis and rapid progressive glomerulonephritis (RPGN). Due to the limited number of patients with these individual aetiologies, statistical calculations were difficult to conduct (Figure 3.3).

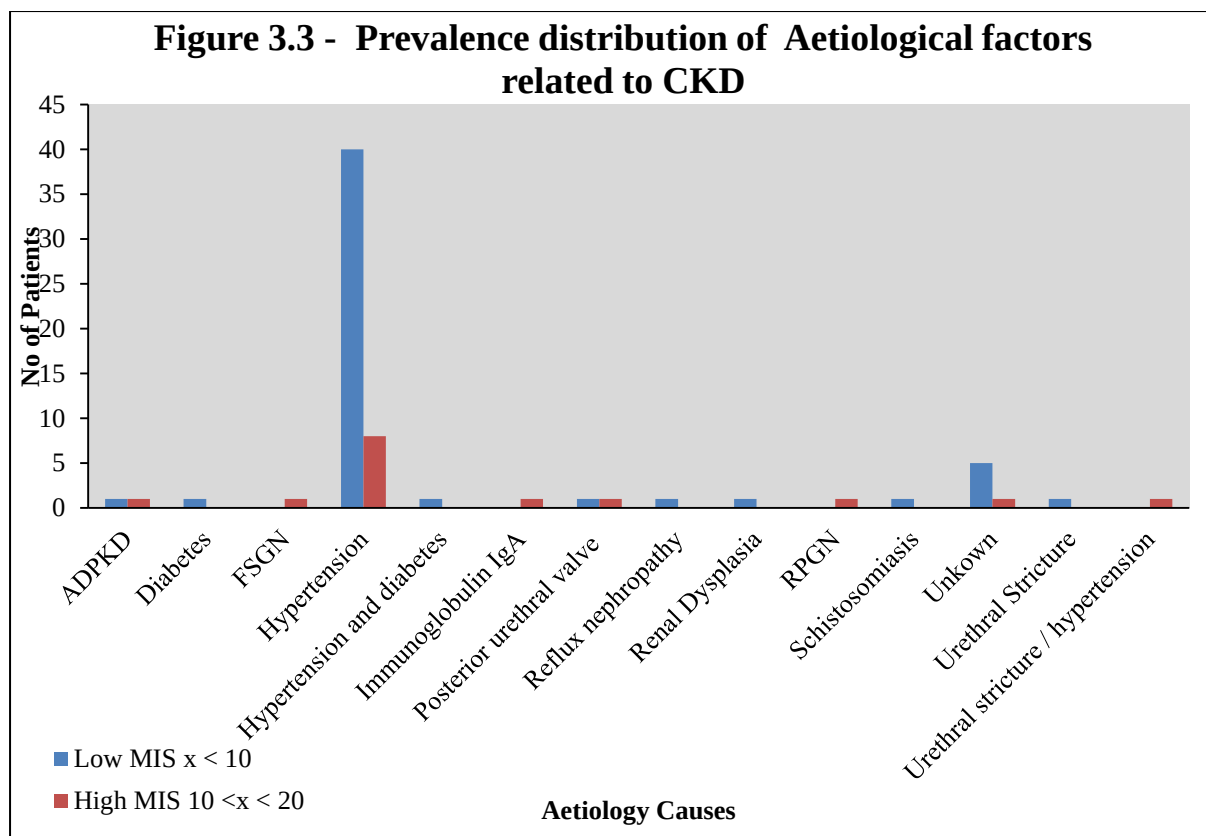


Figure 3.3: Prevalence distribution of aetiological factors related to CKD in patients on HD at CMJAH.

3.2 DISCUSSION

In this group of patients at CMJAH, the prevalence of MICS is high. There were no patients with an MIS of zero. The smaller proportion of patients with a higher MIS was most likely due to patients being selected for dialysis, based on their general fitness for transplant. Thus, selection bias does influence these results. It is well worth noting that there were no patients with a very high MIS (21-30) score. This could also reflect the efficacy of the renal unit as a whole in promptly dealing with patients' health related issues and providing them with a holistic approach, thereby keeping them at an optimal level whilst waiting for kidney transplant.

No association was found between Kt/V and MIS in this study. This was in keeping with the study conducted by Kalantar et al, which showed a correlation coefficient of 0.04 between

Kt/V and MIS (6).

There was no significant association between age, sex, time on dialysis and MIS. The average age in the population group was 41 years. This is a relatively young age group, which can make the development of MICS less likely. A larger study population with an equal distribution between age groups needs to be assessed in order to determine the true association between age and MIS. It is interesting to note that the time on dialysis did not have any detrimental effect on MIS. In this study, the average time on dialysis was 6 years. This was the number of years on haemodialysis only. Some of these patients have been on peritoneal dialysis prior to HD. It is unsure whether in these patients; the combined time on peritoneal and haemodialysis has had any effect on MIS. Literature is unclear on the prevalence of MICS in patients on peritoneal dialysis versus haemodialysis. More studies comparing these two dialysis modalities with regard to MICS need to be conducted.

Amongst dialysis patients at CMJAH, hypertension was the commonest aetiology of ESRD. Out of 68 patients, 50 had hypertension, 2 had urethral strictures, 2 had diabetes, 2 patients had ADPKD and in 6 the aetiology was unknown. The remaining 6 patients' aetiologies were documented as FSGS, IgA nephropathy, reflux nephropathy, renal dysplasia, schistosomiasis and RPGN. Diabetes is known as the most prevalent cause of ESRD, accounting for 33% of adult CKD worldwide (98). However, according to the South African renal registry 2013, the commonest aetiologies of ESRD requiring dialysis was glomerulonephritis, hypertension and diabetes in descending order of frequency (99). In the public sector, diabetic patients on dialysis are far fewer than in the private sector. In the SA registry for 2013, 8% of the total number of patients on dialysis, in the public sector were diabetic, whilst in the private sector the figure was 34.7 % higher. In the public sector, less of the diabetic patients are offered renal replacement therapy because of the associated co-morbidities. Only patients who can fund it or have medical insurance are allowed to receive dialysis in private. Due to this

discrepancy in our population group, it is difficult to calculate the association between MIS and aetiology of ESRD, especially in diabetics.

An interesting point to note in this study is the counterintuitive findings of the higher frequency of hypertension in those with low MIS scores. Whilst obesity, hypercholesterolemia and hypertension are well known cardiovascular risk factors for mortality and morbidity in the general population, studies in “reverse epidemiology” have shown that these physiological states actually increase the survival of patients with ESRD on dialysis. In particular Kalantar and colleagues were able to show a higher risk of death amongst those with systolic and diastolic blood pressure values <120 and <70 mmHg, respectively on maintenance haemodialysis (100). This was in accordance with the studies conducted by Iseki et al, and Zager et al, who were able to demonstrate the relative increase in mortality in those with a SBP < 110 mmHg on haemodialysis (101, 102). The existence of MICS has been implicated as one of the main cause of this “reverse epidemiology” in MHD patients. The overwhelming effect of MICS has resulted in decreased survival rates amongst patients. This means that they do not live long enough to demise from the consequences of hypertension. Other factors such as survival biases and time discrepancy between competitive risk factors may also result in the phenomenon of reverse epidemiology (101-102). Many of the hypertension-related issues surrounding “reverse epidemiology” are based on observational studies. Therefore, more prospective randomised clinical trials may be necessary in order to investigate the effects that different blood pressure targets have on clinical outcome of patients with ESRD in our population group. This concept of reverse epidemiology could be a valid explanation as to why, in our study, there were a lower percentage of patients with hypertension, in the group with higher MIS. A prospective study into the survival rates of patients with a higher MIS on haemodialysis, including their level of blood pressure control and the association thereof, would provide valuable information that

may further support the concept of reverse epidemiology.

There are 2 recent studies that suggest racial differences in survival rates amongst CKD patients are due to varied nutritional and inflammatory profiles (103, 104). These two studies have showed that in African Americans the mortality and morbidity rate is significantly lower than in Caucasians. African Americans seem to be less affected by the inflammatory processes that are associated with CKD. This implies that racial disparity in nutrition and inflammatory measurements amongst those on dialysis may have a bearing on differences in clinical outcome. In our study, the black patients accounted for 93% of the population group and when comparing race and MIS, there was no significant association, *p*-value of 0.12. The small population group could also account for the lack of significant association between race and MIS. A bigger population group with equal number of patients per racial-identity is needed for a more fair and accurate comparison.

According to the study by Kalantar et al, patients with higher MIS were found to have profound anaemia (6). In our study we divided co-morbidities into those related to CKD (i.e.: hypertension, anaemia, erectile dysfunction, IHD, neuropathy and tertiary hyperparathyroidism) and those which are not related to the CKD. Our data has shown that there is a significant association between MIS and CKD related co-morbidities. Interestingly, patients with lower MIS had a higher percentage of CKD related co-morbidities. It is important to note that “hypertension” was included amongst this list of CKD-related co-morbidities and “hypertension” on its own showed significant association with MIS. Whether including hypertension into this list, may have had an influence on the *p*-value (whilst correlating MIS with CKD related co-morbidities) is questionable and can be seen as a bias. It would have been more statistically appropriate to assess the *p*-values whilst correlating

individual co-morbidities with the MIS rather than grouping them.

Failed peritoneal transplant and failed renal transplant had no association with MIS. One can presume that inflammatory processes that might have taken place previously do not influence current MIS.

In the study by Kalantar et al, a significant association with MIS and risk for hospitalization and mortality was shown (6). In our study, total annual hospitalisation rate (irrespective of duration of stay and reason for admission) had a significant association with MIS. Although it may seem that there was a significant association between the two variables, it is important to note that more than half of these admission were for vascular access. Admissions, apart from those needing vascular access, were mainly as a result of complications of CKD itself, ie: poor blood pressure control, fluid overload and anaemia. Kalantar et al and Ho L et al were able to show the significant associations between MIS and hospitalisations that were mainly related to infections and cardiovascular diseases, rather than mere complications of CKD (6, 84).

3.3 LIMITATIONS

There are a number of limitations to this study. In the public sector, our dialysis unit selects patients based on their age, baseline functional and nutritional status. Due to the potential complications and expensive nature of renal transplant, appropriate patient selection is mandatory for a successful outcome. Thus, selection bias is a factor in this study. Patients are generally middle aged and of a good physical fitness prior to entering the dialysis programme. MICS is less likely to develop in this group of patients.

A larger study sample with patients having more wider/higher ranges of MIS would have had a more meaningful impact on the comparisons between the different variables. In our study, MIS was scored as being low (0-10) and high (10-20), as there were virtually no patients with

a score above 20. Comparing the measured variables in ESRD patients (ie hospitalisation and co-morbidities) with a control group that had an MIS score of less than 5, might have been of more statistical significance. Further studies with larger sample sizes and healthier controls are needed to confirm whether a positive correlation between MIS and these variables are present.

Correlating MIS with individual co-morbidities rather than grouping them under “CKD related or non-CKD related co-morbidities,” could have provided a more statistically meaningful data.

This study has particularly focused on haemodialysis patients. Some of these individuals had been on peritoneal dialysis prior to HD. Therefore, the total time spent on “dialysis” is more than what is calculated. It is worth questioning whether in this subset of patients, the exposure to peritoneal dialysis could have influenced the development of MICS. A cross-sectional study comparing HD and peritoneal dialysis patients and their risk of developing MICS could be of value. There is indeed a large discrepancy amongst the racial groups in this study. Ninety-three percentage of the study population consisted of black patients, making the comparison between racial groups and their association with MIS statistically problematic.

3.4 CONCLUSION

The findings of our study suggest that higher MIS was associated with higher hospitalization frequency, hypertension and renal failure associated co-morbidities. Most of the results of this study can be qualified in a similar study population and sample size. Due to the nature of patient selection for dialysis programme, there can be selection bias that confounds some of these results. There is no association between age, sex, time on dialysis, Kt/V and MIS. Race and MIS also did not have a significant association. In order to get a better understanding on whether racial differences has an association with nutrition and inflammatory status , a bigger

population group with equal number of patients in terms of race needs to be studied. The aetiology of ESRD had no association with MIS. However, hypertension in particular showed statistical significance with MIS, which could be explained with the theory of “reverse epidemiology”. Due to lack of adequate patient numbers with diabetes and other known intrinsic renal disease, it was difficult to assess the true association between these variables and MIS. Poor grouping of co-morbidities and the lack of larger sample sizes with a wider range of MIS’s are significant limitations in this study. Despite these limitations, the MIS proves to be a practical and convenient scoring system that can be used by a dietitian, trained nurse or physician. The score assesses malnutrition and inflammation, which are the two major indicators of poor dialysis outcome; it helps to identify patients at risk of complications and higher mortality. The current study although small in its sample size and with its limitations, was able to show the strong association between frequencies of hospitalization, renal failure associated complications and MIS. By effectively managing renal failure, associated complications and other contributory factors, which lead to the development of MICS, clinicians, could improve poor clinical outcome in dialysis patients.

APPENDIX A

MIS SCORING SYSTEM

Patient case No:

COMPREHENSIVE MALNUTRITION INFLAMMATION SCORE				
(A) Patients' related medical history				
1 - Change in end dialysis dry weight (overall change in past 3-6 months)				
0		1		2
No decrease in dry weight or weight loss < 0.5kg		Minor weight loss {>0.5kg but <1kg}		Weight loss more than one kg but <5%
				3
				Weight loss > 5%
2 - Dietary intake:				
0		1		2
Good appetite and no deterioration of the dietary intake pattern		Somewhat sub-optimal solid diet intake		Moderate overall decrease to full liquid diet
				3
				Hypo-caloric liquid to starvation
3 - Gastrointestinal (GI) symptoms:				
0		1		2
No symptoms with good appetite		Mild symptoms ,poor appetite or nauseated occasionally		Occasional vomiting or moderate GI symptoms
				3
				Frequent diarrhoea or vomiting or severe anorexia
4 - Functional capacity (nutritionally related functional impairment):				
0		1		2
Normal to improved functional capacity , feeling fine		Ocaasional difficulty with baseline ambulation or feeling tired frequently		Difficulty with otherwise independent activities (e.g. going to bathroom)
				3
				Bed/chair ridden, or little to no physical activity
5 - Co -morbidity including number of years on dialysis:				
0		1		2
On dialysis less than one year and healthy otherwise		Dialysis for 1-4yrs, or mild co-morbidity [excluding MCC*]		Dialysis >4 years, or moderate co-morbidity [including MCC*]
				3
				Any severe, multiple co-morbidity [2 or more MCC*]

(B) Physical Exam (according to SGA criteria):				
6 - Decreased fat stores or loss of subcutaneous fat(below eyes,triceps,biceps,chest):				
0		1		2
Normal(no change)		mild		moderate
				3
				severe
7 -Signs of muscle wasting(temple,clavicle,ribs,quadriceps,knee,interosseous):				
0		1		2
Normal(no change)		mild		moderate
				3
				severe
(C) Body mass index:				
8 -Body mass index: BMI= Wt(kg)/Ht2(m)				
0		1		2
BMI> 20kg/m ²		BMI: 18-19.99kg/m ²		BMI: 16-17.99kg/m ²
				3
				BMI<16kg/m ²
(D) Laboratory Parameters:				
9 - Serum albumin:				
0		1		2
albumin> 04.g/dL		albumin: 3.5-3.9g/dL		albumin: 3.0-3.4g/dL
				3
				albumin< 3.0g/dL
10 - Serum TIBC(total Iron Binding Capacity): +				
0		1		2
TIBC>250mg/dL		TIBC: 200-249mg/dL		TIBC: 150-199mg/dL
				3
				TIBC <150mg/dL
Total Score = sum of above 10 components (0-30):				

*MCC (Major comorbid conditions) include CHF (congestive heart failure) class 3 or 4, full blown AIDS(Acquired immunodeficiency syndrome), severe CAD (Coronary artery disease), moderate to severe COPD (Chronic obstructive pulmonary disease), major neurological sequela, and metastatic malignancies or recent chemotherapy.

+ Suggested equivalent increments for serum transferrin are > 200(0), 170-199(1), 140-169(2), and < 140 mg/dl

APPENDIX B

ETHICS CLEARANCE CERTIFICATE



R14/49 Dr Anu Abraham

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M150411

NAME: Dr Anu Abraham
(Principal Investigator)

DEPARTMENT: Internal Medicine
Charlotte Maxeke Johannesburg Academic Hospital

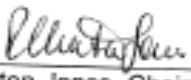
PROJECT TITLE: The Prevalence of Malnutrition Inflammation
Complex Syndrome in Maintenance Haemodialysis
Patients at Charlotte Maxeke, Johannesburg General Hospital

DATE CONSIDERED: 24/04/2015

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Graham Paget

APPROVED BY: 
Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 19/06/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I agree to submit a yearly progress report

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C

DATA COLLECTION SHEET

Patient No	Age	Race	Sex	MICS	Kt/V	No.of months on dialysis	Annual hospitalisation frequency	Aetiology of ESRD

Abbreviations:

kt/v : Adequacy of dialysis

MICS: malnutrition inflammation complex

ESRD: end stage renal disease

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