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Nutritional factors and clinical outcomes of patients with end stage kidney disease: implications for practice from researching the practice framework

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Nutritional Factors and Clinical Outcomes of Patients with End Stage Kidney Disease

Implications for practice from researching the practice framework

A thesis submitted in fulfilment of the requirements for the award for the degree

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by

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Certification

I, Maria C.F. Chan, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Health and Behavioural Sciences, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

Maria C.F. Chan

September, 2013

Dedication

This thesis is dedicated to

Romuald and my parents

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Declaration of professional editorial intervention

This thesis has received professional editorial advice from Dr. Amy Nisselle, BSc(Hons), PhD (University of Melbourne) in accordance to the guidelines set by the Deans and Directors of Graduate Studies (DDOGS) in conjunction with the Council of Australian Societies of Editors (CASE), now known as the Institute of Professional Editors (IPEd). The thesis editing advice has been strictly adhered to

- Standard D
- Standard E

Dr. Nisselle's current and former areas of academic specialisation are not similar to that of the PhD candidate.

Abstract

Chronic kidney disease (CKD) is a major public health problem with significant clinical, societal and psychosocial burdens. Nutrition has been an integral part of medical management in patients with CKD for more than a century; its importance has shifted away from the pre-dialysis stages since the 1970s due to technological advances in renal replacement therapy (RRT), namely dialysis and transplantation. However, nutrition abnormalities can emerge before or during dialysis and continue to be associated with poor outcomes. This suggests a need to revisit nutrition management in end stage kidney disease (ESKD) to gain a broader insight into its effects on clinical outcomes.

The aim of this thesis was to examine the relationships between nutritional factors and clinical outcomes in people with ESKD, addressing the question, "Is nutrition management good enough only when it starts at or near dialysis initiation?"

This thesis was built on a "research in practice" framework. A series of studies was conducted using retrospective data on clinical cohorts attending the renal unit at the St. George Hospital, Sydney.

Study I examined the available data from all attending patients at the initiation of dialysis from 2000 to 2010. This study examined the association between nutritional parameters at the initiation of dialysis and mortality in the clinical cohort (2000-2010, n =167). The hypothesis was that poor nutrition at the start of dialysis predicted high mortality risk. The mean glomerular filtration rate (GFR) at the start of dialysis was 8.0±2.7 mL/min/1.73m^2; about half (52.1%) of the patients were rated as malnourished or scored B or C using subjective serum albumin (s-albumin) and malnutrition (SGA score B or C) independently predicted mortality over the 10 year study period (*P* <0.0001, *P* <0.0001, *P* =0.01 and *P* =0.02 respectively). Overweight and obesity defined as body mass index (BMI) ≥26 kg/m^2 did not show any advantage on survival

(*P* =0.73). The combination of malnutrition and overweight/or obesity (SGA B and C + BMI ≥26 kg/m^2) was global assessment (SGA). Older age (>65 years), presence of peripheral vascular disease, reduced associated with a three-fold increase in mortality risk with adj. HR 2.96, 95% CI: 1.12–7.33, *P* =0.02 compared to being well nourished with a BMI <26 kg/m^2 (referent). Being well nourished (SGA = A) was found to be associated with lower mortality risk irrespective of the levels of s-albumin and BMI. Thus, malnutrition at the start of dialysis was found to be an independent predictor of mortality. In addition, no statistical difference in survival was observed between the early and late start groups, which commenced dialysis with a GFR equal and above, or less than, 7 mL/min/1.73m^2. Therefore, the results supported the recommendations in the literature that with careful clinical management of ESKD, including nutritional inputs, dialysis can be started at lower levels of GFR. This has tremendous healthcare cost implications.

A multidisciplinary pre-dialysis assessment clinic was established in 2002 following the preliminary analysis of data on the clinical cohort after two years. Study II of the thesis focused on the cohort attending the pre-dialysis clinic. This study was conducted in two parts.

Study IIa was a cross-sectional study of the nutritional characteristics of patients first attending the new multidisciplinary pre-dialysis assessment clinic during the period 2002 to 2008 (n =210). The hypothesis was that a high prevalence of nutritional abnormalities was present before starting dialysis. The mean GFR was 17.3±6.5 mL/min/1.73m^2 with 40.5% of patients rated as malnourished (SGA score B or C). Energy and protein intakes correlated positively with GFR, being *r* =0.17, *P* <0.01 and *r* =0.29, *P* <0.0001 respectively. Intakes of energy, protein and other micronutrients were sub-optimal in a large number of patients. This was attributed to reduced renal function, symptoms burden (51.0%), self-imposed inappropriate dietary regimen (17.1%) and possibly also poor eating habits. Thus, the patients who mainly presented to the clinic

in CKD stages 4 to 5 had a high prevalence of abnormal nutrition parameters before dialysis was required.

In Study IIb, the reference data collection period was extended for a further 4 years to enable analyses on baseline data for a ten year period (April 2002 to March 2012, n=501). In the preliminary clinic evaluation eighteen months after it started, patients had low GFR on presentation and the prevalence of malnutrition was high. We hypothesized as the clinic became more established, earlier referral with higher levels of GFR would occur over time and better nutritional status in the first clinic assessment would be achieved. For ease of comparison, the data were divided into two halves, or two 5-year periods, comparing patients referred between April, 2002 and March 2007 (period 1) to those referred between April 2007 and March 2012 (period 2). GFR was 16.7±6.7 vs. 22.1±9.1 mL/min/1.73m^2, *P* <0.0001 in periods 1 and 2 respectively, so patients were enrolled in the clinic earlier in the second half of the study period. The prevalence of obesity (32.0% vs. 44.7%, *P* <0.01) and diabetes (33.0% vs. 51.4%, *P* <0.0001) increased significantly over time – parallel to the obesity and diabetes epidemics in the general population while the malnutrition rate remained high at 39.7% vs. 42.0% (*P* =0.62) despite no significant increase in prevalence. Thus the prevalence of malnutrition remained high despite earlier referral for nutrition intervention.

In conclusion, nutrition abnormalities merged during the decline of kidney function before the initiation of dialysis. Nutritional factors, along with older age (>65 years), and co-morbidities at the initiation of dialysis independently predict mortality. To answer the question “Is nutrition management good enough only when it starts at or near dialysis initiation?” the answer is NO. Through research in practice, the results of this thesis suggested structured nutrition management should be implemented well before dialysis is required and even before the pre-dialysis stage to improve health outcomes in patients with ESKD.

Publications

Publications in support of this thesis

Peer-reviewed publications

1. Chan M, Kelly J, Batterham M and Tapsell L. Malnutrition (Subjective Global Assessment) Scores and Serum Albumin Levels, but not Body Mass Index Values, at Initiation of Dialysis are Independent Predictors of Mortality: A 10-Year Clinical Cohort Study. *J Ren Nutr* **22**(6): 547–557, 2012.

   Remark: this article has been selected for use in the Journal of Renal Nutrition online continuous professional education (CPE) program, an educational activity approved by the Commission on Dietetics Registration, USA.

Submitted manuscripts

1. For Journal of Renal Nutrition:

   Chan M, Kelly J, Batterham M and Tapsell L. A high prevalence of abnormal nutrition parameters found in pre-dialysis end stage kidney disease: Is it a result of uraemia or poor eating habits?

In preparation for submission

1. For Nephrology:

   Chan M, Kerr E, McTaggart S, Collett G, Tranter S Kelly J, Batterham M and Tapsell L. The change in clinical and nutrition profiles, and preference for renal replacement therapy of patients at enrolment to the multidisciplinary pre-dialysis assessment clinic between 2002–2012.

List of oral presentations

1. Chan M, Kerr E, McTaggart S, Collett G, Tranter S Kelly J, Batterham M and Tapsell L Nutritional status is associated with the future treatment choice - renal replacement therapy vs. conservative care in ESKD patients. ANZSZ ASM September, 2013 (Brisbane, Australia).
2. Chan M, Kelly J, Batterham M and Tapsell L. Nutritional characteristics and dietary intake of patients at enrolment to the pre-dialysis assessment clinic. Dietitians Association of Australia 30th National Conference, May 2013 (Canberra, Australia)
3. Chan M, Kelly J, Batterham M and Tapsell L. Self-reported appetite and adequacy of energy and protein intakes in patients with non-dialysis chronic kidney disease, Dietitians Association of Australia 30th National Conference, May 2013 (Canberra, Australia)
4. Chan M**,** Kelly J, Batterham M and Tapsell L. Malnutrition (SGA) and serum albumin levels, but not body mass index (BMI) values at initiation of dialysis are independent predictors of mortality: a 10-year clinical cohort study. This study has been presented in three congresses and symposium and published in the relevant congress proceedings:
    a. Medical Symposium, South Eastern Sydney Local Hospital Network, October, 2011 (Sydney, Australia).
    b. 29th International Society of Blood Purification (ISBP) Annual Meeting, 9th–11th September, 2011 (Beijing, China).
    c. 47th Australian and New Zealand Society of Nephrology (ANZSN) Annual Scientific Meeting,(ASM) September 2011 (Adelaide, Australia).

List of poster presentations

1. Chan M, Tranter S, Josland E, Kerr E, McTaggart S, Collett G, Kelly J, Batterham M and Tapsell L. Nutritional profile of patients at enrolment to the multi-disciplinary

pre-dialysis clinic, 2002 to 2012. 41st Renal Society of Australasia Annual Conference, June 2013 (Hobart, Australia).

2. Chan M, Tranter S, Josland E, Collett G, Kelly J. Title: Association of nutritional status and the future choice of dialysis option in patients attending the multidisciplinary pre-dialysis assessment clinic. 41st Renal Society of Australasia Annual Conference, June 2013 (Hobart, Australia).
3. Chan M, Kelly J, Batterham M and Tapsell L. Nutritional characteristics and dietary intake of patients attending the pre-dialysis assessment clinic. Medical Symposium, South Eastern Sydney Local Hospital Network, October, 2012 (Sydney, Australia).
4. Chan M, Tranter S, Josland E, Collett G, Kelly J. Association of nutritional status and the future choice of dialysis option in patients attending the multidisciplinary pre-dialysis assessment clinic. Medical Symposium, South Eastern Sydney Local Hospital Network, October, 2012 (Sydney, Australia).
5. Chan M, Tranter S, Josland E, Kerr E, McTaggart S, Collett G, Kelly J, Batterham M and Tapsell L. Nutrition profile of patients at enrolment to the multidisciplinary pre-dialysis assessment clinic between 2002–2012. Medical Symposium, South Eastern Sydney Local Hospital Network, October, 2012 (Sydney, Australia).
6. Chan M, Kelly J, Batterham M and Tapsell L. Nutritional characteristics and dietary intake of patients attending the pre-dialysis assessment clinic. Proceedings of the 16th International Congress of Nutrition and Metabolism in Renal Disease (ICNMRD), June, 2012 (Honolulu, Hawaii).
7. Chan M, Kelly J, Batterham M and Tapsell L. Self-reported appetite and intake adequacy in patients with non-dialysis chronic kidney disease. Proceedings of the 16th ICNMRD, June, 2012 (Honolulu, Hawaii).

Other significant publications, presentations and posters during PhD candidature – selected publications ONLY

Book chapters

1. Kopple J Massry S and Kalantar-Zadeh K. *Textbook of Nutritional Management of Renal Disease*. Third Edition. Elsevier Publishing, Chapter 34: Nutritional management of renal transplantation. Authors: Maria Chan and Steve Chadban, 2013.
2. Trevino-Becerra, A. (editor) *Hemodialysis Esquematica*. Chapter 27: Nutrition, exercise and hemodialysis. Authors: Maria Chan and Alejandro Trevino-Becerra, Publisher, Prado (Mexico) and translated into Spanish, 2013.
3. Harris, D, Rangan, G, Kairaitis, L and Elder, G. *Pocket Guide to Basic Clinical Dialysis* 2 edition. Authors: Michelle Ryan, Maria Chan and Murielle Ryan. Chapter 2 Nutrition. Publisher, McGraw-Hill Australia PTY LTD. 2012.
4. Nolph, and Gokal´s *Textbook of Peritoneal Dialysis.* Springer. Chapter 21: Protein-energy malnutrition/wasting during peritoneal dialysis. Authors: Juan Jesús Carrero, Olof Heimbürger, Maria Chan, Jonas Axelsson, Peter Stenvinkel, Bengt Lindholm, 2008.

Peer reviewed publications

1. Johnson DW, Atai E, Chan M, Phoon RKS, Scott C, Tussaint N, Turner GI, Usherwood T, and Wiggins, K. KHA-CARI guideline: Early chronic kidney disease: detection, prevention and management. *Nephrology* **18** (2013) 340–350
2. Manning F, Harris K, Duncan R, Walton K, Bracks J, Larby L, Vari L, Jukkola K, Bell J, Chan M and Batterham M. Additional feeding assistance improves the energy and protein intakes of hospitalised elderly patients. A health services evaluation. *Appetite* **59**(2): 471–477, 2012.

3. Avesani CM, Trolonge S, Deleaval P, .Baria F, Mafra D, Faxen-Irving G, Chauveau P, Teta D, Kamimura MA, Cuppari L, Chan M, Heimburger O and Fouque D. Physical activity and energy expenditure in haemodialysis patients: an international survey. *Nephrol Dial Transplant* **27**(6): 2430–2434, 2012.
4. Chan M, Nutrition, diabetes and chronic kidney disease, Australian Diabetes Educator Volume 15 Number 3, August 2012, pp17-23
5. Chadban S, Chan, M, Fry K, Patwardhan A, Ryan C, Trevillian P and Westgarth F. Nutritional management of diabetes mellitus in adult kidney transplant recipients, *Nephrology* 2010; 15, S37–S39
6. Chadban S, Chan, M, Fry K, Patwardhan A, Ryan C, Trevillian P and Westgarth F. Nutritional management of anaemia in adult kidney transplant recipients, *Nephrology* 2010; 15, S40–S42
7. Chadban S, Chan, M, Fry K, Patwardhan A, Ryan C, Trevillian P and Westgarth F. Nutritional interventions for the prevention of bone disease in kidney transplant recipients *Nephrology* 2010; 15, S43–S47
8. Chadban S, Chan, M, Fry K, Patwardhan A, Ryan C, Trevillian P and Westgarth F. Nutritional management of hypophosphataemia in adult kidney transplant recipients. *Nephrology* 2010; 15, S48–S51
9. Chadban S, Chan, M, Fry K, Patwardhan A, Ryan C, Trevillian P and Westgarth F. Nutritional management of overweight and obesity in adult kidney transplant recipients *Nephrology* 2010; 15, S52–S55
10. Chadban S, Chan, M, Fry K, Patwardhan A, Ryan C, Trevillian P and Westgarth F. Nutritional management of hypertension in adult kidney transplant recipients. *Nephrology* 2010; 15, S56–S61
11. Chadban S, Chan, M, Fry K, Patwardhan A, Ryan C, Trevillian P and Westgarth F. Nutritional management of dyslipidaemia in adult kidney transplant recipients. *Nephrology* 2010; 15, S62–S67

12. Chadban S, Chan, M, Fry K, Patwardhan A, Ryan C, Trevillian P and Westgarth F. Protein requirement in adult kidney transplant recipients. *Nephrology* 2010; 15, S68–S71
13. Chan M, Patwardhan.A, Ryan C, Trevillian P, Chadban S, Westgarth F and Fry K. Evidence-based guidelines for the nutritional management of adult kidney transplant recipients. *J Ren Nutr* **21**(1): 47–51, 2011.
14. Cheema B, Abas H, Smith B, O'Sullivan A, Chan M, Patwardhan A, Kelly J, Gillin A, Pang G, Lloyd B, Berger K, Baune BT and Fiatarone Singh M. Effect of resistance training during hemodialysis on circulating cytokines: A randomized controlled trial. *Eur J App Physio* **111**: 1437–1445, 2011.
15. Fry K, Patwardhan.A, Ryan C, Trevillian P, Chadban S, Westgarth F and Chan M. Development of evidence-based guidelines for the nutritional management of adult kidney transplant recipients. *J Ren Nutr* **19**(1): 101–104, 2009.
16. Cheema B, Abas H, Smith B, O'Sullivan A, Chan M, Patwardhan A, Kelly J, Gillin A, Pang G, Lloyd B and Fiatarone Singh M. Randomized controlled trial of intradialytic resistance training to target muscle wasting in end-stage renal disease: The PEAK study. *Am J Kidney Dis* **50**(4): 574–584, 2007.
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18. Ash S, Campbell K, MacLaughlin H, McCoy E, Chan M, Anderson K, Corke K, Dumont R, Lloyd L, Meade A, Montgomery-Johnson R, Tasker T, Thrift P and Trotter B. Evidence-based practice guidelines for the nutritional management of chronic kidney disease. *Nutrition & Dietetics* **63**: S33–S45, 2006.

List of poster presentations

1. Chan M, Avesani C, Carrero J, Faxen-Irving G, Stenvinkel P, Lindholm B and Heimburger O. Comparison of total energy expenditure measurements from armband and indirect calorimetry estimations in a sample of dialysis patients. 44th

Australia and New Zealand Society of Nephrology (ANZSN) Annual Scientific Meeting, September 2008 (Hobart, Australia).

2. Chan M**,** Tranter S, Kelly J and Tapsell L. Nutritional characteristics of patients attending pre-dialysis assessment clinic. 44th ANZSN Annual Scientific Meeting, September, 2008 (Hobart, Australia).

Clinical practice guidelines

1. The Caring for Australasians with Renal Impairment (CARI) guidelines: the management of people with chronic kidney disease (CKD) stages 1–3. Authors: Maria Chan and David Johnson. www.cari.org.au/ckd_earlyCKD_underdev.php (July 2012)
   a. Modification of lifestyle and nutrition interventions for management of early CKD.
   b. Multidisciplinary or multifaceted renal care in early CKD.
   c. Vitamin D therapy (supplementation) in early CKD.
2. The Caring for Australasians with Renal Impairment (CARI) guidelines: the nutritional management of adult kidney transplant recipients. Authors: Steven Chadban, Maria Chan, Karen Fry, Aditi Patwardhan, Catherine Ryan, Paul Trevillian, Fidye Westgarth. Nine articles in *Nephrology* **15** supplements, 2010, and available from www.cari.org.au/trans_nutrition_published.php.
3. Evidence–based guidelines for the nutritional management of adult kidney transplant recipients. Authors: Steven Chadban, Maria Chan, Karen Fry, Aditi Patwardhan, Catherine Ryan, Paul Trevillian, Fidye Westgarth. Available from http://daa.collaborative.net.au/files/DINER/TransplantNutrition_Guidelines_FINAL_090628.pdf. Complementary patient education material developed and available at the Dietitians Associations of Australia (DAA) website – Dietetic Information and Nutrition Education Resources (DINER).

4. Evidence-based practice guidelines for the nutritional management of chronic kidney disease. Authors: Ash S, Campbell K, MacLaughlin H, McCoy E, Chan M, Anderson K, Corke K, Dumont R, Lloyd L, Meade A, Montgomery-Johnson R, Tasker T, Thrift P and Trotter B. Available from http://daa.asn.au/for-health-professionals/daa-endorsed-practice-guidelines-and-practice-recommendations.

Invited lectures/workshops

1. Chan M. "Nutrition and Renal Failure". University of Hong Kong, June 2013 (Hong Kong).
2. Patwardhan A, Ryan C and Chan M, (workshop leader), Evidence and Practice Guidelines for the Nutritional Management of Adult Kidney Transplant Recipients 16th International Congress of Dietetics, September 2012 (Sydney, Australia).
3. Chan M, Patwardhan A, Lambert K, and Crosby C (workshop leader). Evidence and practice guidelines for the nutritional management of people with chronic kidney disease stages 1–3, early to moderate renal insufficiency (GFR 30–90 mL/min/1.73m^2). 16th International Congress of Dietetics, September 2012 (Sydney, Australia).
4. Nutrition assessment in end stage kidney disease (pre-congress lecture), 29th International Society of Blood Purification (ISBP) Annual Meeting, 9th–11th September, 2011 (Beijing, China).
5. Nutrition management of renal disease (four lectures and workshops), National Kidney Foundation of Malaysia, June 2011 (Kuala Lumpur**,** Malaysia).
6. Three lectures: (1) Pre- dialysis nutritional management for post dialysis outcome; (2) Evidence-based nutrition guidelines for adult renal transplant recipients; and (3) Nutrition and hemodialysis. Annual Update on Nutrition and Metabolism in Renal Disease, May, 2011 (Mexico City, Mexico).
7. Evidence-based nutrition guidelines for adult renal transplant recipients. 15th ICNMRD, May, 2010 (Lausanne, Switzerland).

8. Nutritional management of patients undergoing peritoneal dialysis. Renal Management Course, Baxter Scientia, Peaking University Third Hospital, April, 2010 (Beijing, China).
9. Oral nutrition support in renal failure. Parenteral and Enteral Nutrition Society of Asia (PENSA) Congress, June, 2009 (Kuala Lumpur, Malaysia).
10. Evidence-based nutrition guidelines for adult renal transplant recipients. 14th ICNMRD, June 2008 (Marseilles, France).
11. Lectures and workshops – Nutrition management in renal failure: Renal update, Dietitians Association of Hong Kong, August, 2006 (Hong Kong).
12. Nutrition and dialysis, plenary lecture, 13th ICNMRD, February, 2006 (Merida, Mexico).

Awards

1. 2nd Prize – Medical Symposium, South Eastern Sydney Local Hospital Network, October, 2011 (Sydney, Australia). Title: Malnutrition (SGA) and serum albumin levels, but not body mass index (BMI) values at initiation of dialysis are independent predictors of mortality: a 10-year clinical cohort study. Authors: Chan M, Kelly J, Batterham M and Tapsell L.
2. Top ten poster - 41st Renal Society of Australasia Annual Conference, June 2013 (Hobart, Australia). Title: Nutritional profile of patients at enrolment to the multi-disciplinary pre-dialysis clinic, 2002 to 2012. Authors: Chan M, Tranter S, Josland E, Kerr E, McTaggart S, Collett G, Kelly J, Batterham M and Tapsell L. A three minutes oral presentation is to be delivered by one of the co-authors, Dr. Shelley Tranter (Clinical nurse consultant, SGH).
3. Top ten poster - 41st Renal Society of Australasia Annual Conference, June 2013 (Hobart, Australia). Title: Association of nutritional status and the future choice of dialysis option in patients attending the multidisciplinary pre-dialysis assessment clinic. Authors: Chan M, Tranter S, Josland E, Collett G, Kelly J. A three minutes oral presentation is to be delivered by one of the co-authors, Dr. Shelley Tranter (Clinical nurse consultant, SGH).

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List of Abbreviations

ACE-I	Angiotensin-converting enzyme inhibitors
AKI	Acute kidney injury
APD	Automatic peritonreal Dialysis
ADAT	Appetite and diet assessment tool
Adj. HR	Adjusted hazard ratio
ARB	Angiotensin II receptor blockers
ASCVD	Atherosclerotic cardiovascular disease
BMD	Bone mineral disorders
BMI	Body mass index
BW	Body weight
CAD	Coronary artery disease
CARI	Caring for Australasians with Renal Impairment
CKD	Chronic kidney disease
CLD	Chronic lung disease
CRP	C reactive protein
CV	Cardiovascular
CVD	Cerebral vascular disease
CI	Confidence interval
CrCl	Creatinine clearance
DM	Diabetes mellitus
DPI	Dietary protein intake
EBP	Evidence Based Practice
EE	Energy expenditure
EI	Energy intake
ESKD	End stage kidney disease
FFM	Fat-free mass

GFR	Glomerular filtration rate
HD	Haemodialysis
HT	Hypertension
HR	Hazard ratio
IBW	Ideal body weight
kcal	kilocalorie
K/DOQI	Kidney Disease Outcomes Quality Initiatives
KDIGO	Kidney Disease: Improving Global Outcomes
LBM	Lean body mass
MAC	Mid-arm circumference
MAMC	Mid-arm muscle circumference
nPCR	Normalised protein catabolic rate
PA	Physical activity
PAL	Physical activity level
PD	Peritoneal dialysis
PTH	Parathyroid hormone
PEW	Protein energy wasting
PPV	Positive predictive value
PVD	Peripheral vascular disease
QOL	Quality of life
RCT	Randomised control trial
RDI	Recommended daily intake
REE	Resting energy expenditure
RR	Relative risk
RRT	Renal replacement therapy
TSF	Triceps skinfold
s-albumin	Serum albumin
SGA	Subjective global assessment

Chapter 1 Nutrition Management in Chronic Kidney Disease

1.1 Introduction

Chronic kidney disease (CKD) has become a public health problem worldwide,[1-3] including Australia,[4-6] and imposes tremendous clinical, societal and psychosocial burdens. Nutrition has been an integral part of medical treatment of people with end stage kidney disease (ESKD) for more than a century,[7-10] in particular, to alleviate symptoms, to control complications and to retard disease progression. Since the 1970s, technological advances in renal replacement therapy (RRT), namely dialysis and transplantation, have shifted the emphasis and resources to manage people on RRT. Thus the role of nutrition therapy in the prevention and management in non-dialysis or pre-dialysis stages seemingly receives less significant attention. Nutrition abnormalities emerge during the decline of kidney function even before reaching dialysis,[11, 12] and poor nutrition status at the start of dialysis is known to associate with undesirable outcomes.[13-15] Furthermore, there is a growing body of evidence suggesting not all ESKD patients benefit from dialysis, especially elderly patients and patients with a high number of co-morbidities.[16-18] Therefore, there is a need to revisit and gain a broader insight into the role of nutrition management in the non-dialysis stages and its effects on outcomes after initiation of dialysis. This information is needed to formulate management strategies and health care planning to improve clinical outcomes of these patients irrespective of the management pathway chosen: dialysis or conservative (no-RRT). This first chapter summarises the available evidence regarding the nutritional management of adult patients with ESKD, specifically in relation to pre-dialysis factors affecting post-dialysis outcomes. The literature search includes background and rationale for formulating the research design of studies in this thesis, up to and including the final planning stage in June 2007.

1.2 Overview of medical management of kidney disease

1.2.1 Stages of chronic kidney disease and nutrition

The three basic functions of the kidney are excretion, regulation and hormonal balance.[19, 20] As kidney function declines, these functions become impaired and lead to a stage of uraemia. Uraemia is a word derived from two ancient Greek words *ouron* (urine) and *haima* (blood) to describe the presence of increased amounts of urea and other nitrogenous end products of protein and amino acid metabolism in blood.[21, 22] Examples of protein waste products are guanidines, acids, ammonia, phosphates, uric acid, oxalate, phenols, aromatic and aliphatic amines and middle molecules. Table 1 summarises the main functions of the kidney and the consequences of impaired function.

Table 1-1 Primary functions of the kidney and consequences of impaired function

Renal function	Normal	Impaired
Excretory	Metabolic waste products, especially protein waste (e.g., creatinine, urea, ammonia, uric acid), other metabolites and toxins	⇒Accumulation: uraemia build-up of fluid, electrolytes, metabolites, toxins
Regulation	• Acid-base balance • Homoeostasis • Fluid and electrolytes balance • Blood pressure (nitric oxide, renin-angiotensin system) • Metabolism (glucose and lipids)	⇒ Uncontrolled: • acidosis • hypertension • glucose and lipid abnormalities
Endocrine (hormonal balance)	• Parathyroid hormone (PTH), vitamin D, calcium and phosphate metabolism • Erythropoietin/haemoglobin synthesis • Degradation of hormones, e.g., insulin, glucagon, PTH	⇒ hormonal imbalance: • osteodystrophy • anaemia • glucose intolerance

As kidney function deteriorates, the build-up of uraemic toxins and deranged metabolism exert detrimental effects on the body. Dialysis, a life-sustaining therapy is required to substitute the function of the diseased kidney to control these complications. Eligible patients who meet the stringent criteria may go on a waitlist for kidney transplantation, which helps to regain kidney function.

In order to achieve a standardised language and protocols to guide best practice, the clinical practice guidelines Kidney Disease Outcomes Quality Initiatives, National Kidney Foundation (NKF K/DOQI™)[23, 24] and Kidney Disease: Improving Global Outcomes (KDIGO)[25] classify CKD into five stages based on the glomerular filtration rate (GFR), a measure of kidney function. According to KDOQI guidelines, CKD is defined as "either kidney damage or GFR <60 mL/min/1.73m^2 for more than 3 months, and kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies".[23] Table 1-2 summarises the classification and treatment goals for the five stages of CKD.

Table 1-2 Stages of CKD and clinical action plan

Stage	GFR (mL/min/1.73m^2)	Description	Treatment goal
1	≥90	Renal damage with normal or ↑ GFR	Diagnosis, treatment of co-morbid conditions, slowing progression, cardiovascular disease risk reduction
2	60–89	Renal damage with mild ↓ GFR	Estimate progression
3	30–59	Moderate ↓ GFR	Evaluate and treat complications
4	15–29	Severe ↓ GFR	Preparation for renal replacement therapy
5	<15 (+ dialysis)	Renal failure	Renal replacement therapy (dialysis) if uraemia present

Adapted from K/DOQI™: Definition and classification of stages of CKD; Guideline 2: Evaluation and Treatment.[23, 24]
GFR= Glomerular filtration rate

Once the GFR falls below 30 mL/min/1.73m^2 or stage 4 CKD, patients enter the pre-dialysis phase; tertiary care by the nephrologist and the multidisciplinary renal team is recommended[23, 24, 26] to prepare for the future dialysis program in stage 5 or when GFR falls below 15 mL/min/1.73m^2.

1.2.2 Risk factors for CKD progression and mortality

Treatments in CKD focus on prevention, risk reduction of developing CKD, or, once CKD is developed, to reduce progression rate and the risk of developing complications

associated with traditional risk factors (Table1-3) and non-traditional risk factors (Table 1-4).[23, 27, 28]

Traditional risk factors are risk factors that have been defined and validated in prospective studies in the general population. Non-traditional risk factors are those that occur as a consequence of impaired renal function. Their prevalence and severity increase as kidney function declines. Tables 1-3 and 1-4 list the risk factors for the development of CKD, the factors affecting progression and mortality once CKD is developed. Patients with CKD are at increased risk of developing cardiovascular (CV) disease and CKD is now regarded as an independent risk factor for CV disease.[28] CV disease is prevalent in CKD patients, varies between 25–50% depending on stages and may account for 50% of all mortality.[29] It manifests from early stages of renal insufficiency and CV events occur even before dialysis is required. Therefore, to reduce the risk of, and treat, CV disease are as vital as managing kidney failure itself. CKD and CV disease share many common risk factors; therefore the risk factors for cardiovascular disease and its relationship with CKD are also listed in Tables 1-3 and 1-4. It is beyond the scope of this literature review to discuss all individual risk factors in detail; information collated is based on a number of significant publications, clinical practice guidelines and reviews,[1, 27, 30-34] with a focus on nutrition and related factors.

Table 1-3 Risk factors (traditional) for chronic kidney disease and cardiovascular disease

Risk factors	Chronic kidney disease		Cardiovascular disease (development of)	Mortality	Comments (Information based on clinical practice guidelines and reviews[1, 27, 30-35] and selected references)
	development of	progression			
Increased in age	+	unconfirmed	+	+	Sarnak et al.[29]
Ethnicity (Australian aboriginal/ African American)	+	unconfirmed	+	+	Hoy[36]
Exposure to nephrotoxic drugs / chemicals	+	+	Not established	Not established	Singh et al.[37]
Cardiovascular disease/ left ventricular hypertrophy	+	unconfirmed	n/a	+	Sarnak et al.[29]
Diabetes mellitus (glycaemic control)	+	+	+	+	UK Prospective Diabetes Study (UKPDS),[38] Diabetes Control and Complications Trial (DCCT),[39] Australian Diabetes, Obesity, and Lifestyle Study (AusDiab),[40] Klein et al.,[41] Grundy et al.[42]
Dyslipidaemia – ↑ LDL cholesterol	unconfirmed	unconfirmed	+	+	Werner et al.,[43] Atherosclerosis Risk in Communities (ARIC) Study.[44] ↑ LDL cholesterol is risk factor for CV disease, but association with future loss of eGFR remains unresolved
Dyslipidaemia – ↓ HDL cholesterol	unconfirmed	unconfirmed	+	+	Toth,[45] Vaziri[46]
Dyslipidaemia – ↑ triglycerides	unconfirmed	unconfirmed	+	+	Vaziri[46]
Family history of heart disease	Not established	Not established	+	unconfirmed	Pohjola-Sintonen[47]
Family history of kidney disease	+	+	Not established	unconfirmed	
Gender (male)	+	+	+	unconfirmed	Eriksen et al.[48]
History of acute kidney injury (AKI)	+	+	Not established	Not established	Basile[49]
Hypertension	+	+	+	+	Haroun et al.[50]
Kidney/urinary tract stones	unconfirmed	unconfirmed	Not established	Not established	Clayman et al.,[51] Gillen et al.[52]
Menopause	Not established	Not established	+	Not established	Kannel et al.[53]

Table 1-3 continued

Metabolic syndrome (MetS)	+	unconfirmed	+	unconfirmed	Kurella et al.,[54] Hu et al.,[55] Qiao et al.[56] Absolute CV risk of MetS does not appear higher than those of individual components
Nephron mass (low), e.g., low birth weight, nephrectomy	+	+	Not established	Not established	Luyckx et al.,[57] Hoy et al.[58]
Obesity	+	+	+	+	Fox et al.,[59] Hubert et al.,[60] Hsu et al.[61]
Physical inactivity	+	unconfirmed	+	Not established	Hallan et al.[62]
Proteinuria/Albuminuria	+	+	+	+	Sarnak et al.[29]
Psychosocial stress/ disadvantages	+	unconfirmed	+	Not established	
Smoking	+	+	+	+	Hallan et al.,[62] Haroun et al.[50]
Urinary tract infection	+	+	Not established	Not established	
Urinary tract obstruction	+	+	Not established	Not established	

"+" denotes positive effect; LDL = low density lipoprotein; HDL = high density lipoprotein; UK = United Kingdom

n/a= not applicable
Not established = relationship is unknown and is unlikely to present
Unconfirmed = relationship is suspected and awaits further studies for evidence

Table 1-4 Risk factors (non-traditional) for CKD progression and mortality

Risk factors	CKD progression	Cardiovascular disease Risk factors altered by CKD	Mortality	Comments (Information based on clinical practice guidelines and reviews,[1, 27, 30-34] and selected references)
↓ s-albumin	unconfirmed	unconfirmed	+	Low base line albumin appear to associate with faster rate of GFR decline in diabetic patients
Anaemia	+	+	+	Deicher et al.[63]
Bone mineral disorders/ ↑ calcium x phosphate products	+	+	+	Schwarz et al.,[64] Tomiyama et al.,[65] and Voormolen et al.[66]
Cardiovascular disease	+	n/a	+	Coresh et al.[67] Cardiovascular morbidity and mortality increase once eGFR is below 60 mL/min
CKD, ↓ GFR/ stage CKD	n/a	+	+	Sarnak et al.,[29] Tonelli et al.,[68] Fried et al.[69] Faster rate of progression associated with ↓ baseline kidney function
Dyslipidaemia – ↑ LDL cholesterol, ↓ HDL cholesterol and ↑ triglycerides	unconfirmed	+	+	As listed in Table 1-3a, Massy et al.[70]
Electrolyte imbalance	+	+	unconfirmed	Weir et al.[71]
Family history of CKD	+	Not established	unconfirmed	
↑ Homocysteine	unconfirmed	unconfirmed	unconfirmed	Samuelsson et al.,[72] Finocchiaro et al.[73]
Inflammation/ infection	+	+	unconfirmed	Stenvinkel et al.[74]
Malnutrition/ protein and energy wasting (PEW)	unconfirmed	+	unconfirmed	Through effects of inflammation, atherosclerosis and oxidative stress[74, 75]
Oxidative stress	unconfirmed	+	unconfirmed	Modlinger et al.[76]
Proteinuria/ albuminuria	+	+	unconfirmed	Jafar et al.[77]
↑ Renin-angiotensin system activity	+	+	unconfirmed	Remuzzi et al.[78]
Thrombogenic factors	unconfirmed	+	unconfirmed	
Uraemic toxicity	+	Not established	unconfirmed	

Table 1-4 continued

↑ Uric acid	unconfirmed	unconfirmed	+	Johnson et al.,[79] Suliman et al.[80] Uric acid level associated with calcium/phosphate metabolism, dyslipidaemia, inflammation. Independent effects on progression and mortality unconfirmed
↓ Vitamin D	unconfirmed	unconfirmed	unconfirmed	Mehrotra.[81] Vitamin D insufficiency and deficiency evident and associated with bone mineral disorder, albuminuria, CV disease in this population. However, relationship with CKD progression unconfirmed
Volume overload (fluid)	unconfirmed	+	unconfirmed	

"+" = positive effect, CKD = chronic kidney disease; LDL = low density lipoprotein; HDL = high density lipoprotein; s-albumin = serum albumin

n/a= not applicable
Not established = relationship is unknown and is unlikely to present
Unconfirmed = relationship is suspected and awaits further studies for evidence

Many of these modifiable risk factors are nutrition-related, namely: hypertension (HT); dyslipidaemia; diabetes mellitus (DM, glycaemic control); metabolic syndrome; obesity; anaemia; bone mineral disorders (BMD), including serum calcium x phosphate products; CV disease; inflammation; malnutrition / protein and energy wasting (PEW); oxidative stress; proteinuria; increased uric acid; low vitamin D level; and fluid volume overload. Due to the complex metabolic derangements in kidney failure, the efficacy of nutrition intervention alone and/or as adjunct therapy to pharmacological management has been inconclusive and requires further controlled trials. The studies of effects of nutrition interventions on individual nutrient or food component modification, such as protein and sodium, will be further explored in this review.

1.2.3 Medical management of non-dialysis CKD: an overview

Medical management of non-dialysis CKD focuses on prevention, risk identification, ongoing monitoring and treatment to slow down the rate of decline of renal function. These treatments are predominantly by pharmacological agents. Due to the kidneys' key roles in energy and nutrient metabolism, nutrition and exercise interventions are inseparable parts of management of CKD. The main treatment objectives are to manage the known modifiable risk factors discussed in the previous section. Priority interventions[23, 33, 82, 83] that are known to be effective in slowing the disease progression are (1) to control blood pressure using angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor antagonists or blockers (ARB), which have proven renoprotective effects and calcium channel blockade, and (2) to achieve optimal glycaemic control in patients with diabetes. Observational studies indicated the association of abnormal clinical parameters and kidney disease progression (Table 1-4). However, further intervention studies are required to examine the reno- protective effects of modifying these factors e.g. lipid-lowering therapy and dietary protein restriction. The Study of Heart and Renal Protection (SHARP) [84] commenced in

2003 aimed to answer if cholesterol-lowering therapy using a combination of simvastatin and the cholesterol-absorption inhibitor ezetimide could reduce cardiovascular events and survival. Unfortunately, dietary monitoring and modifications were not included in the study. In consistent results on disease progression were found in various low protein diets studies which will be discussed in detail in section 1.4.1. Other important interventions are to prevent or manage CV disease and other uraemic-related complications, such as fluid and electrolytes imbalance, acid-base balance, anaemia and bone disease management. The rate of decline of GFR may not be regular; it is also important to prevent and correct any factors that may lead to acute decline in renal function, including volume depletion, obstruction of urinary tract, intravenous radiographic contrast, use of certain medications such as nonsteroidal anti-inflammatory agents (NSAIDs), antihypertensive medications, antimicrobial agents and immunosuppressants.[23, 83] In clinical practice, dietitians are required to understand the medications commonly used in this population and their effects on nutrition management; examples are the drug-nutrient interaction of phosphate binders and iron or potential hyperkalaemic effects associated with the use of ACE-I and ARB. A list of commonly used medications is presented in Appendix A.

1.3 Causes and consequence of nutrition abnormality in ESKD: an overview

1.3.1 Introduction

By CKD stage 3 to 4, significant biochemical and haematological derangements and nutritional abnormalities may exhibit with various levels of severity. These abnormalities become more severe as GFR deteriorates;[12, 85] as patients get closer to stage 5, RRT or a conservative care pathway for management of ESRD is considered. Although clinical and nutritional status of many patients may improve after dialysis starts,[86-88] dialysis does not completely replace the function of the kidney or correct all the metabolic abnormalities associated with uraemia; patients remain in a state of

chronic uraemia. The dialysis process itself also introduces a new set of problems, altering nutrition requirements due to nutrient losses into dialysate, protein degradation and catabolic effects of dialysis.[89, 90] Therefore nutritional status continues to be compromised. Factors causing nutrition abnormalities and consequences are summarised in Table 1-5. All these factors are interrelated to alter energy, protein and nutrient requirements, either increased or decreased due to the decreased clearance or altered metabolism.

Table 1-5 Factors causing nutrition abnormalities and consequences in ESKD

Impaired function and other causes	Factors	Nutritional abnormality
Impaired excretion/ accumulation	Uraemia Build-up of fluid, electrolytes, metabolites, toxins ↓ Urine output	↑ Symptom (e.g., nausea, poor appetite, gastrointestinal symptoms taste change) leading to ↓ dietary intake ↑ Potassium ↑ Phosphorous ↑ Uric acid Fluid restriction Augmentation of proteinuria
Regulation/ Uncontrolled homeostasis	Acidosis Hypertension Glucose and lipid abnormalities ↑ Fibroblast growth factor 23 (FGF-23)	↑ Protein degradation ↑ Serum lipids ↑ Glucose
Hormonal imbalance	Insulin resistance Osteodystrophy Anaemia Glucose intolerance Leptin	↑ Protein wasting Increased iron, vitamin B_{12} and folate requirements Altered vitamin D/ calcium/ phosphate requirements
Dialytic factors (for patients on dialysis program)	Biocompatibility Nutrient losses ↑ Energy expenditure Inadequate dialysis Frequent blood sampling and losses Peritoneal dialysis-related abdominal distension, fullness and constipation	↑ Catabolism ↑Protein degradation ↓ Dietary intake ↑ Protein wasting ↑ Glucose load, ↑ triglycerides ↑ GI symptom, ↓ appetite
Miscellaneous clinical factors	Co-morbidities Medication Frequent hospitalisation Inflammation Obesity	Drug-nutrient interaction, altered nutrient availability and metabolism ↑ Nutrition requirements
Age and life cycle-related factors	Older age (> 65 years) Osteoporosis Sarcopenia Poor dentition ↑ Physical inactivity ↓ Functional capacity ↓ Independency ↓ Memory	↓ Dietary intake Altered vitamin D/ calcium/ phosphate requirements ↓ Ability to obtain/ prepare foods
Psychosocial	Depression Loss of income Poor food preparation skill	↓ Dietary intake ↓ Quality of life (QOL)s

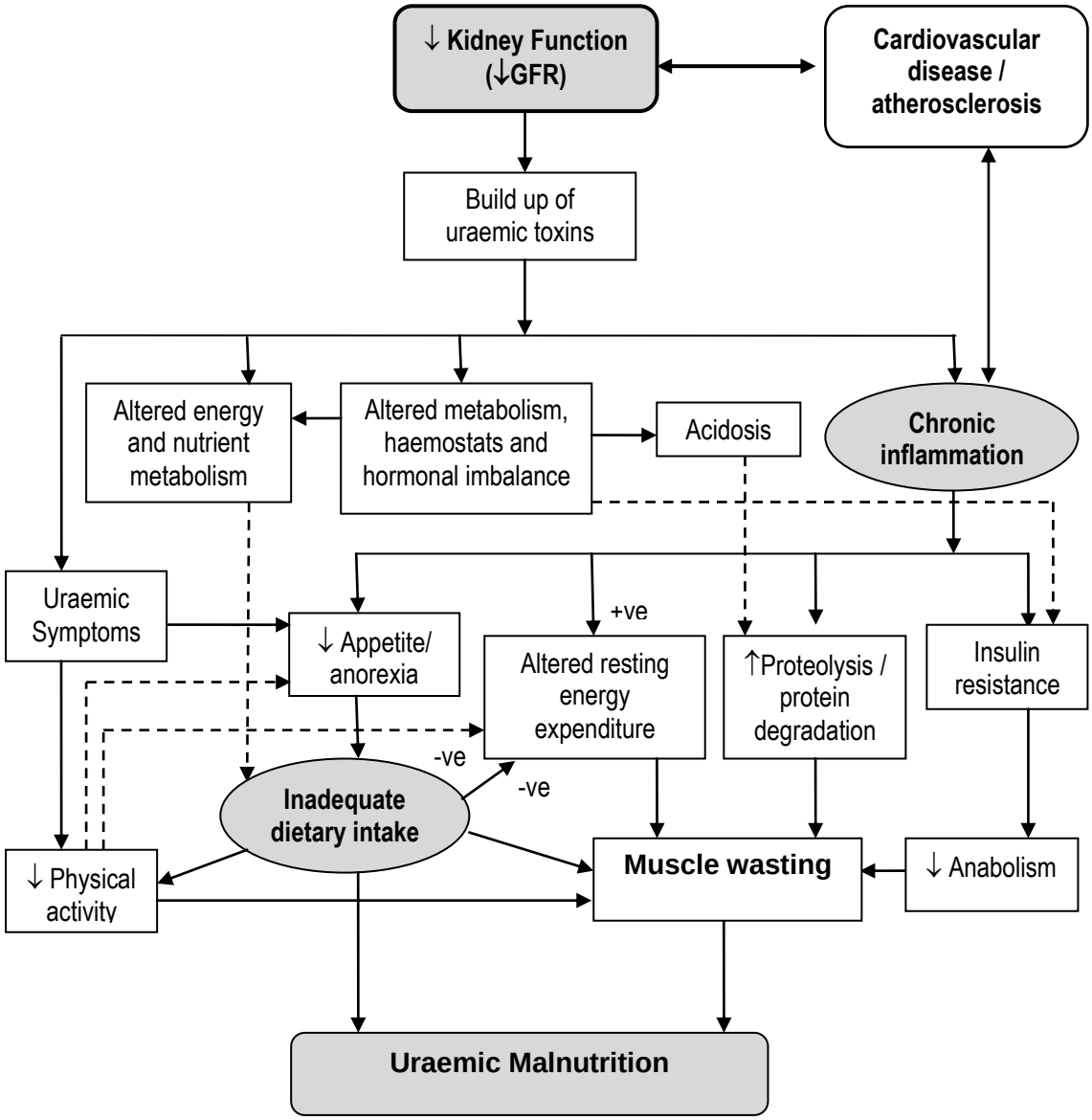
1.3.2 Overview of malnutrition in ESKD

Malnutrition is associated with detrimental consequences in patients with ESKD. In general terms, malnutrition is defined as "the condition that develops when the body does not get the right amount of the vitamins, minerals, and other nutrients it needs to maintain healthy tissues and organ function".[22] It can be under-nutrition or over-nutrition. Under-nutrition is "a consequence of consuming too few essential nutrients or using or excreting them more rapidly than they can be replaced; whereas over-nutrition is usually a result of "eating too much, eating too many of the wrong things, not exercising enough or taking too many vitamins or other dietary replacements".[22] In patients with ESKD, uraemic malnutrition generally refers to patients with kidney disease, who have suboptimal nutritional status characterised by reduced body weight, depleted fat stores, loss of somatic protein (muscle mass) and low levels of visceral proteins such as s-albumin, pre-albumin and transferrin.[75] Various nutrition parameters have been examined in longitudinal studies as markers of malnutrition or under-nutrition and predicted poor outcomes; these including a nitrogen index less than 80%,[91] depleted total body potassium,[92] low s- albumin,[15, 93, 94] reduced MAMC,[15] reduced energy intake (<25kcal/kg/d),[15] reduced appetite,[95-97] subjective global assessment (SGA) [13, 14, 98, 99] and related composite score such as malnutrition inflammation complex syndrome (MICS).[100] Prevalence of malnutrition is high in patients with ESKD, it has been reported to be approximately 28% to 40% in stages 4 to 5 non-dialysis patients [85, 98]; 39% to 55% in incident dialysis patients (at the start of dialysis),[13, 99] and 20% to 76% in prevalent or established dialysis patients.[101, 102] Malnutrition is associated with morbidity and mortality,[90, 91, 98, 103-105] hospitalisation[13, 98, 106] and poor quality of life (QOL).[107, 108]

The cause of uraemic malnutrition or PEW is multifactorial,[109, 110] and is a consequence of metabolic and hormonal derangements in kidney failure (Table 1-5, Figure 1-1). The main factors are reduced spontaneous energy and protein intake[11] due poor appetite[111] and taste aversion to foods caused by uraemic toxicity, altered energy expenditure

(EE),[112, 113] dietary restriction, inflammation,[95] catabolism,[114] metabolic acidosis,[115, 116] altered hormone response,[117] altered gastrointestinal function[118] and dialytic factors (in dialysis patients).[119, 120] These problems are also compounded by osteoporosis and sarcopenia which are commonly found in the aging population with or without CKD.

Figure 1-1 Mechanism associated with the development of uraemic malnutrition in ESKD



Abbreviation: "+ve"= positive, "-ve"= negative

It is well accepted that there are two types of malnutrition: Type I is defined as "true" malnutrition related to uraemia *per se*, such as inadequate intake of energy and protein, physical inactivity and inadequate dialysis (in patients on dialysis). Type II malnutrition is caused by inflammation which leads to malnutrition and cardiovascular disease and is also known as malnutrition, inflammation and atherosclerosis (MIA) syndrome.[74, 75] It is characterised by elevated inflammatory markers (e.g. CRP) and pro-inflammatory cytokines (e.g. interleukin-1 and tumour necrosis factor-α); these are known to inhibit appetite and increase protein catabolism, leading to protein energy wasting (PEW). Table 1-6 summarises the features of type I and II malnutrition

Table 1-6 Features of type I and type II malnutrition

Clinical and nutritional Parameters	Malnutrition	
	Type I	Type II
S-albumin	Normal to moderate ↓	↓
Co-morbidity	Uncommon	Common
Presence of inflammation, e.g. ↑ C reactive protein (CRP)	No	Yes
Dietary protein and energy intake	↓	Normal to ↓
Resting energy expenditure	Normal	↑
Oxidative stress	↑	↑↑
Protein catabolism	Normal	↑
Improved by dialysis and nutritional support	Yes	Probably not unless underlying clinical cause is managed

Adapted from Stenvinkel et. al.[75]

Type I and Type II malnutrition may co-exist, continue to overlap, and change magnitude during the course of decline of kidney function and use of RRT. As shown in Figure I-1, all contributing factors are interrelated and in a vicious circle compounding the effects of each other. Therefore, treating the cause of inflammation and ensuring adequate protein and energy intake (EI) to manage PEW are of equal importance. The consequences of malnutrition on clinical outcome and survival will be discussed further in section 1.3.4.

1.3.3 Overview of overweight and obesity in ESKD

While under-nutrition is known to associate with poor outcomes, on the other hand, the overweight and obesity paradox has created much debate in the renal community on its effect on outcome and survival. A body mass index (BMI) level between 25.0 to 29.9 is categorised as overweight and a BMI ≥30.0 is categorised as obese.[121] The factors[122, 123] leading to the development of overweight and obesity are excess caloric intake, physical inactivity, insulin resistance, genetics, epigenetics, comorbidity and medications that alter metabolism, such as steroids.

In the general population, overweight and obesity are associated with the development of a number of chronic and clinical conditions, such as HT, dyslipidaemia, DM, CV disease, cerebral vascular disease (CVD) and some types of cancer.[60, 124, 125] The "J-curve" relationship is observed between mortality risk and the range of BMI levels, in that underweight and being obese are associated with higher mortality risk.[126, 127] However, high BMIs or obesity appear to exert protective effects in the dialysis population;[105, 128, 129] this is known as "reverse epidemiology".[130-132] The "reverse epidemiology" phenomenon in ESKD is not well-understood but may reflect that highest risk individuals with earlier stages of CKD die from cardiovascular disease without progressing to CKD stage 5. However, other researchers reported the "J-curve" relationship between BMI and survival was evident in the Australian ESKD population.[133] Overweight and obesity have different impacts on clinical outcomes depending on CKD stages and treatment. Such effects on the dialysis (haemodialysis [HD] or peritoneal dialysis [PD]) and transplantation populations are very different to those patients not yet on dialysis and are beyond the scope of this thesis to discuss these mechanisms. In general, there is a lack of detailed published studies for the non-dialysis CKD population to describe the association between BMI and mortality, and the evidence of "reverse epidemiology" has been inconclusive.[134] In the Framingham

Heart Study, obesity showed an increased risk in the development of CKD,[135] probably mediated through other risk factors such as CV disease, HT, DM, insulin resistance, metabolic syndrome, inflammation, prothrombotic state, a cluster of metabolic risk factors collectively called atherosclerotic cardiovascular disease (ASCVD).[122] In a number of cohorts, obesity has been identified as an independent predictor for CKD.[59, 61, 136] Patients with high waist-to-hip ratios or central adiposity appear to have the highest risk of developing CKD.[137] Obesity is not just a risk factor for CKD, but also accelerates progression as it enhances hyperfiltration and hyperperfusion, irrespective of the presence of HT, and magnifies the effects of HT on albuminuria to increase kidney injury.[138] Other obesity-related metabolic disorders that magnify CKD development and progression are IgA nephropathy,[139] diabetic nephropathy, stone disease (urate nephropathy)[140, 141] and obesity-related glomerulopathy (ORG), a form of focal segmental glomerulosclerosis (FSGS).[138, 142]

Wasting can occur in overweight or obese CKD patients or patients could gain fat stores and lose muscle mass. In a retrospective analysis that included approximately 70,028 incident HD patients,[143] high BMI (defined as ≥25 kg/m^2) had lower hazard of death (HR, 95% CI: 0.85, 0.83–0.87; *P* <0.001) compared to those who had a BMI <25 kg/m^2. However, the protective effect of high BMI was limited to those patients with normal or high muscle mass as measured by urinary creatinine (UCr) >25th percentile of the study population, that was 0.55 g/d. Whereas patients with high BMI with inferred low muscle mass, defined as UCr <0.55 g/d, had increased mortality risk (HR, 95% CI: 1.14, 1.10–1.18; *P* <0.001). In a prospective cohort of patients who were assessed close to or just after the initiation of dialysis, PEW was found to be a predictor of mortality in both obese and non-obese sarcopenia patients.[144] These studies suggested the importance of body composition rather than BMI alone to predict mortalities.

In addition to malnutrition and obesity, other consequences of nutritional abnormalities listed in Table 1-5, such as osteodystrophy due to altered vitamin D, calcium and phosphate requirements, are all important contributing factors to poor clinical outcomes.

1.3.4 Nutritional factors affecting outcomes and survival in patients with ESKD

Many nutrition abnormalities emerge during the decline of kidney function[12, 74] and are present at the start of dialysis.[145, 146] Longitudinal survival studies (Table 1-7) identified a number of nutritional and related factors at the commencement of dialysis associated with poor outcomes of ESKD patients. The significant factors affecting outcome included: older age (> 65years); presence of co-morbidities, such as cardiovascular disease and DM; low kidney function, measured by serum creatinine clearance (CrCl) or GFR; and nutritional factors, such as low BMI, reduced serum albumin (s-albumin), reduced EI, reduced muscle mass, history of weight loss, reduced hand grip strength and malnutrition scored using the subjective global assessment (SGA). SGA is a diagnostic tool for malnutrition based on the clinician's subjective judgement on medical and physical assessment of a patient.[147-150] The role of SGA in nutritional assessment in CKD will be discussed in Section 1.5.2.

These studies indicated high prevalence of malnutrition (42–55%) and presence of nutrition abnormalities at the start of dialysis. However, the interpretation of the relationship between malnutrition and renal function varied depending on a number of factors, including patient selection criteria and history of pre-dialysis nephrology care. Most importantly, despite nutrition status usually improving after dialysis started,[86, 87] the extent of improvement during the first year of treatment depended on the nutritional status at the time of initiation of dialysis; therefore baseline nutritional parameters predicted the value at the end of one year study period.[87] Thus, it comes into view that pre-dialysis nutritional status has influence over clinical outcomes after initiation of

dialysis. Like nutritional status, the closely related QOL factor[107, 108] is another important outcome measure in dialysis patients. High prevalence of anaemia (56%), hypoalbuminaemia (52%) and depressive symptoms and poor physical function score measured by Short Form Health Survey (SF-36) were observed in a study of 422 incident HD patients.[151] While the importance of timely pre-dialysis care to improve clinical outcomes requires further investigation, patient-centred outcome measures such as QOL should also be considered.

Table 1-7 Nutritional and related factors at commencement of dialysis and outcomes

Author/ study Country *Year	Patient number, age (yr) and study duration	Dialysis (GFR at start of dialysis, mL/min/1.73m^2)	Outcome measures	Significant factors and outcomes SGA – malnutrition (%), Relevant non-affecting factors (mortality risk of relevant nutritional factors displayed if appropriate)
CANUSA Study[13] US *1996*	n =680 age: 54.3 (18–82) study: 40 mth f/u: 24 mth	PD (n/a)	Mortality	↑ Age, CV Disease, ↓ CrC, ↓ KT/V, DM (on insulin); ↓ s-alb – per 1g/L ↑, RR (95% CI): 0.94 (0.90–0.97) ↓ % LBM (1%-lower % associated with 3% ↑ in the RR of death) Malnutrition by SGA score (55.4%), for 1 unit ↑ improvement RR (95% CI): 0.75 (0.66–0.85)
			Technique failure	↓ s-alb – per 1g/L ↑, RR (95% CI): 0.95 (0.92–0.95) CCr – for 5L/wk/1.73m^2, ↑ RR (95% CI): 0.95 (0.9 1–0.99)
			Hospitalisation	↓ CCr e^{coefficient} multiplicative factor indicating relative time hospitalised compared to alternative within variable. e^{coefficient} for s-alb =0.95, e^{coefficient} for 1 unit improvement of SGA score =0.82
Rocco[106] US *1996*	n =1752 age: 57.4±15 study: 36 mth f/u: n/a	HD (n/a)	Hospital days/yr	↑ Age, ↓ physical activity, DM primary cause of ESKD, Caucasian, PVD, absence of HT, angina, smoking, CCF, ↓ s-alb (multiple regression analysis, for ↑ of 1.0 g/dL, *r* =0.23, *P* <0.0001)
Barrett[152] Canada *1997*	n =820 age:58.3±15.4 study: till end of April 1995 f/u: 6 mth (all patients)	HD & PD	Mortality	OR (95% CI): ↑ age, 60–70 yr: 2.4 (1.1–5.2) and ≥70 5.0 (2.4–10.5); Presence of cardiac symptoms: OR (95% CI): 3.2 (1.6–6.7), malnutrition-MD assessed (18.7%): 2.5 (1.5–4.2); s-alb: ≤2.5 g/dL, 2.2 (1.1–4.4). *P* values n/a
Chung[99] Korea *2000*	n =91 age: 53 (22–76) study: 52 mth f/u: 24 mth	PD (n/a)	Mortality	↑ Age, malnutrition by SGA score (45.0%) RR (95% CI): 2.38 (1.17–5.35), *P* <0.015 ↓ FFM – for each kg↑, RR (95% CI): 0.92 (0.84–1.00), *P* <0.046

Table1-7 continued

Stenvinkel[14] Sweden *2002*	n =206 age: 52.0±12.8 Study: n/a f/u: 37±2.0 mth	HD and PD (7.0±1.0)	Mortality	Age, gender, DM, CVD, ↓ HGS, ↑CRP Malnutrition by SGA score (39.0%), adj. HR (95% CI): 1.78 (1.31–2.49), *P* <0.001 ↓ s-alb per g/L ↑ – unadjusted HR (95% CI): 0.95 (0.91–0.98), *P* <0.01. adj. HR NS. ↓ LBM (male) per kg ↑, adj. HR (95% CI): 0.95 (0.89–1.00), *P* =0.06 BMI, ↓ LBM (female)
Beddhu[143] USA *2003*	n =70,028 age: ~ 65±14.0 study: 48 mth f/u: not reported	HD (n/a)	Mortality (all-cause and cardiac)	↑ BMI (>30 kg/m^2) with ↓ muscle mass (defined as Cr <25th percentile), all-cause mortality adj. HR (95% CI): 1.14 (1.10–1.18), *P* <0.001 and cardiovascular death adj. HR (95% CI): 1.19 (1.13–1.26), *P* <0.001
Chung[153] Korea *2003*	n =153 age: 53.3±12.3 study:84 mth f/u: 20.8±15.2 (1.0–6.8) mth	PD (n/a)	Mortality	Combined CMD and malnutrition by SGA (48.5%) within CMD group. Adj. HR (95% CI): 9.0 (2.14–32.24), *P* =0.006; Malnutrition by SGA =41.8% in total sample; Malnutrition alone adj. HR, 95% CI: 2.72, 0.17–20.64 (NS)
Wang[154] US *2003*	n =393 age: 55.5±15.0 study: 120 mth f/u: median 13.4 (range 0.1–104.8) mth	PD (n/a)	Peritonitis rate	Male gender ↓ s-alb (Univariate analysis, for 1 g/L ↑, RR (95% CI): 0.79 (0.65–0.95), *P* =0.015
Wiesholzer[155] Austria *2003*	n =377 age: 64.0 (17–89) study:180 mth f/u: 36 mth	HD (n/a)	Mortality	adj. HR (95% CI): • low initial body weight (BMI per 1 kg/m^2 increment) 0.96 (0.94–0.98), *P* <0.0001; diabetic nephropathy 1.3 (1.14–1.65), *P* <0.0001; weight loss within 12 mth of dialysis initiation 2.16 (1.83–2.55), *P* <0.0001
Pupim[156] USA *2004*	n =149 age: 55.2±17.2 (19–90) study: n/a f/u: 12 mth	HD (9.02±5.8, range 0.70–35.8)	Hospitalisation	Mean length of hospital stay per yr of highest vs. lowest quartiles of studied parameters: s-alb 3.83±5.68 vs. 8.96±9.96 day/yr, *P* =0.006; creatinine 4.72±11.57 vs. 12.43±15.15 day/yr, *P* =0.017 CrCl or residual renal function (NS)

Table 1-7 continued

Johansen[157] USA *2004*	n =418,055 age: 56.7±12.8 to 64.3±16.9 study: 78 mth f/u:24 mth (median)	HD and PD (n/a)	Mortality	High BMI, adiposity and fat mass
McDonald[133] Australia *2004*	n =9,679 age: 47–70 study: 121 mth f/u: n/a	PD (n/a)	Mortality	Obesity or BMI >30 kg/m^2: adj. HR (95% CI) for mortality 1.36 (1.14–1.54), *P* <0.05 and technique failure 1.17 (1.07–1.26), *P* <0.01 BMI <20 or >30 kg/m^2 J-curve relationship existed in fractional polynomial analysis
Chandna[158] UK *2005*	n =318 age: ~ 59.3±14.9 study: ~ 10 yr f/u:36 mth	HD and PD (n/a)	Mortality	nPCR levels <0.8 g/kg/d at initiation of dialysis predicted: future low nPCR levels at 3 mth and 1 yr *P* <0.001, and 3 yr *P* <0.01; mortality – adj. HR(95% CI): 1.51 (1.08–2.10), *P* <0.015 Also refer to Table 1-7 regarding the pre-dialysis data
Beddhu[159] USA *2005*	n =5059 age=64±14yr study: 3 yr f/u:1 to 3 yr	HD and PD (CrCl: ranged from 7.8±6.2 to 12.2±6.2 over 4 quartiles)	Mortality	Total protein intake (TPI) using highest quartile as referent (60.2 g/d): those in the lowest quartile (≤32.4 g/d) had adj. HR (95% CI): 1.18 (1.05–1.33), *P* <0.001; Dietary protein intake (DPI) defined as TPI per kg of weight using 1.2 g/kg/d as referent, DPI <0.8 g/kg/d had adj. HR (95% CI): 0.85 (0.73–0.99), *P* =0.04
Araujo[15] Brazil *2006*	n =344 age 18–90 study: 120 mth f/u: n/a	HD (n/a)	Mortality	Adj. HR (95% CI) for mortality: age (>60 yr): 1.87 (1.22–2.87), *P* =0.004 ↓ s-alb: 1.59 (1.02–2.46), *P* =0.04; DM: 1.93 (1.23–3.04), *P* =0.004 ↓ MAMC: 0.97 (0.96–0.99), *P* =0.008 ↑ energy intake (>25 kcal/kg/d): 0.96 (0.92–0.99), *P* =0.03 Gender, KT/V, BMI, TSF

Abbreviation: UK = united Kingdom; ↑ = increased; ↓ =decreased; yr = year; f/u = follow up; mth = month; HD = haemodialysis; PD = peritoneal dialysis; CV = cardiovascular ; CrCl = creatinine clearance; RR = relative risk; OR = Odds ratio; HR = hazard ratio; adj. HR = adjusted hazard ratio; CI = confidence interval; NS = non-significant (statistically); KT/V = dialysis constant x time/ volume of distribution (urea kinetic study); DM = diabetes mellitus; s-alb = serum albumin; BMI = body mass index; LBM = lean body mass; FFM = fat-free mass; MAMC = mid-arm muscle circumference; TSF = triceps skinfold; SGA = subjective global assessment; nPCR = normalised protein catabolic rate; CMD = co-morbid disease
Expression of figures: n±SD – standard deviation; n(n1-n2) – range
* ordered by year

The relationship between levels of kidney function at the time of starting dialysis and nutritional status has seldom been investigated. In a cross-sectional retrospective analysis of 134 incident dialysis patients,[146] the "late start" group (GFR <10 mL/min/1.73m^2) when compared with the "early start" group (GFR >10 mL/min/1.73m^2), had significantly lower levels of s-albumin (36.6±5.0 vs. 39.3±4.8 g/L, *P* =0.02), a lower nitrogen index (%) as measured by the *in vitro* neutron activation analysis reflecting body protein store (88±13 vs. 106±9, *P* <0.0001) and a higher proportion of malnourished patients defined by nitrogen index <85.0% (46/108 vs. 0/46, *P* <0.0001). Late referral to nephrologists, defined as <3 months prior to dialysis initiation, was significantly higher in the late start group too (*P* <0.04). It appeared that patients who started dialysis at lower GFR levels were more likely to be malnourished. Nutrition intervention in the pre-dialysis stage was not reported in this study. While the result of this study suggested dialysis should be started early, in contrast, in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)[145] with 114 incident dialysis patients, the baseline data indicated that even at a mean commencing GFR of 6.2 mL/min/1.73m^2, nutritional status was well-maintained, with 69.0% of patients meeting the normalised protein nitrogen appearance (nPNA) norm of 0.8 g/kg/d; 67.0% of patients had an s-albumin level in the normal range and 71.0% were rated as normal nutrition (SGA score A) at the third month of assessment. In addition, 90.0% of the studied patients received pre-ESKD management defined as care in a nephrology outpatient clinic for at least a month (median 19, range 1.4–256 months). However, the history of nutrition intervention was not mentioned. Two of the survival studies[13, 14] (also see Table 1-6) reported baseline renal function and prevalence of malnutrition, but again there was no mention of the history of nutrition intervention. In the Swedish study,[14] the mean GFR at the start of dialysis was 7.0±1.0 mL/min/1.73m^2 and 42.2% of patients were classified as malnourished. Patients who agreed to participate in the study were assessed within 4 weeks before dialysis started and were less than 70

years of age. In the Canada-USA (CANUSA) Peritoneal Dialysis Study,[13] 55.4% of patients were classified as malnourished and the baseline renal CrCl was 38.8 L/week/1.73m^2. Strict exclusion criteria were applied to patients who consented to participate in the study, such as patients who were unlikely to survive for at least 6 months or who had active systematic inflammatory disease. These studies provided substantial evidence to support that nutrition abnormality and related factors present at the start of dialysis were associated with poor outcomes. These suggest timely nutrition intervention in the pre-dialysis stage may be crucial to improve outcomes. The nutrition status of the non-consented patients was either not known or possibly worse due to unplanned dialysis.

1.3.5 Nutritional intake and abnormalities in non-dialysis CKD stages 4 to 5

As observed in cross-sectional and prospective longitudinal studies (Table1-8), nutritional intakes decrease and nutritional status deteriorates as renal function decreases through stages 4 to 5 CKD, before reaching dialysis. Positive correlations exist between energy, protein and some nutrient intake and GFR.[11, 12, 160] However, these relationships do not appear linear, levelling off after the initial declines and remaining low.[161] In advanced CKD, the reduced nutrition intake was thought to be the biological adaptation of uraemia caused by neurological changes that led to a gradual alteration of the sense of taste.[162] Despite correlated declines in energy, protein and nutrient intakes with GFR, dietary intakes are also likely to be influenced by cultural or regional eating habits and food patterns[161] and diet-reporting behaviour.[163] In a longitudinal study with 1,282 subjects,[158] the authors observed a dramatic and significant reduction of protein intake measured by normalised protein catabolic rate (nPCR) late in the course of progressive CKD when CrCl fell below 15 mL/min, approximately 3 months preceding initiation of dialysis.

Table 1-8 Energy and protein intakes in non-dialyse CKD stages 4 to 5

Author/ study Country *Year Study type [Stratification factor if applied]	Patient number and age (year)	Renal function CrCl/ GFR (mL/min/1.73m^2)	Intake		Nutrition parameters		Comment and relevant findings
			Energy (kcal/kg/d) ***Method***	Protein (DPI) (g/kg/d) ***Method***	BMI (kg/m^2)	s-alb (g/L)	
Pollock[160] Australia *1997* Cross-sectional	n =766 age:61.8±1.1 (range 7–88)	36.1±2.1	n/a	0.89±0.02 *UUN*	24.2±0.3	41.7±0.3	Relationship between GFR and: DPI: *r* =0.50; *P* <0.0001 BMI: *r* =0.23; *P* <0.0001 s-alb: *r* =0.14; *P* <0.0001 (inverse correlations with age, chol, TG and BSL)
Lusvarghi[161] Italy *1998* Cross-sectional	n =484 age:63±15	28.2±16.1	29.0±7.4 *7 day recall*	1.02±0.20 *7 day recall*	25.8±4.3	n/a	Relationship between GFR and protein, lipids and glycides *r* =0.025, 0.30, and 0.29 respectively CKD patients have lower intake of energy, proteins, lipids and carbohydrates compared to population average except higher total lipid and M/UFA intake
Carvalho[164] Brazil *2004* Cross-sectional	n =27 age:57±17	18.0±5.0	23.6±7.8 *24hr recall*	1.04±0.24 *24hr recall*	23.8±3.8	44.0±5.0	Relationship between: Energy intake and BMI: *r* =0.84; *P* <0.05) s-alb and CRP: *r* =0.91; *P* <0.01 (also see Table 1-8)

Table 1-8 continued

Fassett/LORD Study[163] Australia *2007* Cross-sectional	n =113 age: 60±15	40.3±19.4	21.5±7.8 *F-diary*	0.9±0.3 *F-diary*	28.6±6.0	40.2±4.5	Underreporting observed in 70.8% of patients with Goldberg cut-off of EI/RMR <1.27. They were more likely to be female and younger, and have a ↑ BMI and ↑ serum creatinine. Mean energy, calcium, zinc and dietary fibre intakes were all less than recommended
Kopple, MDRD[12] USA *2000* Cross-sectional *[GFR]*	All: n =1,785 age: 51.2±12.9	All: 39.8±21.1	29.4±9.31 *F-diary*	1.00±0.25 *UUN* 1.05±0.34 *F-diary*	27.6±4.1 (M) 26.6±5.4 (F)	40.6±3.9 (M) 39.9±3.4 (F)	Statistically significant difference of various parameters occurred between GFR >37 vs. 21–37 mL/min groups, 21–37 vs. <21 mL/min groups, *P* <0.05. (also see Table 1-8)
	n =540 age: 51.0±12.4	>37 group	31.0±9.30	1.06±0.30 1.13±0.35	28.1±4.1 (M) 26.8±5.6 (F)	41.0±3.9 (M) 40.6±3.2 (F)	
	n =355 age: 51.2±13.6	21–37 group	29.2±10.0	0.97±0.22 1.05±0.34	27.4±4.3 (M) 26.8±5.6 (F)	40.3±3.8 (M) 39.6±3.4 (F)	
	n =204 age: 51.3±13.2	<21 group	26.4±6.90	0.88±0.19 0.90±0.27	26.4±3.7 (M) 26.1±5.3 (F)	39.9±4.0 (M) 38.8±3.7 (F)	
Caravaca[85] Spain *2001* Cross-sectional *[SGA]*	All: n =201 age: 63±13	n/a	n/a	Mean figure for all patient: n/a *UUN*	n/a	n/a	Protein intake (PNA) correlated with renal function (measured by Kt/V urea), *r* =0.53, *P* <0.0001 best fit in quadratic regression curve; or renal function measured by CrCl-Cu, *r* =0.53, *P* <0.0001 in linear regression line. PNA was significantly higher in SGA A vs. SGA B or C groups, *P* <0.05
	SGA A: n =128 age: 61±15	14.6±5.1	n/a	1.04±0.32	29.2±5.8	38.2±4.0	
	SGA B n =62 age: 66±10	12.3±4.1	n/a	0.88±0.22	27.7±5.3	36.0±6.0	
	SGA C n =11 age: 67±9	10.5±4.5	n/a	0.76±0.22	22.6±4.0	34.1±4.0	

Table 1-8 continued

Duenhas[165] Brazil *2003* Cross-sectional *[GFR]*	All: n =487 age: 53.4±15.0	All (mean GFR n/a)	24.9±8.2	0.98±0.32 *F-diary* 0.95±0.36 *PNA*	25.6±4.6	38.0±6.7	Energy intake higher GFR >43 vs. <20 mL/min groups, *P* <0.05. Protein intake (PNA) significantly lower in GFR <43 groups vs. >43 mL/min group, *P* <0.05 (also see Table 1-8). CrCl correlated positively with PNA (*r* =0.30, *P* <0.01), energy intake (*r* =0.17, *P* <0.01) and protein intake (*r* =0.21, *P* <0.01)
	n =126 age: 54.0±13.8	>43 group	25.9±9.2	1.04±0.42 1.15±0.34	27.1±4.7	38.0±7.2	
	n =119 age: 52.8±15.7	30–43	25.5±8.3	0.99±0.37 0.96±0.29	25.0±4.4	38.0±6.3	
	n =127 age: 52.4±16.8	20–29	24.4±7.2	0.91±0.29 0.93±0.29	25.3±4.9	38.0±7.2	
	n =115 age: 54.2±13.7	<20	23.5±7.9	0.88±0.33 0.84±0.29	25.0±4.2	38.0±5.8	
Ikizler[11] USA *1995* Longitudinal	All: n =90 age: 53±15 f/u: 16.8±11.8 mth	All: 35.1±26.1	n/a	0.82±0.28 *UUN*	n/a	38.0±0.5	↓ DPI as ↓ CrCl (*r* =0.46, *P* <0.0001). Reduction became more noticeable when CrCl fell below 25 mL/ml; when CrCl fell below 10 mL/min, protein intake below minimal requirement of 0.6g/kg/d
		>50	n/a	1.01±0.21	n/a	n/a	
		50–25	n/a	0.85±0.23	n/a	n/a	
		24–10	n/a	0.70±0.17	n/a	n/a	
		<10	n/a	0.54±0.16	n/a	n/a	
Chandna[158] UK *2005* Longitudinal	All: n =1,282 age: 55.8±15.5 f/u: 84 mth	All: mean-n/a	n/a	n/a	n/a	n/a	Protein intake (nPCR) significantly different among CrCl groups (*P* <0.001). 2-phase exponential association between nPCR and CrCl observed. Gentle decline of nPCR in mild and moderate renal failure ended in dramatic decline when CrCl reached 15 mL/min
		>50	n/a	1.17±0.31 *UUN*	n/a	n/a	
		25–50	n/a	1.04±0.27	n/a	n/a	
		10–25	n/a	0.93±0.21	n/a	n/a	
		<10	n/a	0.74±0.18	n/a	n/a	

Abbreviation: n/a = not available or not measured; CrCl = creatinine clearance; GFR = glomerular filtration rate; UUN = urinary urea nitrogen; F-diary = food diary; s-alb = serum albumin; PNA = protein equivalent of nitrogen appearance; chol = cholesterol; TG = triglyceride; BSL = blood sugar level; M/UFA = monounsaturated fatty acid; CRP = C reactive protein; EI/RMR = energy intake: resting metabolic rate ratio; vs. = versus; SGA = subjective global assessment; Htc = haematocrit; Ccr-Cu = urea clearance; nPCR = normalised protein catabolic rate
Expression of figures: n±SD – standard deviation; n(n1-n2) – range
* ordered by year

The prevalence of malnutrition measured by SGA ranged from 28–44% in the CKD stages 3 to 5 non-dialysis population, and was associated with poor body composition, vascular abnormality, hospitalisation and mortality (Table 1-9). Strong associations also existed between reduced renal function, nutritional abnormalities, reduced intake and malnutrition. In a longitudinal study over a 12-month period, malnutrition at baseline was associated with mortality, composite end-point of death or dialysis and acute hospitalisation.[98] Furthermore, the relationship between the detrimental effects of uraemic symptoms and renal function (measured by CrCl) was not linear and escalated once CrCl fell below 13 mL/min.[85] All these observations have significant clinical and economic implications for renal services.

In summary, the results of these studies indicated that as renal function declines, dietary energy and protein intakes, nutritional status reflected by nutritional markers such as anthropometrical (body compositions), and biochemical and histological measures all deteriorated. Sub-optimal nutrition intake and status could be detected when GFR dropped below 40 mL/min/1.73m^2. Interestingly, symptoms burden in relation to protein and energy intakes, intake of other nutrients, food components, dietary patterns and food habits were seldom examined. To date, only two studies are known to have examined the dietary intake and nutritional status in the Australian ESKD population,[160, 163] both of which represented samples of much “younger” patients (60±15 and 61.8±1.1 years) with higher levels of GFR (40.3±19.4 and 36.1±2.1 mL/min) than those referred for pre-dialysis management (GFR <30 mL/min) in our setting (Appendix B). Therefore, further study is required in this population in the local setting.

Table 1-9 Relationships between nutritional and related factors in non-dialysis CKD stages 4 to 5

Author/ study Country **Year*	**Patient number and age (yr)**	**Study type**	**Renal function (CrCl/ GFR mL/min/1.73m²)**	**Significant factors associating with reduced renal function Malnutrition (%) Relevant non-affecting factors**
Stenvinkel[74] Sweden *1999*	n =109 age: 52±1	Case with age-matched healthy control (n =22)	7.0±1.0	SGA (malnutrition =44%) in univariate analysis, ↓ s-vitamin E, ↑ CRP, CKD patients: ↑ mean carotid intima-media area (18.3±0.6 vs. 13.2±0.7 mm², *P* <0.0001) and ↑ prevalence of carotid plaques (72.0% vs. 32.0%, *P* =0.001) indicative of rapidly developing atherosclerosis. Related to malnutrition, inflammation, oxidative stress, genetic components
Kopple, MDRD[12] USA *2000*	n =1,785 age: 51.2±12.9	Cross-sectional	39.8±21.1	↓ GFR correlated with ↓ sum of skinfolds/ body fat and ↓ transferrin in male; ↓ transferrin and s-alb in female Decline of GFR may contribute to decline in many nutritional measures related to reduced protein and energy intakes
Lawson[98] Australia *2001*	n =50 age: 69.1 (95% CI: 62.9–75.4)	Prospective case control with 12 mth f/u	SGA A (n =36): 28.5±12.5 SGA B or C (n =14): 20.7±10.9	SGA (malnutrition =28%) Significantly ↑ mortality (21% vs. 3%, *P* =0.04), composite end-point of death or dialysis (50.0% vs. 11.0%, *P* =0.02) and ↑ likelihood of acute hospitalisation (78.0% vs. 23.0%, *P* =0.001) in malnourished group
Caravaca[85] Spain *2001*	n =201 age: 63±13	Cross-sectional	Mean value n/a 14.6±5.1 in SGA = A group and below	SGA (malnutrition =36%) and uraemia score Determinants of malnutrition with OR (95% CI) and *P* value were • co-morbidity: 10.29 (4.73–22.37), *P* <0.0001 • Ccr-cu: 0.96 (0.98–0.94), *P* =0.0015 • Htc: 0.91 (0.85–0.98), *P* =0.014 Ccr (*r* =0.38, *P* <0.0001) and Ccr-Cu (*r* =0.42, *P* <0.0001) correlated with uraemia score in cubic curves. Ascending inflection of uraemia score occurred when GFR <13 mL/min/1.73m², indicating non-linear relationship between effects of uraemia and GFR

Table 1-9 continued

Duenhas[165] Brazil *2003*	n =487 age: 53.4±15.0	Cross-sectional	<43	CrCl correlated directly and significantly with MAMC (*r* =0.20, *P* <0.01). In multiple regression analyses, CrCl, energy and protein intakes independent predictors of BMI (*P* <0.01) and MAMC (*P* <0.05)
Cupisti[166] Italy *2004*	n =70 age: 52±1	Cross-sectional	<15	SGA (malnutrition =28.6%)
Carvalho[164] Brazil *2004*	n =27 age: 57±17	Cross-sectional	18.0±5.0	Fat stores (TSF) depleted in 60% of patients Not CRP nor s-alb

Abbreviation: n/a = not available or not measured; CrCl = creatinine clearance; GFR = glomerular filtration rate; UUN =urinary urea nitrogen; F-diary = food diary; s-alb = serum albumin; PNA = protein equivalent of nitrogen appearance; chol = cholesterol; TG = triglyceride; BSL = blood sugar level; M/UFA = monounsaturated fatty acid; CRP = C reactive protein; EI/REE = energy intake: resting energy expenditure ratio; vs. = versus; SGA = subjective global assessment; Htc = haematocrit; Ccr-Cu = urea clearance; f/u = follow-up
Expression of figures: n±SD – standard deviation; n(n1-n2) - range
* ordered by year

1.3.6 Other nutrition-related factors and outcomes in non-dialysis CKD stages 4 to 5

As CKD progresses, the magnitude of other nutritional abnormalities and related factors also increases. These include:

- anaemia,[167-169] a risk factor for cardiovascular disease in CKD and associated with Malnutrition Inflammation and Atherosclerosis (MIA) syndrome
- the "J-shaped" relationship between systolic blood pressure and occurrence of stroke, seen in a clinical cohort with a median follow-up time of 111 months[170]
- sodium or salt intake, which has been considered a potential modifiable risk factor for the progression of CKD. A reduced sodium intake, together with pharmacologic intervention using ACE-I and ARB, are recommended to control blood pressure[71, 171]
- BMD, including the management of calcium, phosphorous and vitamin D to reduce vascular calcification and prevent hip fracture especially in the elderly[172-174]
- uric acid level, which is prevalent in CKD and associated with CKD progression,[175] has a "J-shaped" relationship with all-cause mortality and is associated with dyslipidaemia, calcium/phosphate metabolism and inflammation.[80]

1.4 Nutrition intervention studies in non-dialysis CKD stages 4 to 5

1.4.1 Protein-restricted diets in non-dialysis CKD stages 4 to 5

Patients with kidney failure are in a state of "protein intolerance" or protein waste "intoxication". The recommended daily intake (RDI) for adults in the general population is approximately 0.75 g/kg/d (0.75 g/kg/d for women and 0.84 g/kg/d for men);[176] this level assumes a coefficient of variation of 12.0% of the estimated average requirement (EAR) of 0.6 g/kg ideal body weight (IBW)/d.[176, 177] Clinically stable non-dialysed CKD patients have similar requirements and nitrogen balance studies have shown subjects

could achieve neutral nitrogen balance with ~0.6 g/kg IBW/d when energy ≥25 kcal/kg/d was ingested. However, with 30–35 kcal/kg/d, it was more likely to reduce net urea generation, and maintain neutral or positive nitrogen balance and body mass. Therefore, 30–35 kcal/kg/d is recommended in clinical practice guidelines for these patients.[178] Other pioneer case reports and clinical studies revealed similar results that different levels of low protein intake (0.4–0.6 g/kg/d) required 35–50 kcal/kg/d to maintain nitrogen balance and control uraemia.[179] The classic "Giovannetti diet" was used to prolong life of terminal ESKD patients provided ~18 g/d of protein, predominantly with foods containing essential amino acids, such as eggs, plus a large quality of non-protein high energy foods to optimise nitrogen balance but limit the build-up of uraemic toxins.[180, 181]

In addition to the rise in serum nitrogenous waste levels, foods that are rich in protein are also rich in sodium, purine/uric acid and phosphates that contribute to uraemic complications. Nevertheless, the use of dietary protein restriction as part of CKD treatment has been controversial, despite being used anecdotally for more than a century. The arguments in the literature for[182-185] and against[186-188] the use of a protein-restricted diet are summarised in Table 1-10. It is beyond the scope of the current review to discuss each of the experimental studies in detail. A number of systematic reviews,[189, 190] meta-analyses[191, 192] and randomised control trials (RCTs)[193-196] supported the benefit of dietary protein restriction in CKD. The details of seven recent RCTs are presented in Table 1-11.

Table 1-10 Summary of the rationale for or against the use of a low protein diet

For	Against
Level of protein intake	
• 0.6 g/kg/d (+ adequate energy) • 0.3 g/kg/d + ketoacids (+ adequate energy)	• Optimal level and duration of intake have not been defined
Efficacy	
Improve signs & symptoms (and reduce on-set of): • ↓ peripheral neuropathy • ↓ insulin resistance • ↓ red blood cell lipid peroxidation • ↓ osteodystropathy • ↓ albuminuria • ↓ proteinuria	• Benefits demonstrated in experimental models but not in clinical trials
Progression rate	
Inconsistent findings due to: • short study duration • inclusion of early and non-progressing CKD patients • inclusion of non-adherent patients • unregulated use of ACE-I • undefined treatment targets and mechanism, e.g., blood pressure, phosphorous Once optimal compliance is achieved, the diet can slow progression rate	• Benefits demonstrated in experimental models but lacking in clinical evidence • No significant slowing of progression
Renoprotective effects	
May help: • ↓ albuminuria • ↓ proteinuria • reduce total sodium, uric acid and phosphate intake	• No additional benefit above the renin-angiotensin system blockade, blood pressure reduction and statin
Safety/adverse effects	
Supervised diet management: • preserve nutrition status • ↑ albumin • maintain body weight and protein stores • does not jeopardise survival after initiation of dialysis	• May induce or further exacerbate malnutrition
Meta-analysis	
• Meta-analysis supports the efficacy of a protein-restricted diet in slowing progression	• Publication bias favouring studies with positive results
Compliance	
• Good compliance noted in a number of intervention studies • Can be measured by urinary nitrogen appearance and dietary assessment	• Compliance is generally poor

Table 1-11 Controlled trials with protein modification in non-dialysis CKD stages 4 to 5

Author/ Study Country *Year	Patient number, age (yr), renal function (GFR or CrCl in mL/min/1.73m^2 or otherwise specified) and study duration	Intervention (sample size)	Outcome measures	Significant findings
Rosman[197, 198] The Netherlands *1984/ f/u study 1989*	n =228 age: 47.8 (15–73) CrCl: 10–60 f/u =>24 mth further f/u: 48 mth	C: Group A1 (n =44) or A2 (n =30): free diet, but if s-urea >25 mmol/L to ↓ protein intake. Remark: A1 and A2 groups had mean 55g/d and 70 g/d protein intake I: Group B (n =35): CrCl 31–60, Pro 0.6 g/kg/d Group C (n =40): CrCl 10–30, Pro 0.4 g/kg/d	• Change of renal function using reciprocal creatinine 1/[cr]	• Conclusion by 1984 (24 mth f/u): regression analysis indicated ↓ in 1/[cr] was 3–5 times lower in protein restricted groups than in control groups • Conclusion by 1989 (48 mth f/u): limited benefit except in patients with glomerular disease
Ihle[194] Australia *1989*	n =64 age: 37 (19–69) CrCl: 14.4 f/u: 18 mth	C: regular diet (~0.75–1.0 g/kg/d) (n =33) I: 0.4 g/kg/d Pro, PO_4 <700 mg/d (isocaloric:35–40 kcal/d) (n =31)	• Development of ESKD defined by development of symptoms necessitating dialysis or serum [Cr] >1300 µmol/L • Nutritional parameters	• 9/33 vs. 2/31 of C vs. I group developed ESKD (*P* <0.01). Significant fall of CrCl in C compared with I group • No difference in nutrition indexes and nutritional status maintained
Williams[199] UK *1991*	n =95 age: 45±2 CrCl:23–28 f/u: 19±3 mth	C: no Pro or PO_4 controlled diet (n =32) I_1: Pro 0.6 g/kg/d, PO_4 800 mg (n =33) I_2: $P0_4$ 800mg + binder (n =30) All with energy: 30 kcal/kg/d	• Renal function • Nutrition indexes	• No difference in change of renal function and nutrition indexes

Table 1-11 continued

Locatelli[200] Italy *1991*	n =456 age: 48.5 (18–65) Cr: 133–619 umol/L f/u: 24 mth	C: regular diet (1.0 g/kg/d) (n =230) I: 0.6 g/kg/d (isocaloric:35–40 kcal/d) and 30 kcal/kg/d Stratified into three groups according to severity of renal insufficiency or serum Cr (μmol/L) level: Group A: 133–221 (n =216) Group B: 222–442 (n =187) Group C: 443–619 (n =53)	Reaching end-point: doubling of the baseline plasma creatinine or need for dialysis	• Borderline advantage of study diet to reach end point (*P* =0.06), but insignificant effects on slowing disease progression rate • Nutritional status and blood pressure maintained
D'amico[195] Italy *1994*	n =128 age:~54.0±12.7 CrCl: 15–17 f/u: 27.1±21.8 mth	C: controlled protein (1.0 g/kg IBW/d) (n =65) I: low protein (0.6 g/kg IBW/d) (n =63) Energy: 30–35 kcal/kg IBW/d and controlled for sodium, phosphorous and lipids	End-point: halving the CrCl	C (40%) vs. I (28%) reached end-point during study period (*P* =0.038) Significant independent factors: baseline CrCl (Coefficient =–0.7874, *P* =0.02) and proteinuria (Coefficient =+1.0033, *P* =0.000) Nutritional status maintained in study group
Klahr/MDRD[193] Kopple/MDRD[201] USA *1994/1997* (Data of VLPD omitted) *Levy[202]* *2nd analysis and follow-up study* *1996*	n =585 age: 38.6±8.9 GFR: 51.3±14.4 f/u: 26 mth	C: usual diet (1.3 g/kg/d) + PO_4 16–20 mg/kg IBW/d (n =294) I: 0.58 g/kg/d + PO_4 5–10 mg/kg IBW/d (n =291) Energy: not specified (>25 kcal/kg IBW/d)	• Decline in GFR rate • End-point occurrence of ESKD or death	• Non-linear fall of GFR in I group showing slower decline rate 4 months after commencement of intervention. Overall, marginal benefit of 1.1 mL/min/year ↓ in GFR (NS) • No difference in occurrence of end-point • I: ↑ albumin, ↓ transferrin, ↓ body weight and % fat and arm muscle area in relation to ↓ energy intake *2nd analysis: longer time to renal failure. A 0.2 g/kg/d lower achieved total protein intake associated with 1.15 mL/min/yr slower mean decline in GFR (P =0.011)*

Table 1-11 continued

Meloni [196] Italy *2004* (results of non-diabetic presented)	n =89 age: 62.2±13.4 GFR: 46.8±5.8 f/u: 12 mth	C: free protein diet (level of intake not stated) (n =45) I: low pro diet (0.6 g/kg/d) (n =44) Energy: not specified or instruction not mentioned	• Renal function • Nutritional status	• I: slower decrease in renal function. Mean ↓ in GFR of C vs. I group 6.05±1.23 vs. 3.47±0.26 mL/min/1.73m^2 (P <0.001) • At end of study, energy intake of C vs. I group 2,290±360 vs. 1830±205 kcal/d. Weight loss/ reduced obesity index observed in I group (P <0.05) • No decrease in s-albumin or pre-albumin, no other signs of malnutrition

Abbreviation: MDRD = Modification of Diet in Renal Disease study; RCT = randomised control trial; C = control group; I = intervention group; GFR = glomerular filtration rate; CrCl = creatinine clearance; mth = month; Cr = creatinine; Pro = protein; PO_4 = Phosphorous; ESKD = end stage kidney disease
Expression of figures: n±SD – standard deviation; n(n1-n2) - range
* ordered by year

To date, the Modification of Diet in Renal Disease (MDRD) study has the most rigorous study design among all RCTs to examine the efficacy of a low protein diet on the rate of decline of renal function.[193] At the end of the 2.2 year follow-up (range 0–3.7), the low protein diet group compared to the usual diet group resulted in a small absolute benefit of 1.1 mL/min/year decrease in GFR. In this study, the low protein diet and the control groups were instructed to consume 0.58 vs. 1.30 g/kg IBW/d of protein respectively; but by the end of the study period, the estimated intake was 0.70 vs. 1.10 g/kg IBW/d. The estimated EI was lower in the low protein group and showed an increase in albumin but a reduced arm muscle mass. Overall, the nutritional status did not deteriorate. In the secondary analysis and follow up of the MDRD study,[202] each 0.2 g/kg/d lower protein intake was associated with a 1.15 mL/min/year slower mean decline in GFR (*P* =0.011), and the estimated proportion of patients reaching renal failure or death within three years of follow-up was 30.0% vs. 51.0% for a protein intake of 0.6 g/kg/d compared to 0.8 g/kg/d. The key factors for not achieving the distinctive slower progression rate in the initial analyse were: a) not all types of kidney disease progress at the same rate, for example, patients with polycystic kidney disease could be less responsive to the diet therapy; and b) possible insufficient statistical power. RCTs[193, 203] and Cochrane systematic review[204] indicated the use of a very low protein diet (VLPD), ~0.3 g/kg/d of protein supplemented with ~ 0.3 g/kg/d essential amino acid or Ketoacid analogues were effective in controlling uraemic symptoms, postponing dialysis and maintaining nutritional status. Although these products are not available in Australia, they should potentially be considered in patients with very advanced kidney failure not planning for dialysis. Furthermore, in countries where dialysis treatment is expensive and not readily available, this regimen should be made available to patients with ESKD.

The inconclusive and debatable recommendation for the levels of protein restriction could be a result of a number of study limitations in previous research. In addition to those described in the MDRD study, the followings factors should also be considered:

- the definition of an end-point, such as the rate of fall of GFR, change of kidney injury markers, appearance of symptoms, initiation of dialysis or death. The effect of modifying protein intake may have effects on some, or a combination of these parameters. If untreated, nutritional status deteriorates rapidly towards CKD stage 5 and may accelerate the initiation of dialysis
- the heterogeneity of the design of the trial, for example, CKD diagnosis, stages of CKD or GFR levels, co-morbidities, level of protein restriction, duration of intervention, heterogeneity of baseline nutritional status (e.g., obesity and malnutrition), and the duration of the occurrence and severity of these conditions
- controlling confounding or competing factors, such as the use of ACE-I, dietary sodium reduction for HT control or the role of hyperphosphataemia
- consideration of energy prescriptions for individuals, e.g., adjustment for underweight, normal or overweight patients
- consideration of other nutrients and dietary or food components, such as fruit, vegetables and fish, which may affect cardiovascular health
- patients' acceptance due to the willingness to follow the diet and /or the lack of a viable dialysis program in certain countries.

Based on the current evidence, the recommended protein and energy intakes for CKD stages 4 to 5 are 0.75 to 1.0g/kg IBW/d and 30–35 kcal/kg IBW/d respectively.[205, 206]

1.4.2 Other nutrition interventions in non-dialysis CKD stages 4 to 5

In addition to the protein modification studies, there are a limited number of intervention trials on other nutritional or related factors in CKD stages 4 to 5 (Table 1-12). The most

important has been weight reduction in decreasing proteinuria, blood pressure and serum lipids, all modifiable risk factors for CKD progression. In a small RCT of 5 months' duration of patients with proteinuric nephropathies, a hypocaloric diet resulted in weight loss accompanied by reduced proteinuria.[207] In another 12-month RCT, a hypocaloric diet induced weight loss, which had a comparable effect to the anti-hypertensive medication Captopril on reducing proteinuria.[208] In these small, short-term studies in CKD patients, weight loss through hypocaloric dietary intervention reduced proteinuria. However, larger, long-term studies are needed to examine these effects on renal outcomes, including the rate of decline of renal function or time to reach ESKD.

For patients with diabetic nephropathy, a low iron-available, polyphenol-enriched, carbohydrate-restricted (CR-LIPE) diet[209] appeared to be superior than a standard restricted protein diet of 0.8 g/kg/d in slowing down the CKD progression rate, reaching ESKD or death (P <0.01). The energy distribution for protein: fat: carbohydrate: alcohol in the control diet was 25–30:30:35:5–10%; other nutrients and food components were not stated. However these results cannot be generalised due to small sample size and lack of monitoring of diet compliance. Other supportive studies were in CKD stages 1–3 and included one that showed that over 12 months a hypocaloric diet in obese diabetic patients led to significant reduction in body weight (BW), blood sugar, blood pressure, serum lipids, proteinuria and albuminuria, and improvement in GFR.[210]

To date, there has not been any controlled study on the effect of sodium restriction in CKD stages 4 to 5. Retrospective analyses demonstrated the effect of low verses high sodium intake (assessed by urinary sodium level) on slowing the decline of GFR for patients also on a low protein diet.[211] In-depth reviews[71, 212-214] suggest the importance of sodium restriction on blood pressure control and CKD progression based on short-term experimental or physiological studies, or evidence from the non-renal population.

Nevertheless, high sodium intake should be avoided as it attenuates the effects of most antihypertensive drugs.

Table 1-12 Other controlled nutrition intervention in non-dialysis CKD stages 4–5

Author/ study Country *Year	Patient number, age (yr), parameters and study duration	Intervention	Outcome measures	Significant findings
Praga[208] Switzerland *1995*	n =17 age:48.3±10 (34–70) proteinuria: >1 g/d duration: 12 mth	RCT I_1: Hypocaloric diet (1000–1400 kcal/d) (n =9) I_2: Captopril 50–150 mg/d (no change in diet) (n =9)	Weight Proteinuria	I_1 ↓ BMI 37.1±3.3 to 32.6±3.2 Both groups: ↓proteinuria from 3.4±1.7 to 0.7±1.0 g/24 h renal function stable significant correlation between body weight loss and ↓ in proteinuria (*r* =0.69, *P* <0.05)
Morales[207] Spain *2003*	n =30 age:56.5±15.2 (17–74) BMI: >27 kg/m^2 CrCl: 68.1±33.6 (25.9–151.2) mL/min/1.73m^2 duration: 5 mth	RCT C: Usual diet (n =10) I: Hypocaloric diet (n =20)	Weight Proteinuria	I group: ↓ weight by 4.1±3.0% *(P* <0.05) ↓ proteinuria by 31.2±37.0% (*P* <0.005) within group and *P* <0.05 compared to the C group
Facchini[209] US *2003*	n =191 (diabetic nephropathy) age: 60±11 GFR: 63±30 (15–75) mL/min/1.73m^2 f/u: 47±22 mth	RCT Isocaloric C: Standard, protein-restricted diet (0.8 g/kg/day) (n =91) I: Low iron-available, polyphenol-enriched, CHO-restricted diet (CR-LIPE) (n =100)	• Doubling of serum cr • Cumulative incidence of ESKD • All-cause mortality	• Renal death occurred: C vs. I: significant doubling of serum Cr (*P* <0.01) • Cumulative incidence of ESKD or death (*P* <0.01)

Abbreviation: CrCl = creatinine clearance; mth = month; f/u = follow-up; I = intervention group; C = control group; cr = creatinine, CHO = carbohydrate
Expression of figures: n±SD – standard deviation; n(n1-n2) – range
* ordered by year

1.5 Framework of nutritional management of CKD stages 4 to 5

Over the last decade, to guide best clinical practice in renal disease care, including nutritional management, a number of evidence-based clinical practice guidelines have been developed by a number of renal organisations. The process of guideline development was based on rigorous review and grading of scientific evidence to formulate the guidelines. These processes were followed by extensive consultation with experts, clinicians and other relevant stakeholders, including consumers, before the final dissemination of guidelines with graded recommendations. In 2006, the Dietitians Association of Australia (DAA) [215] endorsed the "Evidence-based practice guidelines for the nutritional management of CKD"[205] developed by the Australia and New Zealand Renal Guidelines Taskforce (ANZRGT). The PhD candidate was one of the co-authors of these guidelines. The purpose of the document was to compile and summarise the nutrition components of the following published guidelines:

- Caring for Australasians with Renal Impairment (CARI) Guidelines[83]
- Kidney Disease Outcomes Quality Initiative (K/DOQI^{TM}) Clinical Practice Guidelines[24, 216-220]
- American Dietetic Association (ADA) Medical Nutrition Therapy Evidence-Based Guides for Practice: Chronic Kidney Disease (non-dialysis) Medical Nutrition Therapy Protocol[221]
- ADA Guidelines for Nutritional Care of Renal Patients (3rd Edition)[222]
- European Dialysis and Transplant Nurses Association and European Renal Care Association (EDTNA/ERCA) Guidelines for the Nutritional Care of Adult Renal Patients[223]

The DAA renal nutritional guidelines, the framework for evidence-based practice for the nutritional management of CKD, are summarised in Table 1-13.

The framework of nutritional management in CKD evolved from the nutrition care process based on the concept of medical nutrition therapy (MNT).[221, 224] The four steps of nutrition care process are to: 1) refer patients appropriately to a dietitian to carry out the structured care process, including 2) nutrition assessment, 3) nutrition prescription and intervention, followed by 4) implementation of these processes, including evaluation and monitoring of outcomes.

Table 1-13 Framework for the development of evidence-based practice guidelines for the nutritional management of CKD

Nutrition care process	Clinical questions related to stage of care process	Objectives
Criteria for referral to dietitian	At what level of GFR should patients be referred to the dietitian in order to maximise nutritional intervention opportunities?	• Achieve and maintain desirable weight and adequate nutritional status • Optimise status of comorbidities • Normalise or stabilise biochemical markers • Maintain skeletal muscle stores and strength • Patients to achieve individual goals
Nutrition assessment	Which specific measures best reflect nutritional status or change in nutritional status in CKD?	
Nutrition prescription/ intervention	What are the goals of the intervention? What is (are) the appropriate nutritional intervention(s) to optimise nutritional status in CKD and prevent malnutrition?	
Implementation and management	What is the optimal method of implementation and follow-up to ensure nutritional status is maintained or improved?	

Adapted from Ash[205], Splett[225] and Hakel-Smith.[224]

1.5.1 What do the guidelines say?

The guidelines for nutritional management of CKD stages 4 to 5, including dialysis, are summarised in Table 1-14.

Despite the availability of these comprehensive evidence-based guidelines, there are limitations and gaps in knowledge and practice strategies to meet the needs of everyday clinical practice; in particular, in the domains of nutritional assessment, prescription/intervention and implementation, including evaluation and monitoring. The following sections will further explore these areas of practice in CKD stages 4 to 5.

Table 1-14 Evidence-based practice recommendations for the nutritional management of non-dialysis CKD stages 4 to 5

Evidence-based statements (Adapted from Ash[205]) **(and Level of evidence adapted from NM&MRC)[226]**	
Levels of evidence	***definition***
I	*evidence obtained from a systematic review of all relevant randomised controlled trials.*
II	*evidence obtained from at least one properly designed randomised controlled trial*
III-1	*evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).*
III-2	*evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group.*
III-3	*evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group*
Opinion	*Consensus*
Criteria for referral to dietitian	
Clinical question: At what level of GFR should patients be referred to the dietitian in order to maximise nutrition intervention opportunities? **CKD Stage 4 –** GFR 15–29 mL/min (Level III) **CKD Stage 5 –** GFR <15 mL/min (Level I)	
Nutrition assessment	
Clinical question: Which specific measures best reflect nutrition status or change in nutritional status in CKD? **CKD Stage 4** **Evidence statement (level of evidence):** • Maintained percentage oedema-free (dry) actual body weight reflects optimal nutritional status (Level II) • BMI =18.5–25, reflects optimal nutritional status (Level IV) • SGA and percentage ideal body weight (BMI) reflect change in nutritional status (Level IV) • Total body nitrogen (TBN), dual X-ray absorptiometry (DEXA) or bioelectrical impedance (BIA) reflect long-term nutritional adequacy (Level IV)	
Nutrition assessment	
CKD Stage 5 **Evidence statement (level of evidence):** • Maintained percentage oedema-free (dry) actual BW reflect optimal nutritional status (Level II) • BMI =23–26, reflects optimal nutritional status (Level II) SGA maintained or improved reflects nutritional status (Level III-3)	
Nutrition prescription/intervention	
Clinical question: What are the goals of nutrition intervention for CKD? **Evidence statement (level of evidence):** • Achieve and maintain desirable weight and adequate nutritional status (Level III-2) • Optimise status of comorbidities, blood glucose control in diabetes and fluid and sodium control in hypertension, phosphate control in hyperparathyroidism, lipid control and weight management (Level III-2) • Maintain skeletal muscle stores and strength, using SGA, total body nitrogen (TBN) and dual energy x-ray DEXA (Opinion)	

Clinical question:
What are the prescriptions for appropriate nutrition intervention(s) to optimise nutritional status and prevent malnutrition in CKD?

Evidence statement (level of evidence):

- Energy intake of ≥146 kJ/kg IBW/day (35 kcal/kg IBW/day) with a moderate protein restriction to prevent protein energy malnutrition (Level II). For patients >60 years, energy intake of 125 kJ/kg IBW/day is recommended (Level III-2)
- Protein intake for patients with GFR <25 mL/min/1.73m^2, 0.75–1.0 g/kg IBW/day and should not be <0.75 g/kg IBW/day; ≥50% should be high biological value (Level II)

Other nutrients: refer to guidelines

Implementation and management

Clinical question:
What are effective methods of implementation to achieve positive outcomes in CKD?

Evidence statement (level of evidence):

Education

- Pre-ESKD education forms an important part of management strategy to slow progression of renal disease and may have a beneficial effect (Level II)
- Nutrition counselling should encompass appropriate protein and energy intake (Level III-2 and Level IV)
- Nutrition counselling should include fluid, sodium and potassium intake and weight management (Level IV and Opinion)
- Every patient should receive intensive nutrition counselling based on an individualised care plan (Opinion)

Monitoring and evaluation

- Recommended times for initial consultation 45–60 minutes and review 20–30 minutes (Opinion)

* National Health and Medical Research Council (NM& MRC) designation of levels of evidence[226]

1.5.2 Nutritional assessment

Assessment and monitoring of nutritional status are vital to prevent, diagnose and monitor nutritional abnormalities in patients with CKD. No one single parameter can unequivocally measure complex nutritional conditions, therefore multiples parameters are required to interpret nutritional status. This section presents the tools commonly considered in clinical practice to complement the information in Section 1.5.1. Often, a combination of tools is selected depending on the resources, such as dietitian's time and equipment available in the respective institutions. However it is beyond the scope

of this thesis to explore the development of these methods, including their validity and reliability, or to discuss the sophisticated methods mostly used in research, such as total body nitrogen for measuring protein status[91] and doubly-labelled water for measuring EE.[227]

Typical nutritional assessment methods commonly used in clinical practice involve measuring anthropometry, biochemistry/laboratory measures, clinical signs and symptoms, dietary intake, energy balance (exercise and EE, physical activity [PA]), functional capacity and composite assessment tools such as SGA (Table 1-15). Good bedside clinical assessment tools should be inexpensive, easy-to-perform, readily available and good outcome predictors, and have high sensibility, validity, reproducibility and good association with other nutrition parameters.

The most common combination of techniques used in clinical settings is to measure BW (actual weight and oedema-free weight), height, triceps skinfold (TSF), mid-arm muscle circumference (MAMC), waist and hip circumferences, blood results, appetite score, presence of symptoms, dietary intake, PA and exercise, and SGA. The three components of total EE (TEE) are resting EE (REE), thermic effect of food and physical EE.[227]

Total energy expenditure (TEE) = Resting energy expenditure (REE) + Thermic effects of food + Physical energy expenditure

PA levels and exercise are part of the energy balance or EE equation; therefore it should form part of the routine nutritional assessment. In addition, REE increases or decreases as inflammatory state increases or muscle mass decreases respectively, and these alter energy requirements.[112, 113, 228]

Table 1-15 Nutritional assessment parameters commonly used in clinical practice in CKD stages 4 to 5

Remark: Information presented in this table focuses on the assessment of nutritional status. If information for the pre-dialysis CKD stage is not available, relevant information for dialysis patients is presented. The major references are Blumenkrantz et.al.,[229] Pocket Guide to Nutritional assessment of the Patient with CKD,[230] Pupim and Ikizler[231] and K/DOQI guidelines.[216]

Parameters/method	Description	Advantage	Disadvantage
Anthropometry and body composition			
Weight (kg)	Measure of body mass, must use oedema free weight	Quick, simple bedside technique, inexpensive	Does not distinguish muscle and fat mass
BMI (kg/m^2)[12]	Measure of body mass	Quick, simple bedside technique, inexpensive	Does not distinguish muscle and fat mass
Skinfold thickness, TSF and sum of skinfold[12]	Indirect measure of subcutaneous fat	Quick, simple bedside technique, inexpensive	Requires skinfold calliper. Requires training. Must consider inter- and intra-rater reliability
Mid-arm muscle circumference (MAMC)[12]	Indirect measure of muscle mass	Quick, simple bedside technique, inexpensive	Requires skinfold calliper. Requires training. Must consider inter- and intra-rater reliability
Waist circumference (WC)[232]	Indirect measure of abdominal adiposity	Quick, simple bedside technique, inexpensive	Difficult to position measuring tape in obese patients
Waist to hip ratio (WHR)	Indirect measure of abdominal adiposity	Quick, simple bedside technique, inexpensive	Difficult to position measuring tape in obese patients
Bio-impedance analysis (BIA)[112, 233-235]	Indirect measure of fat mass and fat-free mass (muscle mass and body water)	Can be quick, simple bedside technique	Requires BIA equipment, additional capital layout. Measure of fat-free mass[50] doesn't distinguish LBM from extracellular fluid
Biochemistry and other blood parameters			
Serum albumin[236]	Serum protein	Routinely measured, not affected by GFR. Strongly associated with morbidity and mortality	Unreliable marker of nutritional status. Level affected by inflammation (CRP) and hydration status. Is marker of illness rather than nutrition deficit? Slow response to change of nutritional status due to long half-life and large body pool

Table 1-15 continued

Biochemistry and other blood parameters continued			
Pre-albumin[237]	Serum protein	More rapid response than albumin to poor protein intake or re-feeding due to shorter half life and body pool. Not affected by hydration status	Excretion is affected by GFR, so new reference range is needed. Not routinely measured
Cholesterol	Serum lipids	Low level associated with poor dietary intake	Affected by high fat intake and use of lipid-lowering medications
CRP [74, 236]	Serum protein	Not affected by GFR. Rapid response to acute or chronic inflammation. Strongly associated with morbidity, mortality and MIA	Not routinely measured
Ferritin and transferrin	Serum protein	Routinely measured (for anaemia management)	Affected by iron status, blood transfusion, infection and inflammation
Clinical signs and symptoms			
Appetite[95, 96, 238]	Check list, or part of SGA, or as structured scoring method – ADAT	Quick, simple bedside technique, inexpensive. Correlated with dietary energy, protein and nutrient intakes. Associated with hospitalisation and survival	Subjective rating and may not associate with intake accurately
Symptoms[85, 239]	Check list or structured scoring method, or part of SGA	Quick, simple bedside technique, inexpensive. Predicts morbidity and mortality	Subjective rating and may not associate with intake or nutritional status accurately
Muscle wasting	Physical examination as part of SGA	Quick, simple bedside technique, inexpensive	Based on visual appearance to rank severity of depletion without objective measure
Loss of subcutaneous fat store	Physical examination as part of SGA	Quick, simple bedside technique, inexpensive	Based on visual appearance to rank severity of depletion without objective measure
Dietary intake (General reference of dietary assessment methodology based on Freudenheim[240] and Thompson and Subar[241])			
Diet history or diet interview method[242-245]	To ask the respondent to report about past diet	Quick, simple bedside technique, inexpensive. Captures quantity, quality and food patterns (total diet). Literacy of respondent is not required. Relatively low respondent burden and does not affect eating behaviour	Interviewer training required. Problems with errors of memory

Table 1-15 continued

Dietary Intake continued			
24-hour recall[246]	Respondent asked to remember and report all foods and beverages consumed in preceding 24 hours or in preceding day	Quick, simple bedside technique, inexpensive. Literacy of respondent not required. Relatively low respondent burden and does not affect eating behaviour	Intake of previous 24 hour prior to interview only, not reflecting intake of longer duration. Problem of errors of memory, intake often underreported
Food diary/record[246]	Respondent to record foods and beverages and amounts of each consumed over one or more days as specified	Intake quantified, does not rely on recall/memory	High investigator cost and respondent burden. Respondent training and literacy required. Respondent fatigue likely to cause inaccurate recording or alter eating behaviour. May have bias both in selection of sample and in measurement of diet
Food frequency questionnaire (FFQ)[247]	Respondent to report usual frequency of consumption of each food from list of foods for defined period of time. These then used to calculate average daily intake	Low investigator cost and does not affect eating behaviour	Not quantifiably precise and requires population-specific validated FFQ questionnaire. Difficult cognitive task for respondent
Protein – urinary nitrogen appearance[248, 249]	Protein catabolic rate (PCR) (g/day) =6.25 X [UUN (g/day) + IBW weight (kg) X 0.031] + urinary protein losses	Objective laboratory measure of urinary nitrogen excretion (usually 24 hour) to approximate dietary protein intake	Urinary urea and protein collection required. Inaccuracy occurs in extreme body size and during non-steady state of nitrogen balance
Energy balance – exercise, energy expenditure and physical activity			
REE (+ adjusted factors)[227]	By calculation using standard equation, e.g., Harris-Benedict Formulas,[250] adjusted for activity and injury factors	Quick, simple bedside technique, inexpensive	Not specific to CKD population
Questionnaire (physical activity)[251]	PASE Scale, HAP	Quick, simple bedside technique, inexpensive	Indirectly correlated to nutritional status

Table 1-15 continued

Functional capacity			
Hand grip strength (HGS)[252, 253]	Traditionally used for muscle function, and indirectly, nutritional status	Quick, simple bedside technique, inexpensive. Useful continuous and systematic assessment	Requires hand grip dynamometer, additional capital layout
Questionnaire	SF-36 (physical function component),[254] Karnofsky Index	Quick, simple bedside technique, inexpensive	Indirectly correlated to nutritional status
Composite assessment score(s)			
SGA and various versions[147, 150]	Composite assessment of nutritional status based on clinician's subjective rating	Quick, simple bedside technique, inexpensive. High validity, reliability and predictability	Training and inter-rater reproducibility assessment required
Others			
Quality of life (QOL)[255]	Questionnaire, e.g., SF-36[254]	Simple bedside technique, inexpensive	Time spent by patient to complete questionnaire

Abbreviation; ADAT = Appetite and Diet Assessment Tool; REE = resting energy expenditure; SF-36 = Medical Outcomes Study Short Form 36-item questionnaire; PASE = Physical Activity Scale for the Elderly; HAP = Human Activity Profile

SGA is a well validated diagnostic tool for malnutrition in clinical settings,[148] including patients with ESKD.[149, 150, 256] The final score of SGA is based on the clinician's subjective rating of a patient's medical and physical examinations. The medical examination section has four components, including weight and weight history over the last 6 months and recent 2 weeks, dietary intake and change in dietary intake over the last 6 months and 2 weeks, presence of gastrointestinal symptoms (anorexia, nausea, diarrhoea or vomiting) and physical functioning. The physical examination components assess the degree of muscle wasting and loss of subcutaneous fat over seven and three anatomical positions respectively. The presence of ankle oedema in relation to malnutrition is also considered. The strength of SGA is to consider weight history, in particular unintentional loss of BW, and change of dietary intake over time using the subject as his/her own reference. The nutrition status is then categorised as A = well nourished, B = mildly to moderately malnourished and C = severely malnourished. Categories B and C represent different degrees of malnutrition. There are a number of modified SGA versions, which sub-divide the original 3-point scale (A, B and C) to a 4-point[14] or 7-point scale,[147, 149] so that each 1-point change of the scale correlates to a change of nutritional status.[256] These scales may allow longitudinal monitoring of patients' nutritional progress. Another modified SGA tool with a composite additive score is the Malnutrition-Inflammation Score (MIS),[100] which includes BMI, s-albumin, CRP, pre-albumin and total iron-binding capacity. The MIS is well validated in the ESKD population. The prognostic significance of SGA in the pre-dialysis population was revealed in a prospective study that showed malnutrition – scored as SGA B or C – was associated with mortality and hospitalisation rate.[98]

1.5.3 Nutrition prescription and intervention

The background to the clinical practice guidelines and the current literature review detailed the rationale of dietary prescription and intervention for patients in various

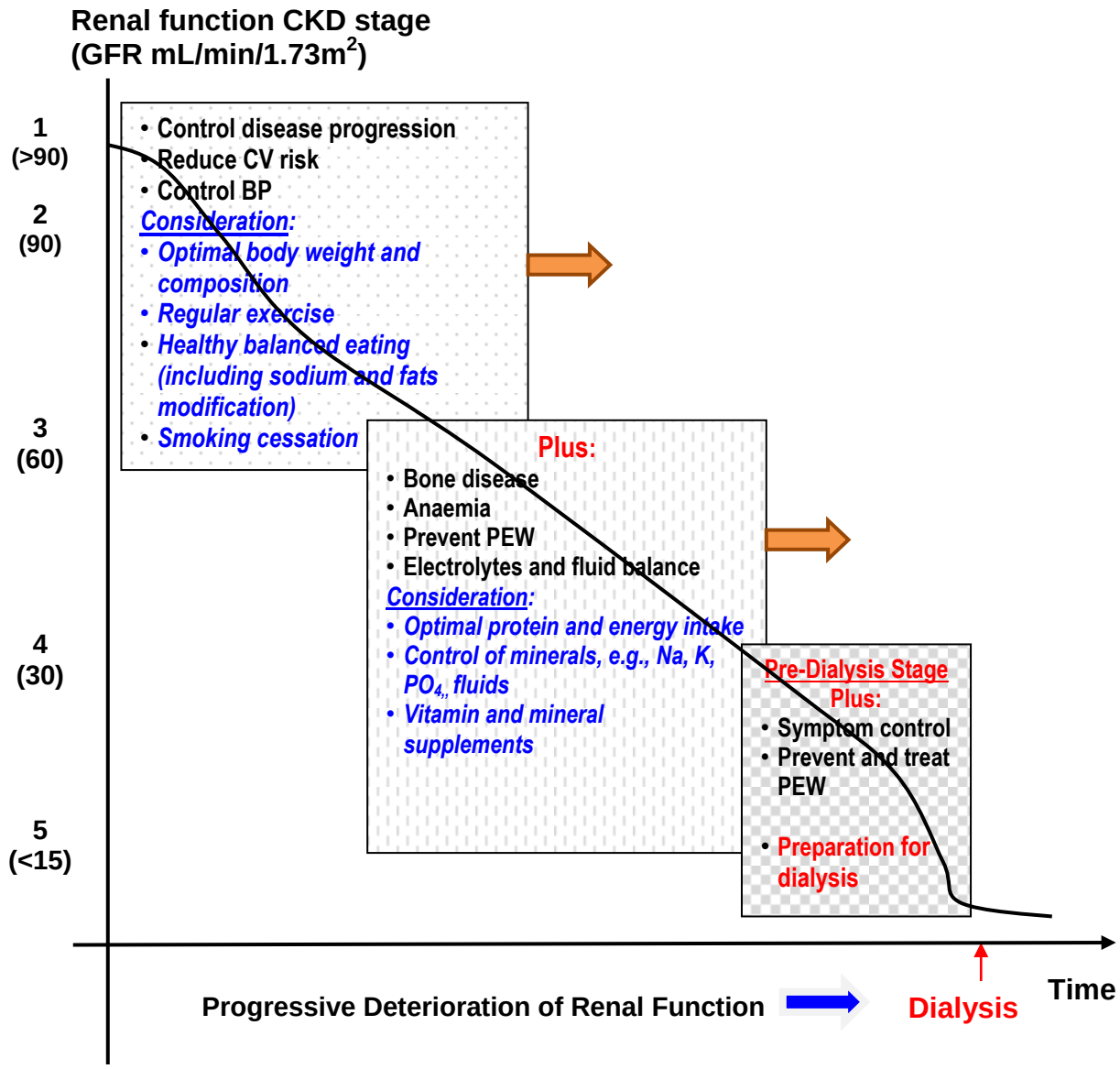
stages of CKD[205, 206] (also see Section 1.5.1 and Table 1-14). Additional nutritional considerations must be considered in the presence of other conditions and co-morbidities, such as malnutrition, overweight/obesity, cardiovascular disease and diabetes, as well as older patients and those who have psychosocial issues. Therefore, nutrition prescription and intervention in ESKD involve multi-nutrient modifications and are complex. In fact, many of these nutrition interventions are recommended to start as early as CKD stages 1 to 3,[222] with additional interventions as CKD progresses (Figure 1-2).

1.5.4 Implementation, monitoring and evaluation

The success of nutritional management relies on proper implementation, namely the delivery of structured care with monitoring and evaluation. These have analogy to exercise training prescription, including the "mode", "intensity", "frequency" and "duration"; in other words, "how to", "how hard", "how often" and "how long" (session time and follow-up duration). As mentioned in Section 1.5.1, which reviewed the guidelines and efficacy of dietary interventions, the effects of intervention can only be evaluated with defined intervention strategies, frequency and duration of intervention. At the time of this literature search, the benefit and efficacy of dietary interventions by a dietitian in patients with non-dialysis CKD stages 4 to 5 was very limited. In a 6-month, prospective, uncontrolled intervention study, dietitian intervention was associated with maintained and improved nutritional status in CKD stage 4 to 5 patients.[257] The nutrition care plan process will be discussed further in Section 1.6, in conjunction with multidisciplinary care.

In summary, the evidence-based guidelines, together with the latest scientific literature, support the structured nutrition care process to better manage patients with ESKD.

Figure 1-2 Schematic diagram showing the goals and objectives of nutrition and lifestyle intervention in all stages of CKD



1.6 Early referral – pre-dialysis multidisciplinary care and the role of nutrition management

There is increasing evidence that timely referral of patients with CKD stages 4 to 5 to nephrologists[26, 258, 259] and the multidisciplinary renal unit[260] for intervention was associated with improved outcomes.[261, 262] Depending on the structure of the intervention, the outcome measures could be clinical (e.g., rate of decline of kidney

function, morbidity, mortality or hospitalisation), behavioural, psychological or knowledge-based. However, the reported benefits have been controversial.

As shown in Table 1-16, the structure of intervention, clinician involvement and the treatment goals varied tremendously among the studies. The intervention ranged from a one-off generic education session to ongoing structured clinic settings over many years until patients started on a dialysis program.

A number of questions have also been raised in an attempt to answer the effectiveness of multidisciplinary care. What is the definition of multidisciplinary care compared with multifaceted or multifactorial care? What is the optimal timing to commence the care? Is generic advice good enough to replace prescriptive intervention? And what is the optimal frequency and duration of intervention and monitoring? Depending on the outcome measures and discipline-specific goal orientation, the ideal "model of care" is yet to be established for CKD stage 4 to 5, especially when economic constraints are considered to justify these resource-intense programs. It appeared that the important elements for success included early referral to the tertiary nephrology unit with adequate and dedicated pre-dialysis program staff and infrastructure, and the availability of a dialysis facility to allow smooth transition to the dialysis program.[263] However the nutritional components in many studies were limited, or of generic nature, with either short duration or not mentioned. As discussed above, it appeared that structured care involving more intense nutrition intervention was associated with better outcomes.[263, 264]

Table 1-16 Multidisciplinary interventions, including nutrition in non-dialysis CKD stages 4 to 5

Study *(ordered by year)*	Patient/ renal function	Intervention	Team involvement	Nutrition component	Outcome measures and findings
Binik[265] Canada *1993* *Longitudinal RCT*	n =204 age:50.2yr Cr >350 µmol/L with rapid increase within recent months	C: standard education (n =92) I: enhanced education (75 min lecture by trained research assistant) (n =87) Non study group (n =25)	Referred by nephrologists blinded to study. I: education given by trained research assistant and interviewed by psychologist	Diet (LP) "discussed" in lecture. Many pt did not inform dietary modifications before Dietitian intervention not specified	Time to initiation of dialysis Results: 4.6 mth difference in time to Dx C: 14.9±12.4 mth I: 10.3±11.8 mth Non-study group: 11.1±15.2 mth χ^2 =6.32, *P* <0.05. after adjusting for creatinine, *P* =0.07
Levin[263] Canada *1997* 2 studies of 2 hospitals: Hospital 1: *Prospective non-RCT* Hospital 2: *Retrospective analysis – compared to historic control*	Hospital 1 n =76 patient info n/a	C: standard care (n =37) I: MDC (n =39) No. of hours per patient-year: 15–33	C: Nephrologist I: MDC – nurse educator, physician, social worker, nutritionist All pt attended session re Dx (RN + social worker)	In MDC – initial & regular f/u	• ↓ Dialysis starts (13% vs. 35%; *P* <0.05) • ↑ Outpatient training (76% vs. 43%; *P* <0.05) • ↓ Hospital days in first month of dialysis (6.5 vs. 13.5; *P* <0.05) • Cost saving >$4,000 per patient
	Hospital 2 n =141 patient info n/a	One-off education program in 2 sessions, plus subsequent ongoing follow-up by primary nephrologist No. of hours per patient-year: 6.5–10	Met individually with: • dialysis physician (30 min) • renal nurse coordinator (30 min) • social worker (1 hr) with focus on modality selection and access planning. Then followed by group session with renal dietitian (30 min)	In one-off group program (30 min)	• Success in pre-dialysis access creation (86.3%) However, due to lack of haemodialysis facility, was NOT possible to: • ↓ Urgent dialysis starts • ↓ Hospital admissions/days

Table 1-16 continued

Harris [266] USA *1998* *Longitudinal RCT*	n =437 (primary care) age: 68.5±11.5 yr CrCl: 34±10 mL/min/1.73m^2 f/u: 24 mth	C: academic GP practice (n =231) I: intensive case management (n =206)	C: GP+ referral to nephrologist if required I: renal nurse, renal dietitian, social worker	When referred renal dietitian took detailed dietary history and prescribed low protein, low potassium renal diet individualised to enhance compliance. Assuming 10% dietitian staffing to attend once-weekly clinic	Outcome: renal function, health care use, mortality in 5 yr, medication. Results: no differences to all of the above parameters
Goldstein[267] Canada *2004* *Retrospective case control*	C (did not attend clinic): age =60 (42–70) yr, CrCl =9.8 (7.4–13.8) mL/min/1.73m^2 I (attended clinic): age =57 (44–71) yr, CrCl =9.8 (7.3–12.8) mL/min/1.73m^2 Exclusion: AKI progressing to CKD, previous RRT, failed renal transplant, or <3 mth specialist medical care before starting dialysis	C: not specified (n =26) I: in clinic to meet team individually to discuss management plans with goals set by Canadian National Kidney Foundation (n =61)	C: not specified I: dietitian, nephrologist, nurse educator, pharmacist, social worker. Education: to reduce rate of decline in kidney function, manage biochemical and clinical sequelae of CRI, educate on dialysis modalities and transplantation, arrange dialysis access and smooth transition to pre-emptive living donor transplantation or outpatient dialysis therapy, when indicated	Not specified	Intervention vs. control group: • at start of dialysis has higher s-alb, median (IQR) 3.6 (3.3–3.9) vs. 3.3 (2.7–3.5) g/dL, *P* <0.01 • hospitalisations at 1 yr (7.0 vs. 69.7 d/patient/y, *P* <0.01) and during study (10.8 vs. 57.4 d/patient/y, *P* <0.05). • ↓ Deaths at 1 yr (2% vs. 23%; *P* <0.01) and during study (21% vs. 42%; *P* <0.05)

Table 1-16 continued

Curtis[264] Canada & Italy *2005* <u>*Case control*</u>	Total Canadian + Italian (n =288) Canada (n =152) age: 64±16 yr mean nephrology care prior to Dx: 40±33 mth f/u after Dx start: median 14 mth	Combined Canadian +Italian data: C: standard nephrologist care (n =156) I: formalised multidisciplinary care clinic (MDC) in addition to standard nephrologist (n =132)	Canada: I (MCD group): regular, protocolised clinic and laboratory follow-up of patients with CKD. Nurse educator, physician, social worker, nutritionist, pharmacist	Canada: Regular	Combined analysis: MCD group (I) at dialysis initiation: • ↑ Hb (102 vs. 90 g/L, *P* <0.0001) • ↑ s-alb (37.0 vs. 34.8 g/L, *P* =0.002), • ↑ Calcium (2.29 vs. 2.16 mmol/L, *P* <0.0001). Standard vs. MDC: Adj. HR (95% CI) for survival 2.17 (1.11–4.28), *P* =0.026
	Italy (n =136) age: 60±17 yr mean nephrology care prior to Dx: 43±34mth f/u after Dx start: median 14 mth		Italy: C: programme-dedicated nephrologists and multidisciplinary nurses responsible for implementation of recommended diagnostic and intervention strategies, information, education and support. Formal team accesses nutritionist, psychologist and social worker when necessary	Italy: Access to nutritionist when necessary – no definition given regarding "necessary"	
Hemmelgarn[262] Canada *2007* <u>*Case control*</u>	n =374 age:75.8±6.2 yr GFR:<60 mL/min/1.73m^2 (86% <30 mL/min/1.73m^2) duration: 3.5 yr	C: standard nephrologist care (n =187) I: Initial education + f/u (n =187)	Nephrologist, clinic nurse, registered dietitian, social worker	Discussion re diet in initial session and f/u not specified. Stated discussion of medical management and lifestyle modification to delay progression of CKD and target cardiovascular risk factor reduction	Survival, and risk for hospitalisation Results: 50% reduction of survival risk. HR (95% CI) =0.50 (0.35–0.71), *P* <0.05. No differences in all-cause HR, 95% CI: 0.83 (0.64–1.06) and CV hospitalisation HR (95% CI): 0.76 (0.54–1.06)

Abbreviation: mth = month; C = control group; I = Intervention group; n = number; yr = year; cr = creatinine; CrCl = creatinine clearance; GFR = glomerular filtration rate; Dx = dialysis; IQR = interquartile range; HR = hazard ratio; CI = confidence interval; Hb = haemoglobin; s-alb = serum albumin; CV = cardiovascular; vs. = versus; MDC = multidisciplinary care. Expression of figures: n±SD – standard deviation; n(n1-n2) - range

While it is not possible to isolate the effects of the nutrition components to deduce any advantages from these studies, promising results from controlled[194-196] and uncontrolled[257] nutrition intervention studies, and a case control study[268] supported early intervention in pre-dialysis stages. Therefore, a properly designed and adequately powered RCT is needed to formulate the roles of nutrition intervention in renal disease care. Since the nature of nutrition issues in ESKD is complex and long-standing, ongoing structured care should form the essential part of multidisciplinary care.

1.7 Special consideration for elderly patients

With the aging population, there has been a higher prevalence of older patients with ESKD, with many of them accepted into maintenance dialysis programs.[5, 269] Evidence has suggested that dialysis does not suit everybody and may not offer significant survival advantage or better QOL for these patients.[16, 270, 271] Therefore, a conservative or no dialysis pathway could be a feasible alternative option to reduce disease, social and societal burdens. Patients with advanced ESKD have a high level of symptom burden,[85, 272] such as anorexia, nausea and taste change, which may impair dietary intake of energy, protein and other nutrients. Poor nutritional status, such as malnutrition, low s-albumin, low body muscle and fat stores, are common in ESKD.[85] The presence of comorbidities such as CV disease[273] and poor nutrition[98] are strong predictors of poor outcomes in patients with ESKD not on dialysis. To date, few controlled trials have been conducted to examine the efficacy of nutrition intervention in patients on a conservative pathway. Anecdotally and in clinical practice, nutrition interventions – in particular, low or controlled protein diets – have been used to ameliorate high blood urea level and uraemic symptoms.[9, 180, 195] In the secondary analysis of the MDRD study,[202] patients in the study group (low protein diet) experienced less uraemic symptoms and commenced dialysis at lower levels of GFR.

Furthermore, older patients have additional nutritional considerations due to co-morbidities and age-related factors – such as sarcopenia or osteoporosis – and more demanding psychosocial needs, including provision of food. Patients may decide on the conservative pathway early on in the course of CKD. The challenging question is if aggressive nutrition intervention fulfils the role of nutritional support and symptoms control and if these are appropriate at end of life stages.

1.8 What is known – a summary of the evidence and the need for further knowledge

The literature review has revealed the prevalence of nutritional abnormalities is high in ESKD patients (Tables 1-7, 1-8 and 1-9), in particular, malnutrition measured by SGA (score B or C) and low s-albumin. The presence of these factors at the initiation of dialysis is associated with morbidity, mortality and hospitalisation. However, background uraemic conditions and medical events affecting the baseline nutrition status are largely unknown. In addition, over the last decade there has been much debate on the obesity paradox, that is, if obesity is protective to counteract the effect of malnutrition in the dialysis population. These questions remain unanswered, with data especially lacking for the Australian population. The combination effect of factors has seldom been investigated; it would be useful to examine such effects on mortality, e.g., the combination of malnutrition, s-albumin and overweight/obesity. Furthermore, these abnormalities emerge during the course of gradual decline in kidney function and predicted mortality and hospitalisation. Up to the planning stage of our studies, little was known about the nutritional characteristics of patients who were referred to the multidisciplinary clinic for pre-dialysis education, including the option of conservative treatment. The majority of nutritional studies in CKD were focused on patients who were younger and with higher levels of GFR, and the relationships between renal function, presence of symptoms and dietary intake were seldom explored. The

rationale for the need of further knowledge will be expanded in Section 1.9.2 after the discussion of the hierarchy of study designs in Section 1.9.1.

In view of the high social, clinical and health care financial burden of ESKD, it is necessary to investigate the role of nutritional factors – ranging from blood or laboratory to bedside assessment parameters – on clinical outcomes of patients with CKD stages 4 to 5.

1.9 Special considerations for gaining new knowledge

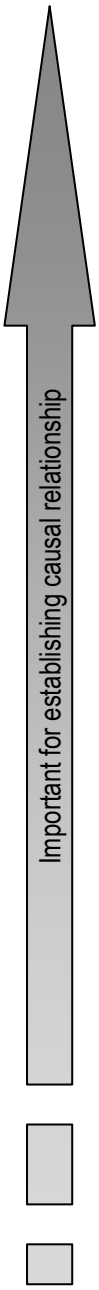
1.9.1 Hierarchy of study designs

The gold standard of study design to examine the effect of factors or interventions affecting health outcome is a RCT. However, there are limitations in RCTs, and well-designed observational studies such as cohort and case control studies may complement the RCTs[274, 275] by providing estimates of treatment effects, or even having similar effects of treatment as RCTs.[276, 277]

Table 1-17 summarises the hierarchy of study designs, and their strengths and limitations, as well as the evidence hierarchy recommended by the National Health and Medical Research Council (NH&MRC).[226] It is extremely challenging to conduct nutritional research of "high hierarchy" in patients with CKD. Firstly, the vast heterogeneity of baseline clinical and nutritional statuses with many confounders and multifaceted treatments should be considered. Often it is unethical to not treat patients to meet basic physiological requirements or to provide well-accepted best practice; one example is to provide nutritional support to malnourished patients. Moreover, an intervention may take a long time to show significant effects or an intervention to reverse a deep-rooted (e.g., previous long exposure) nutrition problem, such as severe malnutrition, could be futile. Often patients with advanced medical conditions are less likely to consent to studies which demand efforts to participate in intervention, or

require regular blood tests or assessment procedures that are considered burdensome. Therefore, selection bias may occur and results may be of low generalisability.

Table 1-17 Hierarchy of study design and evidence level



Study design (Level of evidence)	Strengths	Limitations
Meta-analysis of RCTs (Level I)	• Increased precision of exposure to outcome measured	• Need number of RCTs to perform analysis
RCTs (Level II) Including pseudo-randomised control trail (Level III-1)	• Gold standard • Random allocation of treatment which avoids selection bias or cofounding • Similar distribution of known and unknown variables	• High cost • Trial may be: (1) "unnecessary" if treatment effect is dramatic, confounder can be ignored; (2) "inappropriate" when long-term follow-up is required; (3) "impossible" due to ethical reasons; or (4) "inadequate" due to extensive inclusion and exclusion criteria and may cause low generalisability
Cohort studies (Level III-2) Including comparative study with concurrent control, non-randomised trial	• Can study multiple exposures • Useful in hypothesis generating	• Selection bias in comparison between treated and untreated groups • Some potential to make causal inference • Prospective study may take long time to complete
Case-control studies (Level III-2) Including comparative study without concurrent control, retrospective cohort study, historic control study	• Suitable for studying rare outcomes and outcomes that need long follow-up • Can study multiple exposures • Relatively inexpensive • Useful in hypothesis generating	• Selection bias • Recall bias • Unlikely to infer causal relationship
Case reports (Level IV) Also including case series, cross-sectional studies pre- and post-comparison	• Fast and inexpensive • Hypothesis-generating • Cross-sectional study assesses prevalence of disease, useful in health care planning	• Selection bias • Unlikely to infer causal relationship

Adapted from Black[274] and Jager et al.[275]

1.9.2 Framework of research in practice

One of the main roles of health professionals is to implement evidence based practice to improve the health outcomes of patients. This involves the application of research to policy development and service delivery. However, it is challenging to translate research findings into practice because “practitioners are criticized for failing to base actions on research evidence, while academic research is sometimes condemned as `irrelevant' to practice.” [278]

1.9.2.1 What is evidence based practice (EBP)?

One of the pioneers in this field defined evidence based medicine “is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.[279] The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research” and considering “patient values and expectations” to optimise outcomes. Over the years, this concept has been extended beyond the medical profession and adopted by other health professionals to guide evidence based practice. Individual clinical expertise is the skill acquired through experience and practice; whereas best practice is an adaptation of external evidence from basic science to patient-centred clinical research. In 2012, the International Confederation of Dietetics Association (ICDA) endorsed the consensus statement of a dietetic specific evidence based practice.[280] These guidelines built upon the above concepts and include code of ethics and code of practice for dietitians. Evidence based practice is not just restricted to systematic review, meta-analyse and RCT which are considered as the gold standard of clinical evidence, such as the Cochrane Review,[281] rather it involves tracking down the best external evidence to help answer clinical questions. As discussed in section 1.9.1, some questions about therapy do not require or are suitable to be answered by RCT, especially in chronic diseases, such as CKD management

that require long term longitudinal follow through and involves a vast number of confounding factors.

1.9.2.2 Outcome research

Outcomes research seeks to understand the end results of particular health care practices and interventions.[282-284] It integrates epidemiological, sociological, economic and other analytical sciences to study health services concerning the relationship between need, demand, supply, use and outcome; in particular, to evaluate the structure, process, output and outcome.[283, 284] Or simply, "the process of obtaining data to measure the effect of a intervention on patient care".[285] Examples of four main types of nutrition –related outcome measures in CKD are (1) clinical /medical outcomes: e.g. mortality, weight status, BMI, SGA and CRP; (2) functional outcomes: e.g. ability to prepare meals; (3) economic outcomes: e.g. length of stay, hospitalisations and delays in CKD progression; and (4) Psychological/satisfactory outcomes; e.g. health related QOL and perception of care received.[286]

1.9.2.3 Research in practice

Research in practice is vital to generate nutrition data on which to base practice, and involves examining the health care processes that occur in practices. Indeed "the strength of a discipline, whether in health sciences or management, is associated closely with its research base. Strong research supports a strong profession". [287, 288]

There are two types of practice-related research, practice-*based* and practice-*led*. Practice-*based* research is an original investigation undertaken in order to gain new knowledge partly by means of practice and the outcomes of that practice; whereas Practice-*led* research is concerned with the "nature of practice" and leads to new knowledge that has operational significance for that practice. [289] Often both types of research appear together but there is usually one that is more dominant.

In simple terms, practice-*based* research is to contribute new knowledge. In clinical settings, it often serves to examine the health care processes. Examples in renal care

are: (1) to survey the adoption of evidence based guidelines (K/DOQI)[23] by general practitioners in primary care using semi-structured interviews.[290] Some of the key findings were lack of awareness of the guidelines; expectation for more practice guidance in CKD, persistence of conventional and long-established practice, and uncertainty of timing of nephrologist referral. (2) Survey of renal dietitians regarding the barriers of implementing clinical guidelines (K/DOQI)[216] recommendations and practice recommendations were made as a result of the survey.[291]

If research leads primarily to new understandings about practice, e.g. to advance knowledge about practice, or to advance knowledge within practice, it is classified as practice-*led* research. This research method is commonly used in the creative and performing arts.[289] In clinical settings, to build upon EBP and to make the health practitioner profession more accountable, patient engagement as partners in health research has also led to the concept of practice-*led* research. Examples of practice-*led* research in healthcare are: (1) in the field of medical engineering, a new generation of upper limb prostheses was developed through practice-*led* research. This research evolved through a number of prototypes and models involving the design team and other interested parties.[292] (2) development of an algorithm for dietitians to manage serum phosphate in dialysis patients.[293] (3) various dietary methodologies to estimate energy and protein intakes, e.g. food frequency questionnaire, [247] food record,[243] and structured diet history methods.[242, 245]

1.9.2.4 Closing the gap between research and practice

Despite the considerable resources that have been put into clinical research, relatively little of the research findings are implemented in routine clinical practice. The transfer of evidence to clinical practice requires skill, determination, time, money and planning.[294] Success relies on the integration of four major elements as shown in Table 1-18

Table 1-18 Elements required for transfer of evidence to clinical practice

Element	Application
Good information	Sound research results that can withstand critical scrutiny and answer practical questions
Good accessibility	Accessible and user friendly system for all stakeholders e.g. practitioners, managers, administrators and consumers
Supportive environments	Conducive physical and intellectual environments which value research and uptake of research-based knowledge
Evidence-based promotion of knowledge uptake	interventions that promote the uptake of knowledge and lead to behaviour change

Adapted from "How to put the evidence into practice: implementation and dissemination strategies" NH&MRC, 2000[294]

Bridging the gap between research evidence and practice is not a cookbook style process; it involves innovation, creativity and a range of strategies while taking into account local conditions for making local solutions. The action plan to achieve a change of practice in line with the evidence is outlined in Table 1-19

Table 1-19 Action plan for implementing and disseminating of clinical practice guidelines

Question asked to drive the process		Action plan and steps taken during the progress
1	What is the purpose?	*To develop a statement of purpose*: what am I or the team trying to achieve with rationale
2	Who can help?	*Form a working party with relevant expertise to drive the implementation and dissemination process along:* system leadership, technical expertise and day-to-day leadership
3	What is the situation?	*Develop a formal situation statement:* while ideal clinical practice is difficult to achieve, it is important to identify the current and ideal situations to make possible improvement.
4	Who should be involved?	*Determine target audiences and include representatives of all groups on the committee/working party:* these may include relevant stakeholders and key players, e.g. healthcare professionals in the team, consumers/patients, managers and administrators
5	What are the key messages?	*Formulate and prioritise key messages:* to close the gap between the research evidence and or clinical practice guidelines recommendations by identifying, ranking and prioritising the key messages for further action.

6	What are the aims?	*Set specific objectives:* and avoid broad goals, e.g. to maintain blood pressure < 120/75 rather than "improving blood pressure" control.
7	Is the available information suitable?	*Ensure information suitable for different groups is available:* this means, does it suit the majority of target audience, namely patients, practitioners etc? Examples of different needs for different groups could be due to competing interest of the treatment options (e.g. surgery vs. medication) or homogeneity of the expectation of audience (e.g. different education booklet for different literacy levels)
8	What are the barriers?	*Identify barriers to successful implementation:* it is easier to overcome barriers if they have been identified and described systematically. There are two types of barrier; the first type may occur at various levels – system, professional, community and consumer levels. (e.g. lack of reporting of a ineffective practice) The second type of barrier is that experienced by various target audience within each level (e.g. lack of knowledge of health professionals)
9	Are things on track?	*Review progress* of all of the above steps regularly
10	What are the options	Consider the options available: weighing various strategies vs. effectiveness • Educational outreach visit or academic detailing • Decision-support systems and other reminders • Interactive educational meetings • Multifaceted interventions • Mass media campaigns • Audit and feedback • The use of local opinion leaders • Local consensus processes • Consumer-mediated interventions • Educational materials • Didactic educational sessions • Incentives and penalties • Administrative interventions
11	Designing a program	*Decide which strategies to use:* designing a program and putting the program into action
12	Is support available?	*Ensure support is available at a number of levels:* systemic, professional and consumer supports
13	What is the cost?	*Determine costs and cost-effectiveness of strategies:*

Adapted from "How to put the evidence into practice: implementation and dissemination strategies" NH&MRC, 2000, [294] Bero et.al.[295]

In summary, research in practice serves to indentify clinical problems, generate data, gain new knowledge, translate and transfer available knowledge to practice. The ultimate goals are to optimise care thus improving the clinical outcome of the patients.

1.9.3 Special considerations in current thesis

This thesis was built within the framework of research in practice, a combination of practice-based and practice-led research to close the gap between research and practice in managing patients with ESKD. The first study in this thesis was a retrospective cohort analysis that examined the association of demographic, clinical and nutritional parameters at commencement of dialysis and mortality risk; in particular, subjects with conditions such as malnutrition and overweight/obesity. The survival studies presented in Table 1-7 did not clearly define if the subjects commenced dialysis after an uneventful decline of kidney function, or were combined with those who started dialysis unexpectedly for other reasons, including heterogeneous nutritional implications, such as acute kidney injury (AKI) due to trauma, post-operative complications that have higher metabolic demand, or ex-transplant patients exposed to years of steroid therapy, which is known to increase muscle catabolism and fat stores. Therefore, the nutrition history of those patients was very different from those exposed to chronic uraemia alone. The study in this thesis only included patients who commenced a planned dialysis program after a gradual decline of renal function. The results could therefore have implications for health care modelling if nutrition abnormalities could be identified and rectified before dialysis is needed.

In addition, a number of previous studies had strict patient selection criteria, e.g., not older than 70 years of age, expected to survive for more than 6 months, consent to participate in the study was required, etc. Our study considered “all” patients who commenced dialysis in our unit. Therefore our data was more inclusive, reflecting reality, and therefore have much broader implications.

The “obesity paradox” has created much controversy in the renal community, i.e., if it is protective in patients with ESKD. The effect of overweight (BMI ≥ 26 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) on mortality risk was examined in our study. From previous observations, it could be expected that many overweight or obese patients could become malnourished according to the SGA rating criteria; therefore the combination effects of overweight/obesity and malnutrition were also examined for this thesis. From our understanding, the combinations of effects of nutrition parameters on mortality have been seldom studied.

The timing of when dialysis should start has been subject to much debate. We reviewed the effect of GFR levels at which dialysis should start, and found this was not often considered in previous studies. A multi-centred clinical trial, the Initiating Dialysis Early and Late (IDEAL) trial,[296] set out to answer this question in the year 2000 by randomly assigning patients to start dialysis at 10–14 mL/minute/1.73m^2 (“early start”) or 5–7 mL/min/1.73m^2 (“late start”) with 3 years of follow-up. Patients entered that RCT only with strict selection criteria, so the results could not be generalised. The results of our study may therefore complement the IDEAL trial.

The results of our analyses would potentially provide level III-2 evidence.

The second part of the thesis was a cross-sectional study to examine the baseline clinical and nutrition characteristics of patients enrolled in the pre-dialysis assessment clinic. The majority of studies in the literature (Tables 1-8 and 1-9) were conducted in younger subjects (50–55 years) and were in the earlier stages of CKD (GFR 20–50 mL/min/1.73m^2), whereas our patients were older – with a mean age of 65.7±13.6 years – and had much lower level of GFR – less than 30 mL/min/1.73m^2 (mean =17.0±6.0 mL/min/1.73m^2). In many of the previous studies, dietary protein intake (DPI) was estimated using the urinary nitrogen methods and dietary EI was seldom assessed. Since optimal protein nutrition or nitrogen balance must be accompanied by

adequate EI, the interpretations of adequate intake in these studies were considered to be incomplete. Furthermore, despite poor nutrition status being associated with the presence of uraemic symptoms, the relationship of dietary intake and symptoms was seldom investigated. Therefore, there was a need to examine the relationship of various nutrition factors encompassing GFR, nutritional status, dietary intake of energy, protein micro- and macronutrients, symptoms and eating behaviour in one study. To our understanding, our study was the first to conduct such an examination. Table 1-20 summarises the comparison of study characteristics between the current study and those in the similar studies in literature.

Table 1-20 Comparison of study characteristics of current study and similar studies in the literature

Characteristics	In the literature	Current study (Study 2) with pre-dialysis patients
Age (years)	50-55	Mean age about 66
GFR (mL/min)	15-60	Mean ~ 17
Setting	Research cohorts	Dedicated clinic for pre-dialysis management
Intake assessment Energy Protein Vitamin and minerals Dietary pattern/food groups	 Often missing Often use urinary protein appearance Rarely examined Rarely examined	To be assessed by structured diet history method and nutrient analysis software
Symptoms and eating behaviour	Limited data, especially in relation to dietary intake	To be assessed and relate to dietary intake

In our preliminary evaluation 18 months after the clinic started[297] (Appendix B), patients were reported to enrol in the clinic with a low GFR plus high prevalence of malnutrition. It was suggested to the team to refer patients at higher levels of GFR with possible better nutritional status. Therefore, the next question was if patients were referred earlier at higher levels of GFR, and if the prevalence of nutrition abnormality at enrolment, such as malnutrition, decreased over time. In addition, we examined if the prevalence of obesity and diabetes at clinic enrolment mirrored the obesity and

diabetes epidemics in the general population. The association of nutrition and future choices of RRT by patients was also examined.

The results of the second part of the thesis will provide level IV evidence which would have significant implications to health care planning, in particular, to justify the pre-dialysis assessment program.

Chapter 2 Thesis Design and Methods

2.1 Structure and style of thesis

The current thesis includes chapters that are written in both traditional monograph style and in a format that is consistent with journal article styles. The University of Wollongong Research Student Centre handbook "Guidelines for higher degree research (HRD) candidates on the preparation and submission of HDR theses"[298] was followed.

Chapters that are written in the traditional monograph style are listed as follows:

Chapter 1: Introduction

Chapter 2: Thesis design and methods

Chapter 6: Conclusions, recommendations and future research

Chapters that are written in a format that is consistent with journal article styles are:

Chapter 3: Nutritional and clinical factors of ESKD patients at initiation of dialysis and survival over a ten-year study period (this chapter has been published in Journal of Renal Nutrition)

Chapter 4: Nutritional characteristics of patients attending the pre-dialysis assessment clinic (this chapter has been submitted for publication in Journal of Renal Nutrition)

Chapter 5: Clinical and nutritional characteristics of patients attending the pre-dialysis assessment clinic, a comparison of two five-year periods from 2002 to 2012 (this chapter has been prepared for submission for publication in Nephrology, Asian Pacific Society of Nephrology)

Materials included in each of the journal article-style chapters include:

- Publication status (published, submitted for publication, manuscript prepared for submission, or any combination thereof)
- Where publications are included, details provided include:
    - details of publication, journal where research is published
    - principal author and co-authors, their individual contribution to both the research and journal article
    - abstract and body of the research, which include aims, background, methods, results, discussion, conclusions, practical implications and future directions for the research area
    - relevant supplementary material such as calculations, figures and tables used for the preparation of the manuscript but not included in the final published article
    - summary of the latest evidence since the initial literature review to support research findings and direction of future research.

2.2 Introduction

The literature review indicated that nutritional abnormalities at the initiation of dialysis are associated with adverse outcomes. Many of these factors emerge during the course of deteriorating kidney function well before dialysis is needed and may have carry-on effects that can influence outcomes after starting dialysis. There was a need to gain a broader understanding of how the clinical and nutritional factors in the pre-dialysis stage affect post-dialysis outcomes.

2.3 Aim of the thesis

The aim of this thesis was to examine the relationships between clinical and nutritional factors in ESKD and clinical outcomes.

2.4 Study framework – background

This thesis consists of a series of retrospective analyses of data obtained from routine nutritional assessment records in the renal unit of St. George Hospital in Sydney over time. It is in the framework of 'research in practice' encompassing clinical science, practice research, continuous practice improvement (CPI) and epidemiological methods as discussed in section 1.9.:

- To describe the nutritional problems of ESKD patients from the time of starting dialysis using epidemiological methods
- Nutritional problems appeared to emerge before the start of dialysis. The preliminary data from the first study led to a change of practice (or behaviour) with the establishment of a multidisciplinary pre-dialysis assessment clinic allowing early assessment and intervention.
- To translate research to practice, baseline nutritional data of a "purposed established" pre-dialysis clinic were described, and compared to the clinical practice guidelines recommendations in a cross-sectional – descriptive and analytical study
- Ten years on, through various CPI activities, were we able to identify nutritional problems in a timely manner as the clinic became more mature? A cross-sectional descriptive, comparative and analytical study was conducted to answer this question.

These studies are of *post hoc* nature and broadly divided into 2 major parts. The schematic diagram in Figure 2-1 outlines the framework of the research and shows the steps and sequence of the sub-studies carried out at the defined stages of CKD. The

X-axis represents time and events. The trajectory of deteriorating renal function over time indicates the inevitable consideration of dialysis in ESKD patients once renal function falls below 15% or when GFR is less than 15 mL/min/1.73m^2 (Figure 2-2). A pilot study prior to the commencement of the studies described in this thesis was undertaken in incident dialysis patients (new dialysis patients) from 2000 to 2002. In that study approximately 55% of patients were rated as malnourished (SGA score B or C) at the start of dialysis and less than 30% of the incident dialysis patients were referred for CKD nutrition intervention before dialysis was started[297] (see Appendix B). A preliminary analysis of these data revealed the 1-year mortality rate was approximately 40% in malnourished patients and 10% in well-nourished patients (in house audit; no published data available). It was apparent that poor nutrition status at the initiation of dialysis was associated with adverse outcomes.

In April, 2002, a multidisciplinary pre-dialysis assessment clinic was established by the director of Renal Medicine at the St. George Hospital for timely clinical, nutritional and psychosocial management of patients with advanced CKD. The referral criteria were patients with CKD stage 4 or 5 (or GFR less than 30 mL/min/1.73m^2) who were under the care of St. George Hospital nephrologists. The clinic was coordinated by a renal nurse consultant (CNC) and primarily provided patients with education about CKD management and dialysis options. A social worker, pharmacist and dietitian provided other discipline-specific assessment and preliminary education in this 1-point contact system; further interventions were arranged if required. In particular, the dietitian would arrange further appointments in the Nutrition and Dietetics Department if further nutrition intervention was required.

Broadly, the purpose of this research was to examine the clinical and nutritional characteristics of patients at different stages of treatment pathway in advanced CKD (Figure 2-2)

Figure 2-1 Schematic diagram showing the research framework

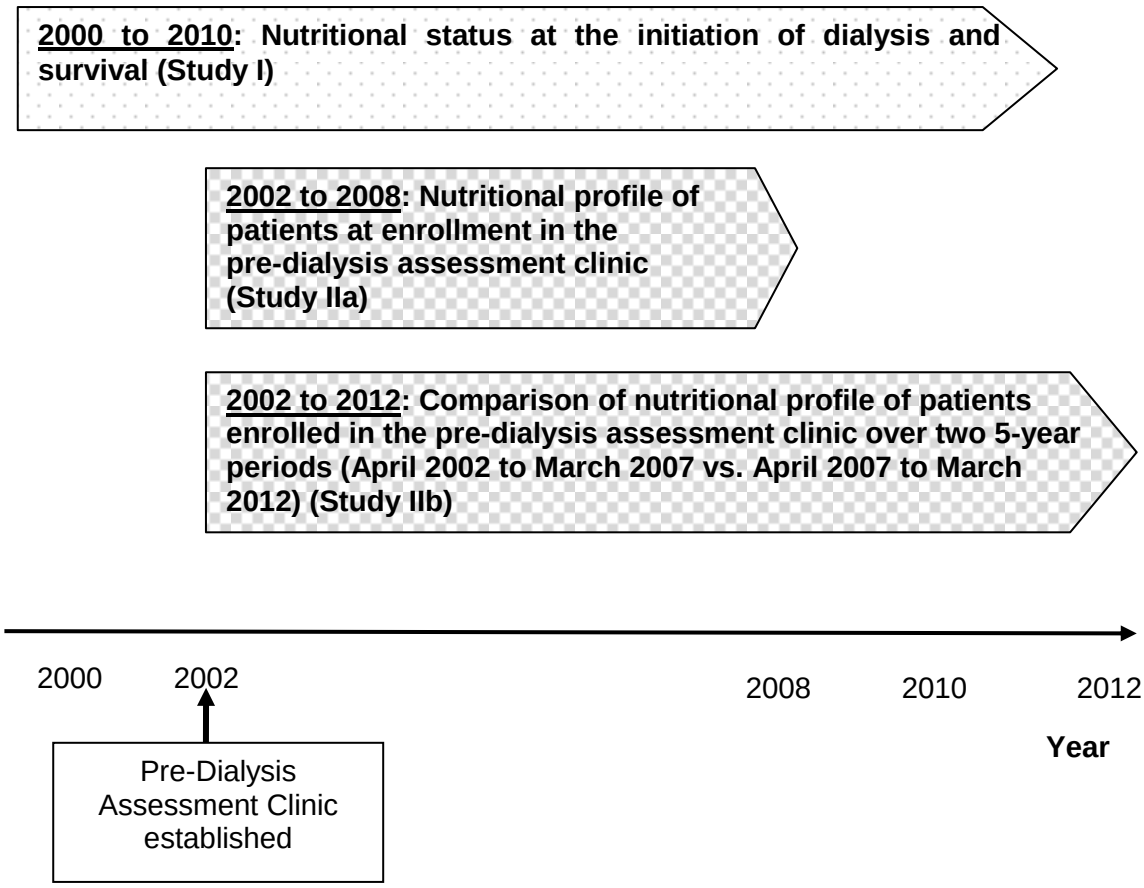
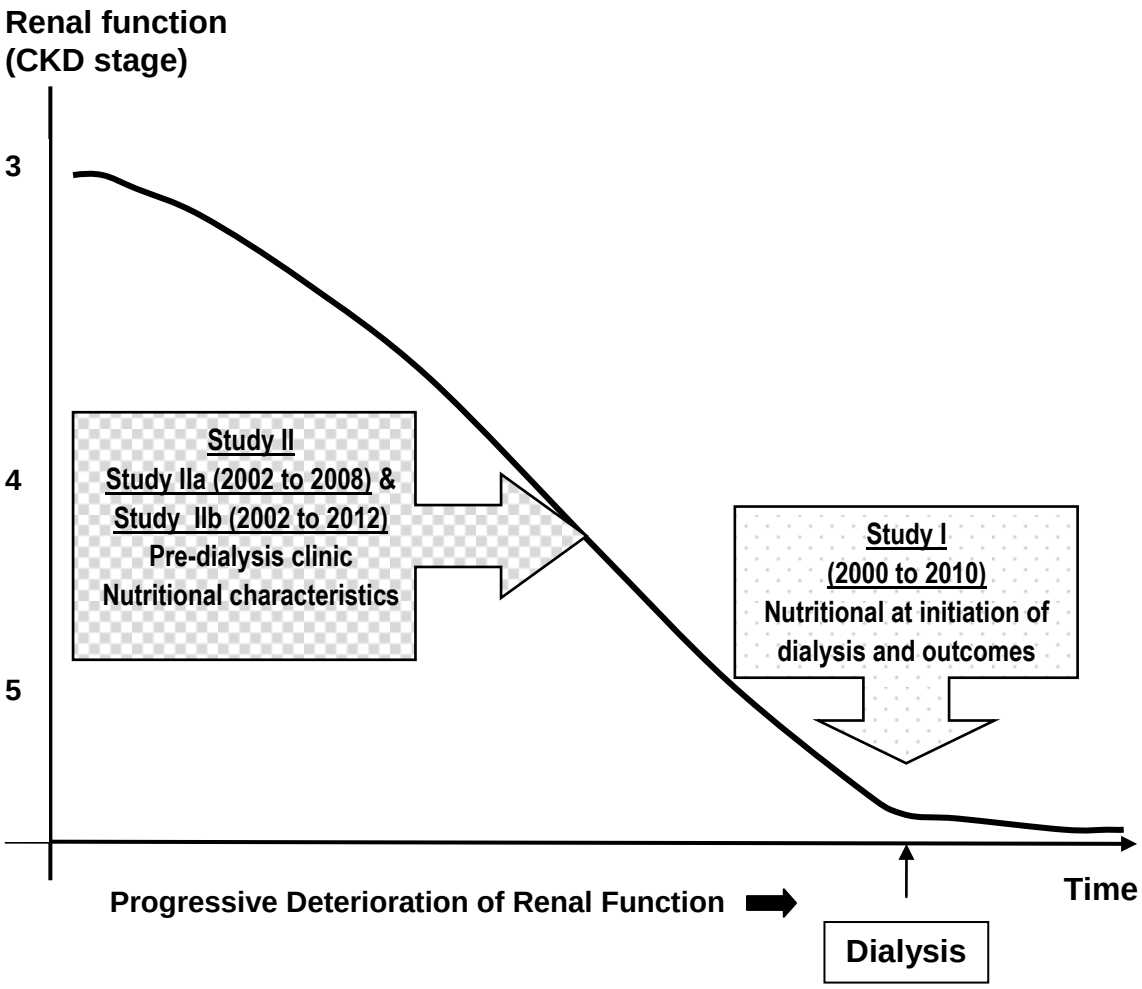


Figure 2-2 Schematic diagram showing the sequence of the research framework



Study I: A retrospective audit was undertaken by reviewing dialysis patient records from year 2000 to 2010. The patients reported in this study were limited to patients who started dialysis between August 2002 and July 2005 and excluded CKD patients who did not progress to require dialysis in this period. The aim of this study was to assess the relationship between measurements obtained at baseline nutritional assessment undertaken at the time of starting dialysis and subsequent survival on dialysis.

Study II: A retrospective study of all patients enrolled in the pre-dialysis assessment clinic established in April 2002. Part a) was a baseline cross-sectional

descriptive study of the nutritional characteristics of patients attending the clinic from 2002 to 2008. Part b) was an analytical study to examine the possible change of baseline initial clinic assessment parameters over a 10-year study period, in particular, between two 5-year periods from April 2000 to March 2007 versus from April 2007 to March 2012.

2.5 Objectives of the thesis

The objectives of the thesis were to:

1) examine the associations of demographic, clinical and nutritional parameters at the initiation of dialysis and survival over a 10-year study period
2) examine the demographic, clinical and nutrition characteristics of patients attending the pre-dialysis assessment clinic
3) evaluate an appetite assessment tool used to assess patients' energy and protein intake in the pre-dialysis assessment clinic
4) examine the change of the prevalence of clinical and nutritional abnormalities of patients attending the pre-dialysis assessment clinic over a 10-year period - first vs, second 5 year period, in particular obesity and malnutrition.

2.6 Hypotheses tested during the thesis

Hypothesis 1: nutritional abnormalities at the initiation of dialysis would be associated with high mortality risk (Chapter 3).

Hypothesis 2: abnormal nutrition would be prevalent in advanced CKD before dialysis was required (Chapter 4).

Hypothesis 3: the subjective rating of a good appetite using the Appetite and Diet Assessment Tool (ADAT)[238, 299] appetite score would be useful in reflecting adequate intakes of protein and energy (Chapter 4).

Hypothesis 4: as the clinic became more established over the 10-year study period, patients with ESKD would be referred to the clinic earlier or at higher levels of GFR for management. Earlier referral may be associated with a lower prevalence of nutritional abnormalities at the time of initial assessment in the pre-dialysis clinic in the second half of the study period (Chapter 5).

Hypothesis 5: in view of the obesity and diabetes epidemics, there would be a higher prevalence of overweight/obese and diabetic patients in the second half of the study period (Chapter 5).

Hypothesis 6: nutritional status would be associated with the future choice of RRT (Chapter 5).

2.7 Study framework and methods

The study rationales, design and methods of various stages are presented under the respective chapters (Chapters 4, 5 and 6). An overview of the study methods is provided in this section.

2.7.1 Study I: Nutritional factors at the initiation of dialysis and mortality

2.7.1.1 Study population and data collection

In Study I, patients of interest were incident dialysis patients. As part of routine care in our unit, patients were referred to the renal dietitian for nutrition assessment and intervention as per clinical practice guidelines recommendations.[205, 216] All assessment and intervention records were kept in the clinical and nutrition records. In this study, records of patients who commenced dialysis between 1st August 2000 and 31st July 2005 were examined, including the all-cause mortality data by 31st July 2010 obtained

from the Australia and New Zealand Dialysis & Transplant Registry (ANZDATA).[5] The ANZDATA registry office was contacted for permission to use the data.

Data were included for analysis from ESKD patients who were older than 18 years of age and commenced a planned dialysis program after gradual decline of renal function. Patients who had started dialysis due to acute kidney injury (AKI) or who had a previous history of RRT were excluded for analysis as their nutritional status was affected by factors other than chronic uraemia, for example, by surgical complications, trauma or use of steroids in the case of ex-transplantation. Other exclusion criteria were those patients who had a planned exit from the dialysis program, for reasons such as living donor transplantation or planned transfer to another unit, and therefore had incomplete assessment by the dietitian within 4 weeks of dialysis initiation.

Data collected were:

- Demographic: age (year) and gender (male or female)
- Clinical data: cause of ESKD; smoking history (current or ex-smoker classified as having "positive smoking history"); presence of comorbidities, including coronary artery disease (CAD), CVD, DM, chronic lung disease (CLD) and peripheral vascular disease (PVD) – ANZDATA classified the presence of co-morbidity as "yes", "suspected" or "no", with "yes" and "suspected" combined as "presence of" for analysis in this study; mortality and cause of death were also extracted
- Nutrition assessment: anthropometric measures; biochemistry; and SGA. Details of these assessments will be discussed in Section 2.7.1.2. Dietary intake assessment was routinely performed but these data were not used in this study
- Other data: "late referral" defined as <3 months of specialist care by nephrologists; dialysis modality at the start of RRT program – defined as the dialysis modality treated at 3 months as present in the ANZDATA; a change of dialysis modality

during the observation period; patients who had moved away from the unit; and date of transplantation (if applicable).

All data were entered into Microsoft Excel and then imported into SPSS version 18 (SPSS Inc, Chicago IL) statistical software program for analysis.

2.7.1.2 Nutrition assessment

For anthropometric measures, the patient's height was measured by the dietitian or nursing staff using a wall-mounted or portable stadiometer (Seca®) to the nearest 0.5 cm. Weight was measured using the Tanita® BWB-600 scale to the nearest 0.1 kg and oedema free or "dry weight" was obtained from the dialysis chart.

$$\text{BMI} = \text{weight (kg)} \div [\text{height (m)}]^2$$

BMI levels were then compared to the clinical practice guidelines,[205] with a healthy range for BMI defined as 22–26 kg/m^2 and BMI ≥ 26 kg/m^2 treated as overweight or obese. Weight history was also recorded, especially the presence and percentage of unintentional weight loss over time. Biochemical data was obtained from the results provided by the pathology services of the hospital, South Eastern Sydney Area Laboratory Services. Data collected were serum creatinine (µmol/L) and s-albumin using bromcresol purple (BCP) methods.

Glomerular filtration rate (GFR) was calculated using Cockcroft-Gault equation:[300]

$$\text{GFR}_{\text{CG}}\,(\text{mL/min}) = \frac{(140 - \text{age}) \times \text{oedema-free body weight (kg)}}{\text{serum creatinine (µmol/L)} \times 0.815}$$

x0.85 if female

GFR was also corrected for body surface area (BSA):

$$\text{BSA (m}^2\text{)} = [\text{weight (kg)}]^{0.425} \times [\text{height (cm)}]^{0.725} \times 0.007184$$

$$\textit{corrected}\ \text{GFR}_{\text{CG}}\,(\text{mL/min/1.73m}^2) = \frac{\text{GFR}_{\text{CG}}\,(\text{mL/min}) \times 1.73\text{m}^2}{\text{BSA (m}^2\text{)}}$$

Malnutrition assessment was performed by the dietitian using the 7-point scale SGA.[147, 149] SGA is a diagnostic tool for malnutrition; once the subject is scored as B or C according to the tool specification, they are categorised as malnourished. That particular version was chosen for longitudinal clinical monitoring in our routine care as it is well-validated in the renal population and used in a number of significant studies. [13, 149, 150, 256, 301, 302] The original SGA[148] rated patients into three categories: A = well nourished; B = mildly to moderately malnourished; and C = severely malnourished. The 7-point scale SGA tool (Appendix C) further divides each category into sub-categories which can be used as continuous variables, with lower numbers indicating more severe degrees of malnutrition. These sub-categories are: A = well nourished (7 and 6); B = mildly to moderately malnourished (5, 4 and 3); and C = severely malnourished (2 and 1). In addition to the medical history and physical examination components explained in Section 1.5.2, the strength of the 7-point SGA is that it also takes into account the "estimated" energy and protein intake compared to the recommended intake.[147] For example, a sustained intake of less than 85% of the recommendation over 2 months would lead to a further deduction of 1-point rating. This method gives more objective measures and strength to rate patients who are likely to fall between two categories. For example, a "healthy looking" patient with <5% weight loss over the last 6 months, but who has sustained dietary intake <85% recommended over the last 3 months, would be scored as B5 or B4 (mildly to moderately malnourished) on the 7-point scale instead of as A (well nourished) on the 3-point scale. For statistical and reporting purposes in this study we only report 3 categories: A = well nourished, B = mildly to moderately malnourished and C = severely malnourished; ratings of B and C were further combined as one "malnourished" group. We didn't consider using the version of patient generated SGA (PG – SGA)[101] because it was not validated in the renal population until in 2005, well after our initial data collection from 2000. Another 2 reasons why we did not consider using PG-SGA were (1) this tool has a built in additive scoring for co-morbidities e.g. cardiovascular disease and haemodialysis etc that affect

our multivariate survival analysis. (2) The version with a 7 point scale used in our studies was superior that the scoring is based on actual diet intake estimation whereas PG-SGA relies on the patients' subjective reporting of eating well or not.

The PhD candidate is the principal renal dietitian of the unit at St George Hospital and performed >95% of the nutritional assessment for patients in this study. The remaining assessments were undertaken by other dietitians in renal rotation from the Department of Nutrition and Dietetics at St. George Hospital. Regular SGA training was conducted for all dietitians within the Nutrition and Dietetics Department. SGA undertaken by different dietitians were compared, with an inter-rater agreement (Kappa statistic) of >0.7.

2.7.1.3 Sample size consideration

In the preliminary analysis, high 1-year mortality in malnourished incident dialysis patients was observed (in-house audit; no published data available). Approximately 30–40% of patients started dialysis due to unexpected events, e.g., AKI with or without previous history of CKD, and with or without subsequent recovering of kidney function; these patients were not considered in our study. Of all the patients (n =330) who commenced dialysis between 1st August 2000 and 31st July 2005, 167 patients (50.6%) met the selection criteria. Although this could be considered "convenience sampling" as these patients were accessible to the PhD candidate, the sample included "all" patients who commenced dialysis in our unit over a 5-year period. In the literature, univariate or multivariate analyses of the association of malnutrition based on SGA score have sample sizes between 91 to 680 with approximately 39–50% prevalence of malnutrition[13, 14, 99, 153] (see Table 1-6). The closest studies[14, 153] had a total sample size of 206 and 153 subjects respectively. Therefore, our sample size of 167 patients with well-defined nutrition background was considered to be appropriate. A retrospective attempt was made to calculate the sample size; unfortunately, none of these

publications reported the median survival time or proportion of death/mortality of the well nourished Vs. malnourished groups to allow sample size calculation for our study.

2.7.1.4 Statistical analyses

Phase I of the study examined the relationship of the baseline clinical and nutritional factors at the initiation of dialysis on survival. Survival was determined from the date of starting dialysis until death, or censored at transplant or at end of the observation period of 31st July 2010. All causes of mortality or death were considered. Reasons that may have altered nutritional status or mortality data during the observational period, such as nutrition intervention, hospitalisation, development of infection or other disease, were not examined.

In our initial analysis and report in the literature, mortality of HD and peritoneal dialysis (PD) was comparable;[14, 303] therefore all data were combined for analysis. Race or ethnicity is often thought to be an important factors affecting survival on dialysis. A higher risk of death has been reported in the Canadian Caucasian patients compared with the minority groups;[304] and in Australia, Indigenous Aboriginal compared with non-Indigenous Australians.[305] However, the differences could be explained largely by measurable case-mix and treatment characteristics.[306] When health care is accessible, survival in aboriginals and Caucasians is similar after adjusting for co-morbidities. [307, 308] Or studied population consisted of approximately 83 .3% Caucasians, the distribution of non – Caucasians was small among different ethnic groups: Australian Aboriginals (1.0%), Chinese (6.6%), Egyptian (1.0%), Indian (3.0%), Maori / New Zealander (3.1%), Pacific Islander (1.0%), Pilipino (1.0%). All patients accessed planned dialysis program with 85.0% attended our nephrologists for at least 3 months prior to starting dialysis. Therefore all data were combined for analysis. Age, s-albumin and BMI were analysed as both continuous and categorical variables; for example, age < or ≥65 years, s-albumin < or ≥33.0 g/L and BMI < or ≥26 kg/m^2. The combined

effects of malnutrition (SGA score B and C), s-albumin (<33.0 g/L vs. ≥33.0 g/L) and BMI (<26 kg/m^2 vs. ≥26 kg/m^2) were also examined. The combined effects of SGA and BMI were determined using the following forms of categorisation:

- Group 1: SGA = A + BMI <26 kg/m^2
- Group 2: SGA = A + BMI ≥ 26 kg/m^2
- Group 3: SGA = B and C + BMI <26 kg/m^2
- Group 4: SGA = B and C + BMI ≥26 kg/m^2

Similar forms of categorisation applied to combinations of SGA and s-albumin, and s-albumin and BMI. The effects of other parameters on mortality were also examined, including obesity and the levels of GFR at which dialysis should start.

All tests were performed using the statistical software SPSS version 18 (SPSS Inc, Chicago IL). Continuous variables were expressed as mean ± standard deviation for normally distributed data and as medians with interquartile ranges (IQR, 25th to 75th percentile) for non-normally distributed data. For continuous variables, comparisons between groups were performed using unpaired sample *t* test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables; categorical variables were compared using the χ^2 test. Survival analyses were performed using the Kaplan-Meier method (univariate analysis) and Cox proportional hazard analysis (multivariate analysis) was used to assess the independent association of baseline parameters and mortality.

A *P* value <0.05 was considered to be statistically significant.

2.7.1.5 Outcome measures

Primary outcome measures were the association of baseline nutritional parameters, in particular, malnutrition, s-albumin, overweight/obesity and all-cause mortality risk.

These are expressed as hazard ratio (HR) and adjusted hazard ratio (adj. HR) with 95% confidence interval (CI). The secondary outcome measures were the association of other baseline clinical factors and the risk of all-cause mortality, in particular GFR and co-morbidities. Other outcome measures were prevalence of various baseline nutritional abnormalities and comorbidities.

2.7.1.6 Ethics approval

The study protocols were approved by the ethics committee of the South Eastern Sydney and Illawarra Area Health Service, NSW, Australia **(03/115 Chan)** (Appendix D)

2.7.2 Study II: Nutritional parameters in patients attending the pre-dialysis assessment clinic

2.7.2.1 Study population and data collection

These studies were retrospective analyses of data collected from the routine nutritional assessment of the pre-dialysis assessment clinic. All patients were referred to this clinic by nephrologists of the St. George Hospital, using recommended referral criteria for patients with ESKD, GFR <30 mL/min/1.73m^2. The clinic attendance was voluntary; therefore not all ESKD patients being prepared for dialysis attended the clinic or patients may have been referred to individual health care professionals for management without going through the clinic. Only data of patients who attended the pre-dialysis clinic were included in analyses. In addition to the routine nutritional assessment records, data were also extracted from doctor's referral letters and clinic and nutrition records. Data collected were:

- Demographic: age (in year) and gender (male or female)

- Clinical data: cause of ESKD, smoking history, presence of comorbidities as described in Section 2.7.1.1
- Nutrition assessment: anthropometric measures, biochemistry, clinical signs and symptoms, dietary intake assessment and SGA. Details of these assessments will be discussed in Section 2.7.2.2. Data of reliable dietary intake assessment was used for further evaluation and analyses.
- Other data: patient's initial preferences for RRT after education by the clinical nurse consultant.

All data were entered into Microsoft Excel then imported into SPSS for statistical analysis.

2.7.2.2 Nutritional assessment

Anthropometric data – measurements of height, weight and BMI – were the same as those described in Section 2.6.1.2. MAMC was taken at the mid-point of the acromial and olecranon processes of patients' right forearms using a non-stretchable steel tape. Measurement was recorded to the nearest 0.1 cm. TSF was then measured at the mid-arm level using a Harpenden skinfold calliper; the average of 3 repeat measures to the nearest 0.2 mm was used. MAMC was calculated using the following formula:

MAMC (cm) = MAC (cm) – 0.314 x TSF (mm)

The results were then compared to the reference standards.[309, 310]

Biochemical data collected were serum creatinine and s-albumin. Calculation of corrected GFR was described in Section 2.6.1.2. A large proportion of our patients (approximately 50%) visited nephrologists in private consulting rooms and had blood tests performed by non-hospital pathology providers using different laboratory methods for s-alb analysis with various reference ranges, e.g., bromcresol purple (BCP) and

bromcresol green (BCG), etc. Therefore, in addition to recording the actual figures, whether the result was above or below reference range was also recorded.

Patients' clinical signs and symptoms in relation to nutrition were recorded. In addition to the criteria for assessing SGA – such as presence of anorexia, nausea, diarrhoea and vomiting – patients were also assessed for the presence of taste change or aversion to foods, a classic symptom of uraemia. Furthermore, patients were asked to rate their appetite using the "Appetite and Diet Assessment Tool" (ADAT) 5-point Likert scale:[238]

Question: Overall, how would you describe your appetite?

(1) Very good
(2) Good
(3) Fair
(4) Poor
(5) Very poor

Dietary intake assessment was performed using a detailed diet history interview method or structured diet history method.[242-244] Patients and their carers were asked to give a detailed description of quantity, quality and frequency of food and beverage consumption. Estimating quantity was assisted by drawings of the protein food serving size, food models and household measuring metric cups and spoons. Detailed assessment was performed in line with best practice while also generating results for use in research analyses. This assessment method was later validated in a pilot study in the pre-dialysis CKD patients by nutrition research students,[245] and showed good agreement with the 3-day food diary for assessing energy and protein intakes. It is considered to be less burdensome to patients as it does not required pre-clinic preparation and limits recording bias. The diet histories were then entered into a computerised nutrients analyses program (FoodWorks Professional Model 2009, Xyris, Brisbane, Australia) to estimate EI, DPI and intake of other macro- (fats, carbohydrates and alcohol) and micronutrients (vitamins and minerals). Patients' daily activities were

questioned with enough detail to score a physical activity level (PAL)[311] for estimating EE and energy requirements using the Schofield equation.[312]

The average daily intake of core foods such as fruit and vegetables was extracted. Records of patients who were unable to report or estimate food intake properly were excluded from analyses, with reasons including language barrier without interpreter service or poor mental status.

The intake of energy and protein was expressed as kcal and g per kg IBW per day – kcal/kg IBW/d and g/Kg IBW/d respectively. For overweight patients, adjusted BW was used[205, 230]

Adjusted BW = IBW + [(oedema-free BW – IBW) x 0.25]

The PhD candidate is the principal renal dietitian of the unit and performed >95% of the nutritional assessment for the patients in this study. In addition, regular SGA training was conducted for all dietitians within the Nutrition and Dietetics Department and achieved high inter-rater agreement (Kappa statistics) of >0.7.

2.7.2.3 Sample size consideration

As these studies were of a *post hoc* nature a sample size calculation was not performed. Study IIa considered the data of all patients enrolled (n =227) in the clinic over a 6-year period; approximately 210 patients were seen by the dietitian with usable data on 205 patients. Studies of a similar nature had sample sizes ranging from 27 to approximately 1,786 (Tables 1-7 and 1-8). Therefore, we considered our sample size was optimal. A retrospective sample size estimate calculation[313, 314] indicated the sample size used was appropriate:

$$\text{Sample size} = \frac{Z_{1-\alpha/2}^2 \times p\,(1-p)}{d^2}$$

$Z_{1-\alpha}^{2}$ = standard normal variate at 5% type 1 error (*P* <0.05) =1.96

p = expected proportion in population based on previous study. The primary nutrition parameter of interest was malnutrition. A previous study conducted in our hospital[98] indicated a prevalence of ~28% or 0.28. Similar studies also indicated ~ 28 to 35% malnutrition rate (Table 1-9). Therefore, ~30% or 0.3 was chosen.

d = margin of error or precision or error rate = 6% or 0.06

$$\text{Sample size} = \frac{(1.96)^{2} \times 0.30\ (1- 0.30)}{(0.06)^{2}}$$

$$= \sim 225$$

OR

$$\text{Sample size} = \frac{\text{DEFF} \times N \times p(1-p)}{d^{2}/Z_{1-\alpha/2}^{2} \times (N-1) + p(1-p)}$$

DEFF = design effect =1

N= population size – it was difficult to estimate the true sample size as many patients had a GFR < 30mL/min and may or may not come through the clinic. Over the 6 year study period, at least 600 patients with a GFR of < 30 mL/min were estimated to be under the care of our unit.

p = proportion or frequency, ~30% or 0.30was used discussed as above

d= confidence limit as % of 100 (absolute ± %) = 5% or 0.05

$Z_{1-\alpha/2 =}$ 1.96

$$\text{Sample size} = \frac{1 \times 600x\ 0.30\ (1-0.30)}{(0.05)^{2}/(1.96)^{2} \times (600-1) + 0.30x(1-0.30)}$$

$$= 211$$

Therefore our sample size was considered appropriate.

Phase IIb of the study was to examine the "nature" of the clinic so data of all patients (n =550) enrolled in the clinic over a 10-year period were reviewed, and data from 501 patients with sufficient nutrition data were analysed.

2.7.2.4 Statistical analyses

All statistical tests were performed using the statistical software SPSS© Statistics. Descriptive statistics were used to examine the prevalence of nutrition abnormalities; continuous variables were expressed as mean ± standard deviation for normally distributed data and comparisons between groups were performed using unpaired sample *t*-test. Categorical variables were compared using the χ^2 test. Correlations between GFR and dietary energy and protein intakes were estimated using Pearson correlation coefficients. Analysis of variance (ANOVA) was used to compare the parameters among three to four categories. The positive predictive values (PPV) of appetite score for adequate energy (≥25 g/kg IBW/d)[178, 310] and protein intake (≥0.75 g/kg IBW/d)[205] were assessed using the two-way contingency analysis table.[315]

A *P* value <0.05 was considered to be statistically significant.

2.7.2.5 Outcome measures

The main outcome measures were the prevalence of nutritional abnormalities of patients attending the pre-dialysis assessment clinic. The secondary outcomes were the relationships between various demographic, clinical and nutritional parameters.

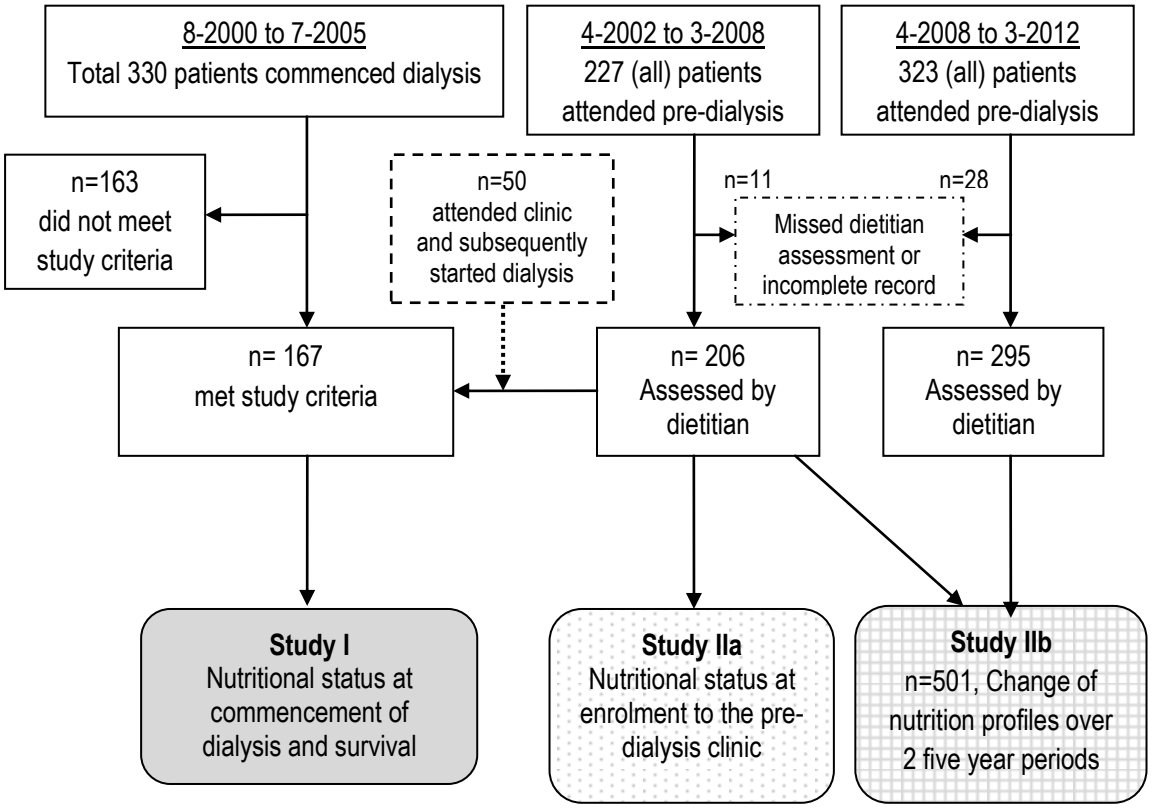
2.7.2.6 Ethics approval

The study protocols were approved by the ethics committee of the South Eastern Sydney and Illawarra Area Health Service, NSW, Australia (**03/134 Chan**, **LNR/12/STG/104** and **LNRSSA/12/STG/105**). (Appendix E)

2.7.3 Patients flow between studies

There were considerable overlapping of patients flow between treatment (dialysis), clinic and studies. Figure 2-3 indicates the flow of patients between various studies in relation to their treatment and clinic attendance. All data were from convenience sample. In study 1, all patients (n=330) commenced dialysis during the defined period were considered, with 167 patients met the selection criteria. In study II, study population was patients attending the clinic itself, so this meant everyone was considered but not all data could be used due to missing dietitian assessment or incomplete records.

Figure 2-3 Patient flow between studies



Chapter 3 Nutritional and Clinical Factors of ESKD Patients at the Initiation of Dialysis and Survival over a Ten-Year Study Period

This chapter has been published as "original research" in the Journal of Renal Nutrition, the official journal of the Council on Renal Nutrition of the National Kidney Foundation**,** USA.

Permission for use of this publication in Chapter 3 in this thesis is described in the guide for "Authors' Rights" in Elsevier Journals.[316]

Remark: material presented in Chapter 3 is a copy of the published article; all scientific units, spelling (USA), abbreviations and punctuations used are in line with the published format, which may be differ to the format used in the other part of the thesis. The referencing system remains consistent within the thesis body.

Title: Malnutrition (SGA) scores and serum albumin levels, but not body mass index (BMI) values at initiation of dialysis are independent predictors of mortality: a 10 year clinical cohort study**.**[317]

Journal issue: J Ren Nutr 22(6): 547–557, 2012

Contribution to research and journal article:

Principal author:

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Role: for conception, design, data collection, analysis and interpretation of data, and preparation of the manuscript.

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   Role: research design and revision of the manuscript.

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   Role: statistical advice, data analysis and revision of the manuscript.

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Abstract

Objective: To examine the associations between demographic, clinical, lifestyle, and nutritional parameters at the start of dialysis and mortality, including the combined effects on nutritional parameters which were seldom investigated in the literature.

Design: 10 year retrospective clinical cohort study.

Setting: Dialysis unit of a metropolitan tertiary teaching hospital in Sydney, Australia.

Subjects: Incident dialysis patients (n =167; hemodialysis, 57.5%; male, 61.7%; age 65.3±13.6 years; diabetic, 24.5%) who commenced on a planned dialysis program.

Methods: Associations were examined between all-cause mortality and baseline demographics, including age and gender; clinical and lifestyle characteristics, including glomerular filtration rate, smoking habits, presence of co-morbidities (e.g., coronary artery disease, diabetes mellitus, and peripheral vascular disease); and nutritional parameters, including body mass index (BMI), serum albumin (s-albumin) levels, and subjective global assessment score (SGA). Associations with combination values for malnutrition, s-albumin (<3.3 vs. ≥3.3 g/dL) and BMI (<26 kg/m^2 vs. ≥26 kg/m^2) were also examined.

Results: Median survival was 54.2 months (interquartile range, 23 to 83), and 52.1% of patients were malnourished (SGA score B and C) at the start of dialysis. Older age (>65 years, *P* <0.0001), presence of peripheral vascular disease (*P* <0.0001), reduced s-albumin levels (*P* =0.01) and malnutrition scores (*P* =0.02) independently predicted mortality. Being overweight and obesity (BMI: ≥26 kg/m^2) did not show any advantage on survival (*P* =0.73). Being malnourished and overweight (or obese) was associated with a 3-fold increase in mortality risk (adjusted hazard ratio [HR], 2.96; 95% confidence interval [CI], 1.12–7.33, *P* =0.02) compared with being well nourished with a

BMI <26 kg/m^2 (referent). Compared with being well nourished (SGA = A), being malnourished with normal or low s-albumin was associated with higher risk, (HR, 2.06; 95% CI, 1.06 to 4.00; *P* =0.03 and HR, 2.86; 95% CI, 1.65–4.94; *P* <0.0001, respectively). There was no statistical difference between mortality risks through any combination of s-albumin and BMI values (*P* =0.54).

Conclusion: Malnutrition and reduced s-albumin levels were found to be independent predictors of mortality, whereas overweight and obesity did not show protective effects.

3.1 Introduction

Protein energy wasting (PEW) and poor nutritional status are common in patients with end stage kidney disease (ESKD) on maintenance dialysis.[75, 318, 319] These are strong predictors of mortality and morbidity and are associated with poor quality of life.[13, 107] Factors affecting nutrition in uremic patients include (1) disturbance of energy, protein and nutrients metabolism,[320] (2) metabolic acidosis,[115] (3) anorexia, taste change and poor appetite that may lead to suboptimal dietary intake,[11, 321, 322] (4) dialysis procedures *per se*,[13] such as bio-incompatibility, inadequate dialysis, protein and other nutrient losses, and peritoneal dialysis (PD) [323] dialysate-induced glucose loading and sense of fullness,[324] (5) hormonal derangement,[325] (6) co-morbidities, such as cardiovascular disease and diabetes mellitus, (7) infection and intercurrent illnesses, (8) chronic inflammation,[75] (9) altered muscle metabolism[326] and physical inactivity,[327] (10) loss of residual renal function,[328] (11) psycho-social issues[329] and poor food management skill, and (12) conditions associated with various stages of lifecycle that require additional nutritional attention, such as menopause, aging-related sarcopenia and poor dentition. Many of these nutrition abnormalities emerge during the progressive decline of renal function before dialysis is required.[11, 98]

In the dialysis population, nutritional factors found to predict mortality risk are anthropometric measures, e.g., low weight to height ratio,[105] low body mass index (BMI) and unintentional weight loss[330]; abnormal laboratory results, such as high level of C-reactive protein (CRP)[74] and low levels of lymphocytes, parathyroid hormone, serum albumin, pre-albumin and hemoglobin[104, 330-334]; poor appetite,[97] muscle wasting,[252] suboptimal intakes of energy and protein,[321] low exercise capacity,[327] poor functional capacity measured by hand grip strength[252]; and malnutrition score using subjective global assessment (SGA).[14] Many of these abnormalities present at the start of dialysis and predicted poor outcomes.[13, 14, 252] However, there has been much debate on the prognostic significance of s-albumin-CRP,[14, 335] BMI[128, 129, 133, 336] and timing of initiation of dialysis.[145, 337] It is necessary to understand the relationships between mortality and these modifiable factors, so that pre-dialysis intervention can be considered to improve outcomes.

3.2 Aim

The aims of the present study were (1) to describe the demographic, clinical and nutritional characteristics in a cohort of ESKD patients who commenced on planned dialysis program in our unit, (2) to examine the associations between these factors and mortality, and (3) to examine the combined effects of nutritional factors on mortality risk, as these methods were seldom investigated in the previous studies.

3.3 Patients and methods

This was a retrospective clinical cohort study involving all incident hemodialysis (HD) and PD patients at the renal unit of The George Hospital, Sydney, Australia between August 1, 2000 and July 3, 2005. All patients were followed until death, or they were censored at transplant or at the end of the observational period of July 31, 2010. This means all patients completed at least 5 years of follow-up over the 10-year study

period. Inclusion criteria were ESKD patients who were older than 18 years and who commenced a planned dialysis program after gradual decline of renal function without history of acute kidney injury (AKI) and renal replacement therapy (RRT). Initiation of dialysis was recommended by the patients' primary nephrologists based on clinical judgments (e.g., when glomerular filtration rate [GFR] was <7 mL/minutes/1.73m^2 or indication of uncontrolled uremic symptoms, e.g., volume overload). Exclusions criteria were patients in whom dialysis was initiated because of AKI with or without recovering renal function, previous history of RRT, planned early discontinuation of dialysis program from our unit (e.g., living donor transplantation or transfer to another units) and incomplete assessment by the dietitian within 4 weeks of dialysis initiation.

Clinical and demographic data extracted from the hospital clinical notes and the Australia and New Zealand Dialysis & Transplant Registry (ANZDATA) included age; gender; race; smoking history (never smoked or combined ex- and current smokers); late referral to nephrologists, defined as <3 months under specialist care before starting dialysis; and co-morbidities such as coronary artery disease (CAD), cerebral vascular disease (CVD), diabetes mellitus (DM), chronic lung disease (CLD), and peripheral vascular disease (PVD). ANZDATA classified the presence of co-morbidity as "yes", "suspected" or "no"; data of "yes" and "suspected" were combined as "presence of" for analysis in this study. Mortality and cause of death were also extracted.

In line with the clinical guidelines[205] which are based on the latest best evidence and expert opinion if a high level of evidence did not exist or was inconclusive, all patients were assessed by the renal unit dietitians, including the author M.C., as part of the routine care. Anthropometric measures included for analysis were height (m), edema-free body weight (kg), BMI = weight÷height^2 (m/kg^2) and weight history (in particular if any unintentional weight loss occurred over the previous 6 months for SGA rating). The previous routine blood results before the first dialysis session were extracted from

clinical notes. These included s-albumin (reference range, 3.3 to 5.3 g/dL) and serum creatinine to calculate GFR using the Cockcroft-Gault equation. The survival risk between the early and late starting groups were compared using the Initiating Dialysis Early and Late (IDEAL) trial intended cutoff of ≥7 and <7 mL/minutes/1.73m^2 as early and late initiation, respectively[338]; further analyses were performed at cutoffs of 8, 9 and 10 mL/minutes/1.73m^2. To elimination the negative effect of acute-phase response of s-albumin due to the insertion of PD catheter, the most recent s-albumin readings before the procedures were used. Other assessment performed by the renal dietitian(s) was SGA[149] which categorises patients as A = well nourished, B = mild-moderately and C = severely malnourished based on the patient's medical history and physical examination. Urea kinetic studies were routinely performed to all patients throughout the study period to meet the optimal national dialysis targets.[339] The clinical practice guidelines[205] defined healthy range for BMI as 22–26 kg/m^2; we considered BMI ≥26 kg/m^2 as obese or overweight. Additional analyses were performed according to the World Health Organization defined categories[121] of underweight, healthy weight range overweight and obese (BMI: <18.5, 18.5 to 25.0, 25 to 30, and ≥30 kg/m^2, respectively) as well as renal-specific BMI categories[205, 310] of undernourished, ideal range, overweight and obese (BMI: <23, 23 to 26, 26 to 30 and ≥30 kg/m^2, respectively). The combined effects of malnutrition (classified by SGA score B or C), s-albumin (<3.3 vs. ≥3.3 g/dL) and BMI (<26 vs. ≥26 kg/m^2) were also examined. For example, the combined effects of SGA and BMI were determined using the following forms of categorisation: group 1 (SGA = A + BMI: <26 kg/m^2), group 2 (SGA = A + BMI: ≥26 kg/m^2), group 3 (SGA = B and C + BMI: <26 kg/m^2) and group 4 (SGA = B and C + BMI: ≥26 kg/m^2). Similar forms of categorisation applied to SGA and s-albumin, as well as s-albumin and BMI combinations.

All tests were performed using the statistical software SPSS version 18 (SPSS Inc, Chicago IL). Continuous variables were expressed as mean ± standard deviation for

normally distributed data and as medians with interquartile ranges for non-normally distributed data. For continuous variables, comparisons between groups were performed using unpaired sample *t*-test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables, whereas categorical variables were compared using the χ^2 test. Survival analysis was performed using the Kaplan-Meier method (univariate analysis) and Cox proportional hazard analysis (multivariate analysis) was used to assess the independent association between baseline parameters and mortality. Effect of age (>65 years), GFR (<7 mL/minutes/1.73m^2), s-albumin (<3.3 g/dL) and BMI (≥26 and ≥30 kg/m^2) as continuous and categorical variables were also examined. *P* <0.05 was considered to be statistically significant.

The study was approved by the ethics committee of the South Eastern Sydney and Illawarra Area Health Service, NSW, Australia.

3.4 Results

Dialysis was initiated in 330 patients in the defined period. Of these, 167 patients (50.6%) met the inclusion criteria. One hundred and sixty three (49.4%) were excluded for analysis because of AKI with or without recovering renal function (32.8%), previous history of RRT (2.1%), planned early discontinuation of dialysis program from our unit (10.3%) and other causes (e.g., <18 years of age, incomplete dietitian assessment within 4 weeks of enrollment, or missing data; 4.2%). The mean age (±standard deviation) of the studied subjects was 65.3±13.6 years (male, 61.7%). Of these patients, 57.5% were on HD and the rest were on PD at day 90 after enrollment; 64 patients (38.3%) switched dialysis modality during the study period. Similar survival rates were reported in the literature for both modalities[14, 303] even after switching from one to the other.[340] As we found similar results by the Kaplan-Meier analysis (*P* =0.89), all HD and PD data were combined for analysis. Twenty-eight patients (16.8%) received a kidney transplant after entry to the study.

The baseline demographic, clinical and nutritional characteristics of the studied patients at the initiation of dialysis are listed in Table 3-1.

Table 3-1 Demographic, clinical and nutritional characteristic of the studied subjects at baseline

Parameters	Total	Male	Female
Number (%)	167	103 (61.7%)	64 (38.3%)
Demographics			
Age (year)	65.3±13.6	65.8±13.9	64.±13.1
**Race, Caucasian (%)	83.3	83.5	82.8
Clinical and co-morbidities			
Haemodialysis at 3 month (%)	57.5	62.1	50.0
Serum creatinine (μmol/L)	800.6±288.1	867.4±314.4	683.0±199.3*
Glomerular filtration rate (mL/minutes/1.73m^2)	8.0±2.7	7.8±2.7	8.2±2.7
Late referral† (%)	8.5	10.6	4.7
Smoking (positive history)‡ (%)	43.7	47.3	35.0
Chronic lung disease§ (%)	15.8	15.5	16.4
Coronary artery disease¶ (%)	46.2	48.5	42.6
Peripheral vascular disease** (%)	24.5	24.5	24.6
Cerebral vascular disease†† (%)	23.9	22.4	26.3
Diabetes mellitus (%)	33.5	34	32.8
Nutritional			
Serum albumin (g/dL)	3.1±0.5	3.1±0.5	3.15±0.5
Weight (kg)	69.5±17.1	73.6±14.5	62.8±18.9*
Body mass index (kg/m^2)	25.9±6.9	25.9.±4.4	25.9±7.7
Malnourished, subjective global assessment score B and C (%)	52.1	48.5	57.8

P value is for comparison of the gender groups
*P <0.0001
†Data missing in 2 patients
‡Data missing in 10 patients
§Data missing in 9 patients
¶Data missing in 9 patients
**Data missing in 9 patients
††Data missing in 9 patients
Expression of figures: n±SD – standard deviation

****** Remark: Australian Aboriginals (1.0%), Chinese (6.6%), Egyptian (1.0%), Indian (3.0%), Maori / New Zealander (3.1%), Pacific Islander (1.0%), Pilipino (1.0%).

Late referral (<90 days) to the nephrologists was noted in 8.5% of patients, and dialysis was commenced with a mean GFR of 8.0±2.7 mL/minutes/1.73m^2. Apart from body weight and serum creatinine, there was no statistical difference between male and female patients for all other demographic, clinical and nutritional parameters. In all, 111 patients (66.6%) died including 2 of the transplanted patients, by the end of the observation period. Three patients were transferred to the other hospitals, but their survival data were obtained from the ANZDATA for analysis. Median follow up time was 53.0 (interquartile range 23 to 83) months with 96.5 (76.3 to108.8) versus 29 (17.0–53.0) months for survivors and non-survivors respectively. The causes of ESKD and death are listed in Table 3-2.

Table 3-2 Causes of end stage kidney disease and mortality

Cause	**%**
Causes of end stage kidney disease (n =167)	
Chronic glomerulonephritis	21.6
Diabetic nephropathy	24.0
Renovascular disease/ hypertensive nephrosclerosis	18.6
Adult polycystic kidney disease	5.4
Analgesic nephropathy	9.6
IgA nephropathy	6.0
Reflux nephropathy/congenital abnormality	4.8
Other or unknown causes	10.0
Causes of death (n =111)	
Myocardial infarction	9.0
Cardiovascular accident	1.8
Cardiac arrest	11.7
Sepsis/infection	15.3
Other causes and illnesses	18.0
Withdrawal due to:	
Refusal/QOL measures	21.6
Cerebrovascular co-morbidities	12.6
Peripheral vascular co-morbidities	4.5
Malignancy	2.7
Unknown causes	2.7

The main cause of ESKD was diabetic nephropathy (24%). The most common cause of death was withdrawal of dialysis due to refusal and quality of life measures (21.6%).

Among the patients studied, dialysis was initiated early in 37.2% (≥7 mL/minutes/1.73m^2) and late in 62.8% (<7 mL/minutes/1.73m^2), with a mean GFR of 9.4 ± 2.2 versus 5.5±1.0 mL/minutes/1.73m^2, respectively; *P* <0.0001. The early-start group in comparison to the late start group had significantly higher BMI (27.5±6.3 vs. 23.3±3.9 kg/m^2, *P* <0.0001) and included fewer malnourished patients (43.8% vs. 66.1%, χ^2=7.8, *P* =0.005). There was no statistical difference between the 2 groups for all other variables. Kaplan-Meier analysis showed no statistical difference in mortality between the two groups (*P* =0.79). Further analysis did not show any statistical difference in mortality between the early- versus late-start groups with the GFR cutoff of 8 mL/minutes/1.73m^2 (10.2±1.2 vs. 6.1±2.2), *P* <0.0001; 9 mL/minutes/1.73m^2 (11.1±1.5 vs. 6.6±2.1), *P* <0.0001; or 10 mL/minutes/1.73m^2 (12.0±1.6 vs. 6.9±2.1), *P* <0.0001. Our data indicated that GFR levels at which dialysis started were not found to have any association with mortality risk.

Among the lifestyle and co-morbidity parameters, PVD was independently associated with higher mortality risk (*P* <0.0001), whereas the significance of CAD disappeared in the adjusted analyses (*P* =0.10). Smoking and all other co-morbidities did not show any statistically significant effect on mortality risks (Table 3-3).

Fifty-eight percent of patients had s-albumin <3.3 g/dL (reference range, 3.3 to 5.3 g/dL). The low s-albumin group, when compared with patients with normal s-albumin levels, has significantly lower s-albumin (2.8±0.3 vs. 3.5±0.3 g/dL, *P* <0.0001), lower GFR (7.3±2.3 vs. 8.8±2.9 mL/min/1.73m^2, *P* <0.0001) and higher prevalence of malnutrition (66.3% vs. 34.2%, χ^2=16.9, *P* <0.0001). There was no statistical difference between the two groups for all other variables. Cox proportional hazard model revealed that the measure of s-albumin, as both a continuous and categorical variable, was independently associated with survival; with *P* =0.01 and 0.01 respectively (Table 3-3).

Table 3-3 Cox proportional hazards analysis (multivariate model) of factors affecting mortality

Parameters	Unadjusted hazard ratios (95% CI)	*P* value	Adjusted hazard ratios (95% CI) *	*P* value
Age (per year increase)	1.08 (1.05–1.11)	<0.0001	1.08 (1.05–1.12)	<0.0001
Age (>65 years)	2.76 (1.51–5.06)	<0.001	3.06 (1.70–5.51)	<0.0001
Gender (male)	1.31 (0.84–2.04)	NS (0.23)	1.33 (0.86–2.06)	NS (0.20)
Glomerular filtration rate (per mL/minutes/1.73m^2 increase)	1.09 (0.98–1.21)	NS (0.10)	1.07 (0.97–1.17)	NS (0.10)
Hemodialysis	0.67 (0.43–1.06)	NS (0.09)	0.75 (0.48–1.16)	NS (0.19)
s-albumin (per g/dL increase)	0.92 (0.87–0.98)	0.01	0.93 (0.89–0.98)	0.01
s-albumin (<3.3 g/dL)	1.60 (0.95–2.71)†	0.08	1.86 (1.17–2.97) †	0.01
Body mass index (per kg increase)	0.97 (0.92–1.03)	NS (0.30)	0.97 (0.92–1.03)	NS (0.30)
Body mass index (≥30 kg/m^2)	0.68 (0.36–1.29)	NS (0.23)	0.67 (0.36–1.27)	NS (0.22)
Body mass index (≥26 kg/m^2)	0.91 (0.52–1.59)	NS (0.73)	0.91 (0.52–1.59)	NS (0.73)
Malnourished, subjective global assessment score B and C	1.76 (1.01–3.05)	0.046	1.74 (1.11–2.72)	0.02
Smoking (positive history)	1.46 (0.95–2.23)	NS (0.09)	1.45 (0.96–2.19)	NS (0.08)
Chronic lung disease	0.85 (0.50–1.45)	NS (0.56)	0.86 (0.50–1.45)	NS (0.56)
Coronary artery disease	1.71 (1.04–2.81)	0.04	1.45 (0.94–2.19)	NS (0.10)
Peripheral vascular disease	2.62 (1.57–4.37)	<0.0001	2.42 (1.57–3.73)	<0.0001
Cerebral vascular disease	1.01 (0.61–1.67)	NS (0.98)	1.01 (0.61–1.67)	NS (1.01)
Diabetes mellitus	1.10 (0.68–1.75)	NS (0.71)	1.09 (0.69–1.74)	NS (0.71)

NS, non-significant

* Analysis with age as categorical variable unless stated otherwise. Hazard ratio adjusted for all other variables including age, gender, dialysis modality, s-albumin, body mass index, subjective global assessment, smoking and all co-morbidities

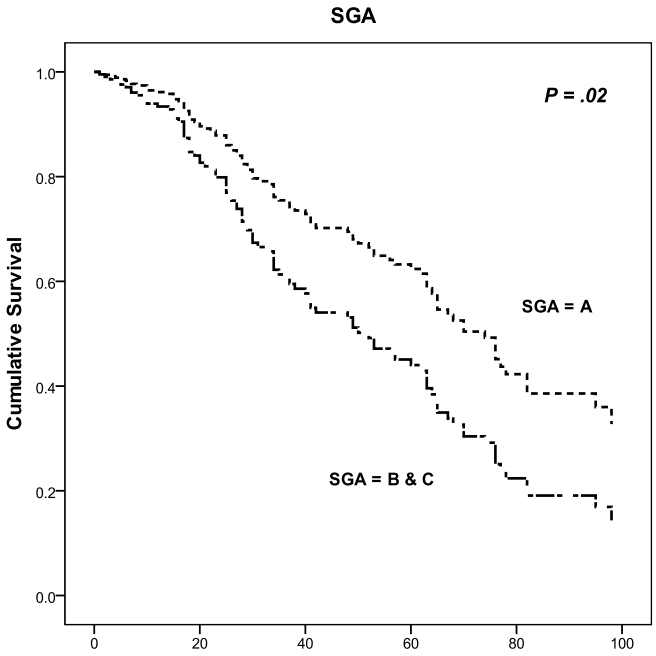
† Analysis with age as continuous variable

More than half of the patients (55.1%) were overweight or obese (BMI: ≥26 kg/m^2), and 17.4% of patients were obese (BMI: ≥30 kg/m^2). Kaplan-Meier analysis indicated no statistical difference in mortality risk between BMI <26 and ≥ 26kg/m^2 (overweight and obese), *P* =0.08 and <30 or ≥30kg/m^2 (obese) groups, *P* =0.11. After adjusting for all other variables, Cox proportional hazards analysis indicated similar effects, (*P* =0.73 and .22 respectively; Table 3-3). Kaplan-Meier analysis showed no statistical difference in mortality between the 4 World Health Organization BMI categories[121] (*P* =0.26) nor among the renal specific BMI categories(*P* =0.72).[205, 310]

Within the cohort, 47.9%, 41.9% and 10.2% of patients were rated as well nourished (SGA = A), mildly to moderately malnourished (SGA = B) and severely malnourished (SGA = C) respectively. Kaplan-Meier analysis indicated a significant difference in the mortality risk between the three groups (*P* <0.0001). After adjusting for all other

variables using the Cox proportional hazard model, the survival curves of SGA B and C merged, and the combined malnourished group (SGA = B and C, 52.1%) showed significantly higher mortality risk compared to the well-nourished group (SGA = A) (adjusted hazard ratio [HR], 1.74; 95% confidence interval [CI], 1.11 to 2.72; *P* =0.02; Table 3-3 and Figure. 3-1). Therefore, malnutrition was found independently associated with mortality.

Figure 3-1 Adjusted survival curves for SGA evaluated at the start of dialysis



SGA, subjective global assessment: A = well nourished; B & C = malnourished.

It is worth noting that the well-nourished group had significantly more diabetic patients than the malnourished group (41.4% vs. 26.4%, χ^2 =4.1 *P* =0.04). The SGA A group had significantly higher BMI (28.9±6.3 kg/m^2) compared with the SGA B and C group (23.1±3.7 kg/m^2), *P* <0.0001. It was important to note that 24.5% of overweight or obese patients (BMI ≥26 kg/m^2) were rated as malnourished (SGA B and C) and within the malnourished group (SGA = B and C), 21% of patients were overweight or obese (BMI ≥26 kg/m^2).

When the combined effects SGA and BMI were examined, after adjusting for all other variables, the SGA = B and C + BMI: ≥26 kg/m^2 group was associated with almost 3-fold increase in mortality risk (HR, 2.96; 95% CI, 1.12 to 7.33, *P* =0.02) compared with SGA = A + BMI: <26 kg/m^2 (referent) (Figure 3-2), although the mean BMI of the SGA = B and C + BMI ≥26kg/m^2 group was significantly higher than the SGA = A + BMI <26 kg/m^2 group (28.4±1.9 vs. 23.3±2.3 kg/m^2), *P* <0.0001. The SGA = B and C + BMI ≥ 26 kg/m^2 group has almost 2-fold higher mortality risk (HR of 1.77; 95% CI:0.95 to 3.30; *P* =0.07) compared with the SGA = B and C + BMI <26 kg/m^2 group despite a significant higher mean BMI of 28.4±1.9 kg/m^2 vs. 21.8±2.8 kg/m^2, *P* <0.0001. This means, among the malnourished groups, those overweight or obese tended to perform worse.

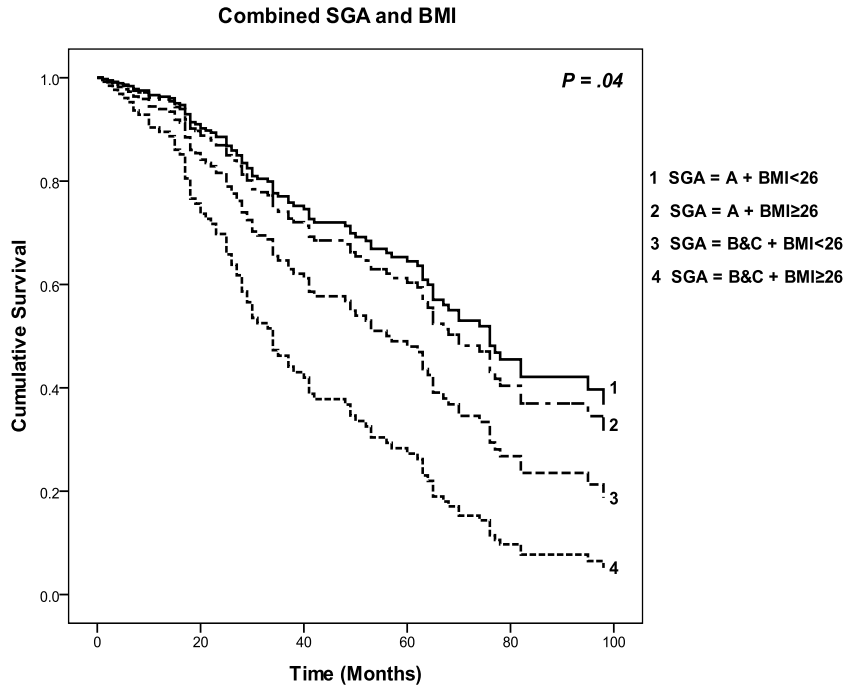
When the combined effects of SGA and s-albumin were examined (Figure 3-3), no statistical difference in mortality risk was observed between the SGA = A + s-albumin ≥3.3 g/dL or SGA = A + s-albumin <3.3 g/dL (HR, 1.25; 95% CI, 0.65 to 2.4, *P* =0.51) although the latter had significantly lower level of s-albumin (3.5±0.2 vs. 2.9±0.4 g/dL, *P* <0.0001). In comparison to SGA = A + s-albumin ≥3.3 g/dL group (referent), the SGA = B and C + s-albumin ≥3.3 g/dL group was associated with a 2-fold (HR, 2.06; 95% CI, 1.06 to 4.00, *P* =0.03) increase in mortality risk despite no difference in s-albumin levels (3.5±0.2 vs. 3.5±0.3 g/dL, *P* <0.90). Among the SGA B and C groups with s-albumin ≥3.3 g/dL or <3.3 g/dL, no statistical difference on mortality risk (*P* =0.26) was observed despite the statistical difference in s-albumin levels (3.5±0.3 vs.

2.8±0.3 g/dL *P* <.0001). An almost 3-fold increase in mortality risk was observed for SGA = B and C + s-albumin <3.3 g/dL compared with the SGA = A + s-albumin ≥3.3 g/dL group (HR, 2.86; 95% CI, 1.66–4.94; *P* <.0001).

There was no statistical difference in mortality risk among any combinations of s-albumin (< or ≥3.3 g/dL) and BMI (< or ≥26 kg/m^2) categories (*P* =0.53).

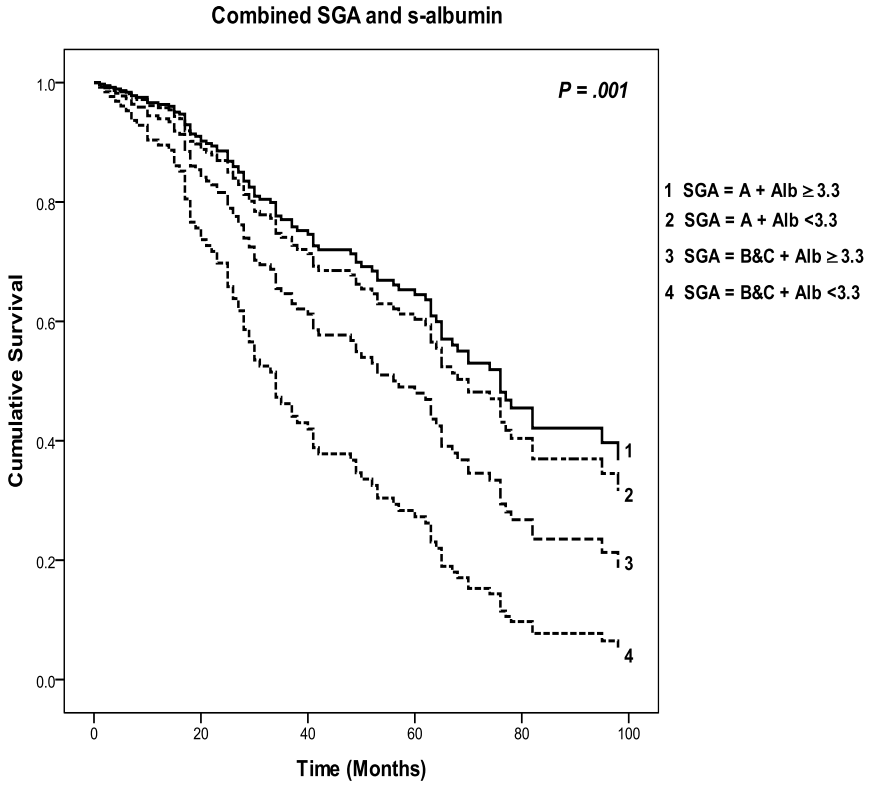
In summary, after adjusting for all variables including age, gender, dialysis modality, GFR level at which dialysis started, s-albumin, BMI, malnutrition score (SGA B and C), smoking and all co-morbidities; older age (>65 years; *P* <0.0001), presence of PVD (*P* <0.0001), reduced s-albumin levels (*P* =0.01) and malnutrition scored as SGA B and C (*P* =0.02) independently predicted mortality. Combined effects of SGA A with BMI <26 kg/m^2 or s-albumin ≥3.3 g/dL were associated with better survival.

Figure 3-2 Adjusted survival curves of the combined effects of SGA and BMI evaluated at the start of dialysis



Note:
Group 1 versus 2 (*P* =0.73), group 1 versus 3 (*P* =0.19), group 1 versus 4 (*P* =0.02), group 2 versus 3 (*P* =0.14), group 2 versus 4 (*P* =0.007), group 3 versus 4 (*P* =0.07).
SGA, subjective global assessment: A = well nourished, B & C = malnourished;
BMI, body mass index in kg/m^2.

Figure 3-3 Adjusted survival curves of the combined effects of SGA and s-albumin evaluated at the start of dialysis



Note:
Group1 versus 2 (*P* =0.51), group 1 versus 3 (*P* =0.03), group 1 versus 4 (*P* <0.0001), group 2 versus 3 (*P* =0.16), group 2 versus 4 (*P* =0.004), group 3 versus 4 (*P* =0.26).
SGA, subjective global assessment: A = well nourished, B&C = malnourished; Alb = s-albumin (g/dL).

3.5 Discussion

Our cohort represented a relatively homogenous group of ESKD patients who showed an uneventful but gradual decline of renal function with no history of AKI and RRT. We observed a high prevalence (52.1%) of malnutrition (SGA score B and C) at the start of dialysis. Malnutrition, together with older age (>65 years), reduced s-albumin levels and presence of PVD independently predicted mortality over the 10-year study period. Gender, dialysis modalities, GFR level at which dialysis was commenced, BMI, positive smoking history, and co-morbidities other than PVD did not show any statistical significant difference on mortality risk.

In search of the optimal timing for when dialysis should start, the IDEAL trial[338] compared the mortality between early (10 to 14 mL/minutes/1.73m^2) and late-start (5–7 mL/minutes/1.73m^2) groups. The mean GFR of the early- and late-starting group resulted at 12.0 mL/minutes/1.73m^2 and 9.8 mL/minutes/1.73m^2, respectively, in the study because of various clinical and social decisions. No statistical difference in survival or clinical outcomes was observed between the early- or late-starting groups. Our cohort study, which included patients with a wider range of clinical implications, also showed no difference in mortality risk when the analyses were performed at the GFR cutoff of 7 mL/minutes/1.73m^2, as initially planned in the IDEAL trial, or at the cut off of 8, 9 and 10 mL/minutes/1.73m^2. Our results supported the recommendations of the IDEAL trial and other observational studies[337, 341] that with careful clinical management of ESKD, including nutritional inputs, dialysis can be started at lower levels of GFR (<7 mL/minutes/1.73m^2).[145, 342] In agreement to the literature, we found no significant difference in mortality risk between HD and PD.[14, 303] This suggests patients should be able to start on either modalities based on their clinical and psychosocial needs when the time is right.

The effects of hypoalbuminemia on mortality have been inconsistent in the literature[343-345] because of reasons such as the presence of inflammation (duration and magnitude), duration and the severity of hypoalbuminmia. The present study indicated that s-albumin levels were an independent predicator of mortality. This result was consistent with the findings of a number of studies,[15, 332, 344, 346] but differed to others.[14, 345, 347] In the latter studies, the predictive effect of s-albumin was ameliorated after adjusting for CRP, and this may be a limitation of our study because CRP was not routinely measured. Therefore, the independent predictive effect of s-albumin as solely nutritional could not be concluded. However, we did consider for other study variables including the known associates of inflammation such as history of AKI, surgery (PD catheter insertion), obesity and other co-morbidities. Thus, it is reasonable to speculate the strong role of poor nutrition, or type I malnutrition caused by a reduced protein and energy intake[75] plays in the predictive effect of s-albumin levels in our study, similar to other reports in the literature. [330, 335]

Similar to previous findings, the SGA rating of malnutrition was found to be an independent predictor of mortality.[14, 346, 348] A sustained reduction of dietary intake is a major determinant of SGA rating, and as we considered sustained intakes of protein and energy of less than 80% of requirements as inadequate, it was reasonable to deduce that the predictive effect of low s-albumin levels constituted a significant nutrition component. It is possible that type I and type II malnutrition coexist with nutritional and inflammatory factors compounding the effects on each other, and their significance cannot be mutually exclusive. We did not examine the effect of the individual components of SGA on survival, but it is known that these individual components reflect long-term changes and are highly predictive of mortality and morbidities, such as unintentional weight loss,[330, 349] reduced dietary intake,[15, 159, 350] poor appetite[95, 97] and muscle wasting.[351] Our study supports the use of SGA at the

start of dialysis as a powerful independent predictor of survival, as previously reported by other researchers.[14, 346, 348]

In contrast to the literature,[14, 15, 346] diabetes was not observed to be associated with higher mortality risk in our study. This may be explained by a higher proportion of our patients with diabetes being well nourished, possibly counteracting the effects of the uremic wasting on mortality over time. Our results were similar to those of the Dialysis Outcomes and Practice Patterns Study (DOPPS) [352] which reported diabetic patients had significantly lower odds of cachectic appearance than non-diabetic patients. Cardiovascular disease was found to be an independent predictor of mortality in several studies.[14, 153, 346] We found CAD to be significant in the unadjusted analyses but the significance disappeared in the adjusted analyses (HR, 1.45; 95% CI, 0.94 to 2.1, *P* =0.10). This can possibly be explained by the unknown duration and severity of cardiovascular conditions in our cohort. Also our patients were much older (mean age, was 65.3±13.6 years compared with 50 to 56 years in these studies), and the age factors may explain some of the variation in our findings. Other reasons could be the varied observational periods or the heterogeneity of uremia-related nutrition effects before starting dialysis in previous studies. Such reasons include unplanned initiation of dialysis due to unforeseen events (e.g., AKI caused by infections and surgical complications), duration of malnutrition and previous transplantation. It is not clear whether dialysis was initiated for the same reasons in all patients in reported studies.

The obesity paradox[129, 336, 353, 354] has created much debate in the renal community regarding the protective effect of obesity in ESKD patients. A recent systematic review[355] of the relationship between BMI and mortality supported the inverse association between BMI and all-cause mortality in adult HD patients, especially in elderly patients. In other studies, [15, 143, 356] it has been argued that when body composition was also considered, the possible protective effect of high BMI is limited to subjects with normal and high muscle mass only. Similar to previous findings,[133, 357] our

study revealed overweight or obesity was not found to have any protective effects, and when combining with malnutrition scores, it was associated with the worst outcome. Our findings echoed the high mortality risk found in those with obese sarcopenia.[144] In addition, the combined effects SGA = A and BMI <26 kg/m^2 were found to have the best survival advantage. Again, higher BMI did not show protective effects with either low or normal levels of s-albumin. Most importantly, being well nourished (SGA = A) was found to be associated with lower mortality risk irrespective of the levels of s-albumin and BMI. Our study highlighted the usefulness of the combined effects of nutritional parameters in predicting outcomes.

There are limitations to our study, the main ones are the lack of measurement of inflammatory biomarkers (CRP), small sample size, and unknown duration and severity of lifestyle factors such as smoking history and co-morbidities (e.g., CAD). We also did not measure the effect of nutrition interventions before and after dialysis initiation. Patients may respond to nutritional management differently depending on the type, severity and duration of their nutritional issues, and the degree of exposure to intervention. Our study points to the need for timely access to structured nutritional care to prevent and manage nutrition abnormalities well before dialysis is required, and if it is required, to help maintain nutrition status on the conservative management pathway.

The strength of this study is the long follow up time in a well defined cohort of patients experiencing relatively homogeneous nutrition effects before dialysis started. It is a good example of how informative research can be conducted within the practice of renal disease care.

3.6 Conclusions

In the study reported here, a high prevalence of malnutrition among patients with ESKD at the initiation of dialysis was observed. During a 10-year period, older age (>65 years), reduced s-albumin levels, presence of PVD, and malnutrition scores were found to independently predict mortality. Other studied factors, such as gender, dialysis modality, GFR level at which dialysis was initiated, BMI, positive smoking history and presence all other co-morbidities were not found to be associated with higher mortality risk. A high BMI was not associated with any survival advantage, and when combined with the presence of malnutrition, it was associated with the highest mortality risk. The combined effects of these simple, readily available nutritional parameters were effective in predicting mortality independently and are highly informative for practice management and evaluation.

Practical Application:

Malnutrition scored by SGA (B and C) at the start of dialysis was associated with high mortality risk irrespective of the levels of BMI and s-albumin levels. Being overweight or obesity did not show any protective effect and was associated with the worst outcome with the presence of malnutrition. These findings suggest nutrition intervention to optimise nutritional status should be considered in patients with ESKD well before dialysis is required.

Acknowledgments

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3.7 Supplement to Chapter 3

This section (Table 3-4) presents the analyses for the hazard ratios (HR) of the mortality risks for the combination effects of SGA, s-albumin and BMI. The graphical presentations are shown in Figures 3-2 and 3-3

Table 3-4 Cox proportional hazards analysis (multivariate model) of combination factors affecting mortality

Parameters		n (%)	Parameter (mean±SD)	Adjusted HR (95% CI)[a]	*P*	Adjusted HR (95% CI)[a]	*P*	Adjusted HR (95% CI)[a]	*P*	*P* (among groups)
SGA	**BMI**		**BMI**							
A	<26	25 (15.0)	23.2±2.2	Referent	-	-	-	-	-	0.04
A	≥26	55 (32.9)	31.5±5.8	1.15 (0.53–2.52)	0.73	Referent	-	-	-	
B&C	<26	69 (41.3)	21.8±2.8	1.67 (0.78–3.61)	0.19	1.45 (0.89–2.38)	0.14	Referent	-	
B&C	≥26	18 (10.8)	28.4±1.9	2.96 (1.20–7.33)	0.02	2.57 (1.29–5.14)	0.01	1.77 (0.95–3.30)	0.07	
SGA	**s-alb**		*s*-**alb**							
A	≥33	46 (27.5)	34.9±2.2	Referent	-	-	-	-	-	0.001
A	<33	34 (20.4)	29.1±4.0	1.25 (0.65–2.41)	0.51	Referent	-	-	-	
B&C	≥33	27 (16.2)	35.4±3.4	2.06 (1.06–4.00)	0.03	1.65 (0.82–3.31)	0.16	Referent	-	
B&C	<33	60 (35.9)	27.8±3.3	2.86 (1.66–4.94)	<0.0001	2.29 (1.30–4.06)	0.004	1.39 (0.78–2.46)	0.26	
s-alb	**BMI**		**s-alb/ BMI[b]**							
≥33	<26	41 (24.5)	35.7±2.8/23.2±2.3	Referent	-					0.53
<33	≥26	32 (19.2)	35.0±1.9/31.6±5.7	1.62 (0.83–3.15)	0.16					
≥33	<26	57 (34.1)	27.5±3.8/21.7±2.8	1.33 (0.74–2.36)	0.34					
<33	≥26	37 (22.2)	28.9±3.3/30.7±4.8	1.27 (0.62–2.61)	0.58					

Abbreviations: HR, hazard ratio; CI, confidence Interval; SGA, Subjective Global Assessment, SGA A, well nourished; SGA B&C, malnourished; BMI, body mass index in kg/m^2; s-alb, serum albumin (g/L)

[a] HR adjusted for age, gender, GFR, albumin, smoking habits, co-morbidities

[b] Adjusted survival curves for serum albumin and BMI combination all fell on one line, and show no statistical difference in mortality among any combination. Therefore, further analysis using different referent(s) were not performed

Expression of figures: n±SD–standard deviation

Chapter 4 Nutritional Characteristics of Patients at Enrolment to the Pre-Dialysis Assessment Clinic

This chapter is written in a format (original research) intended for submission to the *Journal of Renal Nutrition*, the official journal of the Council on Renal Nutrition of the National Kidney Foundation, USA. The supplement to this chapter is intended for submission as a "research brief" for the same journal.

Manuscript title: A High Prevalence of Abnormal Nutrition Parameters Found in Pre-Dialysis End Stage Kidney Disease: Is it a Result of Uraemia or Poor Eating Habits?

Contribution to research and journal article:

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Abstract

Objective: To examine the nutritional characteristics of a cohort of pre-dialysis end stage kidney disease (ESKD) patients.

Setting: Outpatient clinic of a metropolitan tertiary teaching hospital in Sydney, Australia.

Subjects: All ESKD patients attending the multidisciplinary pre-dialysis assessment clinic over a six year period between April 2002 and March 2008.

Methods: Retrospective analysis of data extracted from the routine initial nutrition assessment records. These included anthropometric and biochemical measures, subjective global assessment (SGA), appetite score, presence of symptoms, dietary energy, protein, other macro- and micronutrient intakes.

Results: Of the 210 patients assessed, 60.5% were male; mean age was 65.7±13.6 years with a mean glomerular filtration rate (GFR) of 17.3±6.5 mL/min/1.73m^2. 17.1% and 62.4% were underweight (BMI <23 kg/m^2) and overweight or obese (BMI ≥26 kg/m^2) respectively. 40.5% were rated as malnourished (SGA score B and C) with 19.0% overweight/obese and malnourished. Energy and protein intakes correlated positively with GFR, being r =0.17, P =0.01 and r =0.29, P <0.0001 respectively. Mean energy and protein intakes were 23.7±6.7 kcal/kg IBW/d and 1.18±0.42 g/kg IBW/d, with 62.6% and 13.1% not meeting the recommended intake respectively. 51.0% of patients experienced symptoms, while 17.5% of patients self-imposed a dietary regimen inappropriately due to mistaken belief of dietary needs in ESKD. 41.3% and 80.4% did not consume adequate servings of two fruit and five vegetables per day. Examples of high prevalence of sub-optimal nutrient intake observed were vitamin B_2 (41.2%), vitamin E (61.8%), folate (67.6.2%), vitamin D (100.0%), vitamin A (52.9%), magnesium (94.1%), zinc (64.2%) and dietary fibre (80.4%).

Conclusion: patients presented to the current pre-dialysis assessment clinic with high prevalence of abnormal nutrition parameters associated with decreased renal function, symptoms burden, habitual intake and in some individuals, self-imposed inappropriate diets. This clinic may provide an opportunity to optimise nutritional status of ESKD patients before dialysis is required.

4.1 Introduction

Poor nutritional status and presence of protein energy wasting (PEW) at the start of dialysis are associated with morbidity, mortality and hospitalisation[13-15, 99, 133] (including results of Chapter 3[317]). Thus, timely nutrition intervention is important in end stage kidney disease (ESKD) well before dialysis is required. Indeed, nutritional status deteriorates during the course of decline of renal function,[11, 85] and the presence of nutrition abnormalities is known to associate with adverse outcomes, including accelerated atherosclerosis,[74] mortality and hospitalisation.[98] Cross-sectional[12, 85, 160, 161, 165] and longitudinal[11, 158] studies have established that spontaneous intakes of protein and energy decline as GFR falls. Furthermore, poor appetite, commonly found in dialysis-dependent ESKD patients, has been associated with mortality, morbidity and hospitalisation.[95, 96] On the other hand, over-nutrition, such as the presence of obesity at the start of dialysis, is associated with high mortality risk.[133] However, other researchers found the protective effect of obesity in patients with ESKD, which is known as the "obesity paradox".[129] Historically, nutritional intake studies in ESKD patients have been focused on energy and protein intake. Other nutrients, food patterns or intake of specific foods such as fruit and vegetables have received relatively little attention. In order to establish sound clinical practice, it is necessary to gain a broader insight into nutritional parameters, including dietary intake of energy, protein and other nutrients, information on food patterns, the presence of symptoms and clinical indicators of the nutritional status of these patients. Previous studies have seldom encompassed many of these parameters in one study. It is also worth noting

the growing number of elderly patients entering the advanced renal disease care program[4] with additional age-related nutritional health concerns, such as osteoporosis and sarcopenia.

4.2 Aim

The aim of this study was to examine the baseline demographic, clinical and nutritional characteristics of a cohort of ESKD patients who attended an outpatient pre-dialysis assessment clinic. These included the prevalence of various clinical and nutritional parameters as well their relationship with the decline of renal function.

4.3 Methods

This retrospective study examined clinical and initial nutrition assessment records of all patients attending an outpatient pre-dialysis assessment clinic established in April 2002 through March 2008. Patients referred by renal physicians to this multidisciplinary clinic were predominantly in CKD stages 4 and 5 (GFR <30 mL/min/1.73m^2) and were assessed by the clinical nurse consultant, pharmacist, social worker and dietitian. Exclusion criteria were those patients who missed the dietitian assessment, incomplete or unreliable assessment data, or late referral to the pre-dialysis assessment team during acute hospital admission, with dialysis expected to start within next 1–2 months.

Demographic, clinical and nutrition data collected from hospital records included age, gender, race, smoking habits and presence of co-morbidities, e.g., coronary artery disease (CAD), diabetes mellitus (DM), chronic lung disease (CLD) and peripheral vascular disease (PVD). Nutritional data included for analyses were: anthropometric measures, e.g., height (m); oedema-free body weight (kg); body mass index (BMI weight ÷ height^2, [kg/m^2]) and weight history; mid-arm circumference (MAC) and triceps skinfold (TSF). Mid-arm muscle circumference (MAMC) was calculated using the following formula: MAMC (cm) = MAC (cm) – 0.314 x TSF (mm). The clinical practice

guidelines[205] define a healthy range for BMI of 22–26 kg/m^2; therefore BMI ≥26 kg/m^2 was treated as overweight. Prevalence of renal-specific BMI categories[205, 310] were also examined with undernourished, ideal range, overweight and obese defined as BMI <23, 23–26, 26–30 and ≥30 kg/m^2 respectively. Muscle wasting was classified as MAMC >10% and <50th percentile of the reference standard for age and gender.[309, 310] Blood results closest to and within 2 months of the clinic were extracted from clinical notes; these included serum-albumin (s-albumin) and serum creatinine to calculate GFR using the Cockcroft-Gault equation.[300] Approximately 50% of the blood tests were analysed in private providers instead of the hospital-based laboratory; thus, different analytical methods used for s-albumin with different reference ranges. Therefore, for the s-albumin levels, both actual figures plus whether they were below or within reference ranges were recorded for analysis. The renal dietitian(s) (mainly the author MC) performed the subjective global assessment (SGA),[147, 149] which categorised patients as A = well nourished, B = mild-moderately and C = severely malnourished, based on the patient's medical history and physical examination. The prevalence of combined malnutrition (SGA score = B and C) and BMI (<26 kg/m^2 vs. ≥26 kg/m^2) were also examined. Patients' subjective rating of appetite was assessed using the Appetite and Diet assessment Tool with a 5-point Likert scale:[238] (1) very good, (2) good, (3) fair, (4) poor and (5) very poor; its relationship with energy and protein intake was also evaluated (see supplement to Chapter 4). For easy comparison, appetite scores were combined into "good appetite" (very good and good) versus "reduced appetite" (fair, poor and very poor). The presence of other nutrition-related symptoms were also assessed, e.g., nausea and taste aversion. A "typical day's dietary intake" was assessed by the dietitian using a structured diet history or diet interview method,[242-245] taking into account food frequency and weekend variations. Food pictures and models, household metric measuring cup and spoons were used to assist serving size estimation. Structured diet history method is considered to be a feasible method for the initial outpatient clinic visit compared with the 3-day food record used in other

studies.[12, 165] Urinary nitrogen excretion was not routinely collected in our unit, so we were not able to measure nitrogen appearance to estimate protein intake as in previous studies.[158, 160] Dietary intake data were analysed using a computerised nutrient analyses program (FoodWorks Professional Model 2009, Xyris, Brisbane, Australia) to estimate energy intake (EI), dietary protein intake (DPI) and intake of other nutrients. EI and DPI intakes were expressed in kcal and g per kg IBW (ideal body weight) per day or kcal/kg IBW/d and g/Kg IBW/d respectively. For overweight patients, adjusted body weight (adjusted BW) was used instead of IBW; adjusted BW = IBW + [(oedema-free BW – IBW) x 0.25].[205, 230]

To evaluate possible underreporting, the ratio of EI to resting energy expenditure (REE) was calculated using the Schofield equation.[312] An EI:REE ratio less than 1.27 (known as the Goldberg cut-off value)[358, 359] may indicate possible underreporting of EI; if an EI:REE <1.27 was present, other explanations of low EI were also reviewed, e.g., presence of symptoms and physical inactivity defined as physical activity level (PAL) equal or less than 1.5. PAL is the estimated total energy expenditure (TEE) divided by basal metabolic rate (BMR).[227, 311] In the current study, PAL was rated according to patients' description of their typical daily physical activity including any participation in leisure or structured exercise programs. Average daily consumptions of fruit, vegetable and fish were surveyed and compared to the Australian Guide of Health Eating recommendations of "two fruit and five vegetables"[360] and the American Heart Association's "Healthy diet goals"[361] of at least two servings of fish per week (equivalent to approximately 30 grams per day).

All statistical tests were performed using the statistical software IBM© SPSS© Statistics version 20. Continuous variables were expressed as mean ± standard deviation for normally distributed data and comparisons between groups were performed using unpaired sample *t*-tests. Categorical variables were compared using the χ^2 test. Correlations between GFR and dietary energy and protein intakes were estimated

using Pearson correlation coefficients. Analysis of variance (ANOVA) was used to compare the parameters among three to four categories. The positive predictive values (PPV) of appetite score for adequate energy (>25 g/kg IBW/d)[310] and protein intake (>0.75 g/kg IBW/d)[205] were assessed using the two-way contingency analysis table.[315] *P* values <0.05 were taken as showing a statistically significant difference. This study was approved by the ethics committee of the South Eastern Sydney and Illawarra Area Health Service, NSW, Australia.

4.4 Results

Two hundred and twenty-seven patients attended the pre-dialysis assessment clinic during the study period. Two hundred and ten patients were assessed by the dietitian with 206 reliable dietary assessment records available for computerised nutrient analysis. Patients were predominantly (56.5%) in CKD stage 4 (GFR 15–30 mL/min/1.73m^2) followed by 38.2% in stage 5 (GFR <15 mL/min/1.73m^2) with a mean GFR of 17.3±6.5 mL/min/1.73m^2. Table 4-1 summarises the demographic and clinical characteristics of these patients. The majority of patients (64.3%) were older than 65 years of age (range 17.7 to 88.1) and diabetic nephropathy was the main cause of ESKD (24.2%).

Table 4-1 Demographic and clinical data of patients attending the pre-dialysis assessment clinic

Parameters	n =210
Demographic	
Age (year)	65.7±13.6
Age >65 year (%)	64.3
Age >75 year (%) in total sample	28.1
Gender (% male)	60.5
* Race (% Caucasian)	85.7
Clinical and co-morbidities (%)	
GFR (mL/min/1.73m^2), n =207	17.3±6.5
CKD stages 3:4:5 (%), n =207	5.3:56.5:38.2
Smoking (% positive history), n =188	45.7
Coronary artery disease (%)	34.8
Diabetes mellitus (%)	35.2
Peripheral vascular disease (%)	17.1
Cerebral vascular disease (%)	16.2
Chronic lung disease (%)	10.5
Cause of ESKD	
Chronic glomerulonephritis (%)	16.7
Diabetic nephropathy (%)	24.3
Renovascular disease/ hypertensive nephrosclerosis (%)	21.4
Adult polycystic kidney disease (%)	5.2
Analgesic nephropathy (%)	4.8
IgA nephropathy (%)	9.5
Reflux nephropathy/congenital abnormality (%)	6.2
Other or unknown causes (%)	11.9

Remark: Chinese (6.2%), Egyptian (1.9%), Indian (2.4%),
Maori / New Zealander (2.4%), Pilipino (1.0%), Others (1.4%)
Expression of figures: n±SD–standard deviation

A high prevalence of nutrition abnormalities was found in this cohort. As shown in Table 4-2, 21.5% of patients' body weights were within the ideal weight range of BMI (23.0–26.0 kg/m^2) and 31.4% of patients were obese. The prevalence of malnutrition was high, with 36.7% and 3.8% rated as mildly to moderately (SGA = B) and severely (SGA = C) malnourished respectively. 19.0% of patients were overweight and malnourished. Within the malnourished group, 47.1% of patients were overweight/obese, and within the overweight/obese group, 30.5% of patients were rated as malnourished. 29.1% of patients reported various degrees of unintentional loss of BW 6 months prior to the clinic with an additional 3.8% of patients reporting a sustained weight loss of more than 5% in the past, but stabilised in the 6 months prior to the clinic. 37.3% of patient had s-albumin levels below the reference range.

According to the PEW criteria[310] based on MAMC <90% standard, 28.4% of patients were classified as muscle-wasted, whereas under the SGA physical examination component, 46.7% of patients scored various degrees of muscle wasting, including mild (31.9%), moderate (8.1%) and severe (6.7%) categories.

Approximately 14.8% of patients reported having previous contact with dietitian(s) for various diet interventions, such as lipid lowering and diabetes disease management as an outpatient or acute inpatient of undefined history, duration and frequency. However, these contacts rarely (<5%) related to CKD stage 4 or 5 dietary management with structured care and regular follow-up. Therefore, all of these data were considered as spontaneous intake. As expected, energy and protein intake correlated significantly with GFR: r =0.17, P =0.01 (Figure 4-1) and r =0.29, P <0.0001 (Figure4-2) respectively. However, as shown in Table 4-4, energy and nutrient intake and food habits varied vastly among individuals. Mean EI was low at 23.7±6.7 kcal/kg IBW/d with 87.9% of patients having an EI below the recommended ~35 kcal/kg IBW/d for <60 years of age and ~30 kcal/d for >60 years of age.[205, 216] According to the PEW classification[310] of no less than 25 kcal/kg IBW/d, 62.6% of patients had insufficient EI. 76.2% of patients had an EI:REE ratio (Goldberg cut-off) <1.27 and 41.7% had an EI below REE (ratio <1.00). However, further analysis indicated that these patients, when compared to those with an EI:REE ratio >1.27, had significantly higher prevalence of malnutrition (45.2% vs. 26.5%, χ^2=5.4, P =0.02). Furthermore, the majority of patients (88.3%) were very inactive, with a PAL of 1.5 (sedentary) or less (very sedentary or bed-/chair-ridden), and 22.8% reported a reduced physical function under the SGA sub-category of physical function rating.

Table 4-2 Nutritional characteristics of patients attending the pre-dialysis assessment clinic

Nutritional parameters *(n missing)*	**n = 210**
Anthropometry	
Weight (kg)	76.1±17.0
Unintentional weight loss (presence of) in last 6 months (%)	29.1
Unintentional weight loss >5% in last 6 months (%)	8.1
Unintentional weight loss >5% in the past but stabilised 6 months before clinic (%)	3.8
Body mass index (kg/m^2)	28.1±5.7
BMI <23 kg/m^2 (underweight)	17.1
BMI >26 kg/m^2 (overweight & obese)	62.4
BMI >30 kg/m^2 (obese)	31.4
MAMC (cm) *(n =14)*	24.9±3.7
MAMC % reference standard (%) *(n =14)*	97.8±14.1
MAMC 10% < reference standard (%) *(n =14)*	28.6
TSF (mm) *(n =14)*	16.1±8.6
TSF % reference standard *(n =14)*	108.5±55.5
Biochemistry	
Serum creatinine (µmol/L) *(n =1)*	389.3±121.7
Serum albumin (g/L) *(n =1)*	34.4±6.0
Serum albumin below reference range (%) *(n =1)*	37.3
Malnutrition score	**(%)**
SGA A:B:C (%)	59.5:36.7:3.8
Malnourished (SGA B and C)	40.5
Malnourished + BMI >26 kg/m^2	19.0
Malnourished + BMI >30 kg/m^2	9.5

Expression of figures: n±SD–standard deviation

Table 4-3 Appetite score and presence of symptoms

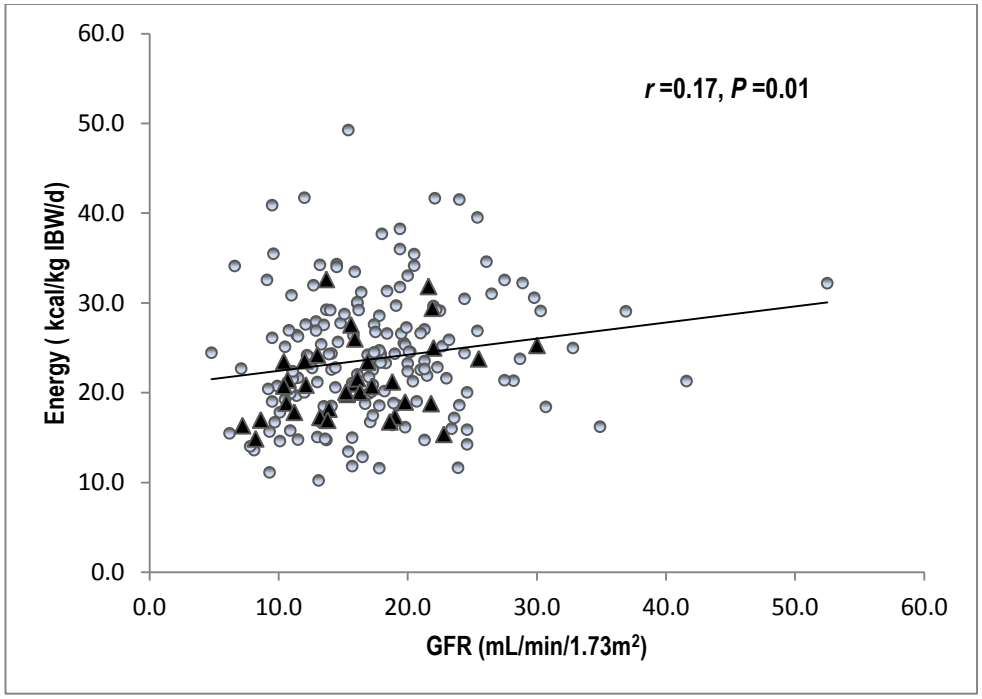
Appetite score: self-rated	**n =210 (%)**
(1) Very good	31.0
(2) Good	39.0
(3) Fair	23.3
(4) Poor	5.7
(5) Very poor	1.0
Combined:	
(1)+(2) = Good appetite	70.0
(3)+(4)+(5) = Reduced appetite	30.0
Symptoms and behaviour	**(%)**
Presence of symptom (self-reported):	
Nausea	20.0
Taste aversion	20.0
Total (compromised appetite and/or nausea and/or taste aversion)	38.6
Presence of symptom (self-reported + prompting by dietitian during intake assessment)	51.0
Inappropriate self-imposed diet	
Restrictive	15.7
In excess	1.4
Total	17.1

Table 4-4 Dietary Intake of patients attending the pre-dialysis assessment clinic

Energy/ nutrients/ foods (n =206 for protein and energy; n missing =2 for all other parameters)	**Recommend-ation**	**Intake/day mean±SD**	**Mean, % recomm-ended**	**% below recommendation (or above if indicated)**
Energy (kcal/d)	-	1575.2±240	-	-
Energy (kcal/kg IBW/d)	30 for >60 yr*‡ 35 for <60 yr*‡	23.7±6.7	-	87.9
	>25†‡		-	62.6
EI:REE	>1.27 (Goldberg cutoff)	1.06±0.27	-	42.7
Protein (g/d)	-	79.2±31.5	-	-
Protein (g/kg IWB/d)	0.75–1.00*‡	1.18±0.42	119.0±51.3	13.1 (61.2 > recommendation)
Protein (% energy)	15–20‡	20.3±4.3	-	-
Fat (% energy)	~30‡	31.7±7.5	-	-
Carbohydrate (% energy)	~50‡	46.8±8.7	-	-
Alcohol (% energy)	-	1.2±3.5	-	-
Monounsaturated fat (% total fat)	~45‡	42.5±8.2	-	-
Polyunsaturated fat (% total fat)	~45‡	22.9±8.8	-	-
Saturated fat (% total fat)	<7§	34.7±10.3	-	-
Thiamine, Vit. B_1 (mg)	1.1–1.2¶	1.6±1.2	137.6±99.7	36.8
Riboflavin Vit. B_2 (mg)	0.9–1.6¶	1.7±1.4	132.5±112.9	41.2
Niacin (mg)	14–16¶	44.7±26.6	280.8±120.1	1.0
Folate (µg)	400¶	395.1±356.3	98.8±89.1	67.6
Vitamin A (µg)	700–900¶	890.4±553.7	108.4±67.0	52.9
Vitamin C (mg)	45¶	100.3±72.6	222.6±160.4	22.1
Vitamin D (µg)	5.0 (19–50yr)¶ 10–15 (>50 yr)¶	3.1±2.5	31.8±33.6	100.0
Vitamin E (mg)	7–10¶	8.2±4.0	94.1±45.5	61.8
Calcium (mg)	1000–1300¶	543.4±277.5	47.8±27.5	96.6
Phosphorous (mg)	1000 ¶	1136.4±441.2	114.0±43.5	40.7
Iodine (µg)	150¶	77.7±44.6	52.6±29.7	94.6
Iron (mg)	8¶ 18 for female (19–50yr) ¶	10.46±5.6	120.1±47.9	36.3
Magnesium (mg)	310–400¶	247.8±83.8	65.2±20.5	94.1
Phosphorous (mg)	1000‡	1129.2±458.3	116.8±78.6	41.6
Zinc (mg)	8–14¶	11.2±9.0	90.6±39.3	64.2
Dietary fibre (g/d)	25–30¶	21.4±8.4	76.0±29.3	80.4
Fruit (serves/d)	2**	2.0±1.5	101.7±70.0	41.3
Vegetable (serves/d)	5**	2.8±1.5	54.75±29.7	89.2
Fish (g/d)	30g§	33.6±52.5	110.7±175.0	60.8

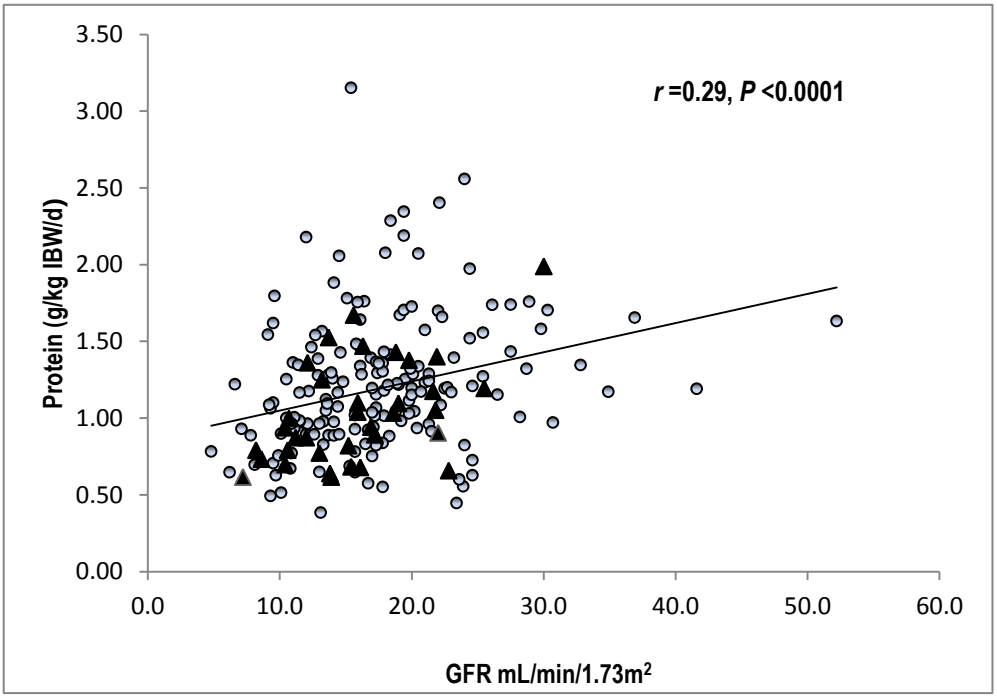
* K/DOQI guidelines[216]
† PEW classification[310]
‡ Evidence-based practice guidelines for the nutritional management of chronic kidney disease[205]
§ American Heart Association[361]
¶ NH&MRC nutrient reference values for the general Australian population [362]
** Go for 2 fruit & 5 vegetables™ campaign[360]
Expression of figures: n±SD–standard deviation; n(n1-n2)- range

Figure 4-1 Energy intake and glomerular filtration rate



▲ Denotes patients with self-imposed inappropriate intake

Figure 4-2 Protein intake and glomerular filtration rate



▲ Denotes patients with self-imposed inappropriate intake

The mean protein intake was 1.18±0.42 g/kg IBW/d with 13.1% below and 61.2% above the ideal range of 0.75–1.00 g/kg IBW/d.[205] 4.9% of patients consumed less than the 0.6 g/kg IBW/d level traditionally prescribed for a low protein diet.[206]

For self-rated appetite scores of “very good” (31.0%), “good” (39.0%), “fair” (23.3%), “poor” (5.7%) or “very poor” (1.0%), the mean EI were 25.4±6.0, 24.2±6.7, 22.0±6.8, 19.4±6.2 and 14.9±1.8 kcal/kg IBW/d respectively (*P* =0.002), whereas the mean protein intakes were 1.32±0.36, 1.17±0.44, 1.13±0.44, 0.86±0.25 and 0.57±0.18 respectively (*P* =0.001). For the combined appetite scores, 70.0% rated “good appetite” (“very good” and “good”) whereas 30.0% rated “reduced appetite” (“fair”, “poor” and “very poor”) with mean energy and protein intakes of 24.7±6.5 vs. 21.3±6.7 kcal/kg IBW/d (*P* =0.001) and 1.24±0.42 vs. 1.06±0.42 g/kg IBW/d (*P* =0.006) respectively. The PPVs of “good appetite” score for adequate energy and protein intakes were 0.41 (95% CI: 0.36–0.45, *P* =0.104) and 0.92 (95% CI: 0.88–0.95, *P* =0.005) respectively. This means, among those who rated “good appetite” (n =143), approximately 41% of patients consumed adequate energy and the rest perceived “good appetite” but did not consume adequate energy. Appetite score for identifying adequacy of protein intake appeared satisfactory (see Section 4.7, supplement to Chapter 4).

In addition to the reduced appetite, patients also reported the presence of classic symptoms of uraemia, including nausea (20.0%) and taste aversion to food (20.0%). These led to approximately 38.1% of patients reporting the presence of symptoms including reduced appetite, and/or nausea and/or taste aversion. However, with further prompting during the in-depth dietary intake assessment by the dietitian, a total of 51.0% of patients and/or their carers disclosed “problems” with eating of various degrees. The mean intakes of energy and protein between the “no symptom” versus “presence of symptom” groups were 25.7±6.3 vs. 21.8±6.3 kcal/kg IBW/d (*P* <0.0001 and 1.33±0.42 vs. 1.05±0.39 g/kg IBW/d (*P* <0.0001) respectively.

Between the BMI <26 kg/m^2 and the overweight/obese (BMI ≥26 kg/m^2) groups, energy intake was 25.1±7.2 vs. 22.9±6.3 kcal/kg IBW/d (*P* =0.02), and protein intake was 1.24±0.47 vs. 1.15±0.39 g/kg IBW/d (*P* =0.14) respectively. It appears that overweight/obese patients consumed significantly less energy per kilogram of weight compared to patients with BMI <26 kg/m^2 while protein intake was similar. However, there was no difference in the total intake of energy (1589.2±491.7 vs. 1569.1±476.0 kcal/d, *P* =0.75) or protein (79.3±34.2 vs. 79.2±30.0 g/d, *P* =0.98).

Furthermore, during the in-depth dietary intake assessment, 17.1% of patients were found to impose inappropriate dietary regimens due to misconceptions of nutrition knowledge for ESKD. Examples of inappropriate restriction (15.7%) included: severe reduction of total fat and sugar intake being mistaken for good eating habits or for lipid-lowering or weight management; limiting fruit and vegetables to control serum potassium when it was not required; and/or severe limiting of protein foods, especially red meat, in an attempt to manage kidney disease. Inappropriate excess food intake (1.4%) was found in diabetic patients to avoid hypoglycaemia ("hypos") and the use of a high protein-low carbohydrate diet for controlling weight. The sources of confusion mainly came from advice from relatives or friends, other health care practitioners and from misinterpreting information from the Internet. The inappropriate intake group, when compared with the spontaneous intake group, had significant reduced mean intake of energy and protein of 21.2±4.0 vs. 24.2±7.1 kcal/kg IBW/d (*P* =0.02) and 1.02±0.33 vs. 1.22±0.44 g/kg IBW/d (*P* =0.01) respectively. The "▲" symbol shown in Figures 4-1 and 4-2 represents the inappropriate energy and protein intakes among all patients, and the majority of self-imposed dietary restrictions had led to suboptimal intake. Within this group of 33 patients, 54.5% were rated as malnourished, mainly as a consequence of self-induced poor intake.

Regarding the other nutrient intakes, the mean intakes of folate, vitamin D, vitamin E, calcium, iodine, magnesium, zinc and dietary fibre were below the RDI.[311] A high

proportion of patients did not meet individual nutrient requirements, in particular for vitamin B_1 (36.8%), vitamin B_2 (41.2%), vitamin E (61.8%), folate (67.6.2%), vitamin D (100.0%), vitamin A (52.9%), magnesium (94.1%), zinc (64.2%) and dietary fibre (80.4%). 41.3% of patients did not consume the recommended two serves of fruit and 89.2% did not consume five serves of vegetables each day. 40.1% of patients had less than five daily serves of bread/grain products, and consumed predominately refined forms of carbohydrates, e.g., white bread and pasta. 60.8% of patients consumed less than the recommended servings of fish (equivalent to 30 g/day). Many of these patients reported inadequate fruit, vegetables and fish intake as their food habits. However the prevalence was not available for all patients due to the retrospective nature of the study.

Across the four categories of GFR range: <10, 10–15, 15–20 and >20 mL/min/1.73m^2 (Table 4-5), patients in later stages of CKD or lower GFR levels were generally older, had lower protein intake, lower BMI and other anthropometric measures. The prevalence of malnutrition and presence of symptoms were also increased as GFR decreased; and were high in all groups. No statistical difference was observed across all groups for the mean EI (P =0.18), which was suboptimal in the majority of patients.

Among the three age groups: <65, 65–75 and >75 years (Table 4-6), anthropometric measures such as BMI and MAMC (% standard) were lower in the >75 year age group, but no statistical difference was found in the TSF (% standard) among the three groups. This reflected that older patients were more likely to be muscle-depleted, but not necessarily lower in their fat stores. No statistical difference was observed for dietary protein and energy intakes between the 65–75 vs. ≥75 year age groups, but these were significantly lower than the <65 year age group (P <0.05).

Table 4-5 Demographic, clinical and nutritional parameters in different GFR ranges

GFR (mL/min/1.73m^2) **n (% of 209 total)** ***(n missing)***	**<10** **20 (9.5%)**	**10–15** **62 (29.7%)**	**15–20** **69 (33.0%)**	**>20** **58 (27.8%)**	***P* value**
Mean GFR (mL/min/1.73m^2)	8.4±1.4	12.5±1.4	17.4±1.4	25.1±5.7	n/a
Age (year)	71.2±13.9	70.8±12.4	66.9±11.8	57.4±13.3*†‡	<0.0001
Serum creatinine (μmol/L)	604.3±152.4	437.6±79*	361.2±72*†	297.5±71.0*†‡	<0.0001
s-alb (g/L)	30.4±6.6	34.9±6.2*	34.0±6.4	35.7±4.4*	0.006
s-alb below reference range (%)	65	38.7	39.1	24.1	0.01
BMI (kg/m^2)	22.7±2.9	26.1±4.3	29.0±4.9*†	30.8±6.7*†	<0.0001
MAMC (% of standard) *(n =14)*	87.7±8.4	95.1±13.2	99.4±13.5*	103.0±15.4*†	<0.0001
TSF (% of standard) *(n =14)*	68.0±24.9	95.0±47.1	118.0±53.5*	126.4±64.9*†	<0.0001
Malnourished, SGA score B and C (%)	80.0	48.4	29.0	31.0	<0.0001
Presence of symptom (%)	75.0	56.5	45.0	43.1	0.05
Energy (kcal/kg IBW/d) *(n =15)*	21.6±8.5	23.0±6.0	23.64±6.6	25.10±6.8	0.18
Protein (g/kg IBW/d) *(n =15)*	0.95±0.37	1.08±0.34	1.24±0.46*	1.31±0.44*†	0.001

Abbreviation: GFR = glomerular filtration rate; s-alb = serum albumin; BMI = body mass index; MAMC = mid-arm muscle circumference; TSF = triceps skinfold; SGA = subjective global assessment

For the continuous variables:

* *P* <0.05 as compared with the GFR <10 mL/min/1.73m^2 group

† *P* <0.05 as compared with the GFR =10–15 mL/min/1.73m^2 group

‡ *P* <0.05 as compared with the GFR =15–20 mL/min/1.73m^2 group

Expression of figures: n±SD–standard deviation

Table 4-6 Demographic, clinical and nutritional parameters across different age categories

Age group (year) **n (% of 210 total)** ***(n missing)***	**<65** **75 (35.6)**	**65–75** **77 (36.7)**	**>75** **58 (*26.7*)**	***P* value**
Age (year)	50.6±10.4	70.3±3.0*	79.1±3.0*†	<0.0001
GFR (mL/min/1.73m^2)	20.3±6.8	16.7±4.8*	13.5±4.9*†	<0.0001
Serum creatinine (μmol/L)	400.0±146.0	376.2±0.094	394.2±120.6	0.48
s-alb (g/L)	35.4±6.9	36.0±5.5	35.7±3.4	0.85
s-alb < reference range (%)	29.7	37.7	46.4	0.14
BMI (kg/m^2)	28.4±6.9	29.3±4.9	26.0±5.7*†	0.003
MAMC (% of standard) *(n =14)*	100.6±16.2	98.7±12.7	93.5±12.2*	0.02
TSF (% of standard) *(n =14)*	108.7±55.4	117.7±54.4	95.8±55.6	0.08
Malnourished, SGA score B or C (%)	21.3	48.1	55.2	<0.0001
Presence of symptom (%)	32.0	66.2	55.2	<0.0001
Energy (kcal/kg IBW/d) *(n =4)*	27.9±6.8	21.2±5.9*	21.8±4.9*	<0.0001
Protein (g/kg IBW/d) *(n =4)*	1.44±0.44	1.07±0.39*	1.01±0.43*	<0.0001

Abbreviation: GFR = glomerular filtration rate; s-alb = serum albumin; BMI = body mass index; MAMC = mid-arm muscle circumference; TSF = triceps skinfold; SGA = subjective global assessment
For the continuous variables:
* *P* <0.05 as compared with the age <65 year group
† *P* <0.05 as compared with the age =65–75 year group
Expression of figures: n±SD–standard deviation

The relationship of demographic, clinical and nutritional parameters between the well-nourished and malnourished groups are summarised in Table 4-7. Patients in the malnourished group were older and had lower GFR, s-albumin and anthropometric measures such as BMI, MAMC and TSF. A significantly higher proportion of these patients experienced symptoms and had reduced intake of protein and energy. However, there was no statistical significance in the presence of co-morbidities except a trend of a higher prevalence of CAD (*P* =0.06) in the malnourished group.

Prevalence of malnutrition (SGA B or C) and presence of symptoms were higher in the older groups, probably due to lower GFR. No statistical difference was observed for serum creatinine and s-albumin among the two groups.

Table 4-7 Subjective global assessment score and demographic, clinical and nutritional parameters

SGA (n =210) *(n missing)*	**A (well-nourished)**	**B & C (mildly to moderately malnourished)**	***P* value**
n (%)	125 (59.5%)	85 (40.5%)	-
Age (year)	62.7±13.8	70.3±12.0	<0.0001
Gender (% male)	58.4%	63.5%	0.46
GFR_{CG} (mL/min/1.73m^2) *(n =1)*	18.8±6.5	14.9±5.7	<0.0001
Serum creatinine (µmol/L) *(n =1)*	0.371±92.9	416.3±151.6	0.008
s-alb (g/L) *(n =1)*	35.1±5.9	33.3±6.0	0.04
s-alb < reference range (%) *(n =1)*	32.0	45.2	0.05
BMI (kg/m^2)	29.3±5.4	26.2±5.6	<0.0001
MAMC (% of standard) *(n =14)*	101.1±14.6	93.3±12.0	<0.0001
TSF (% of standard) *(n =14)*	120.5±58.4	91.5±46.5	<0.0001
Presence of symptom (%)	28.0	84.7	<0.0001
Energy (kcal/kg IBW/d) *(n =5)*	25.7±6.7	20.8±5.6	<0.0001
Protein (g/kg IBW/d) *(n =5)*	1.31±0.43	1.00±0.35	<0.0001
Smoking, positive history (%)	46.6	44.6	0.78
Co-morbidities			
Chronic lung disease (%)	10.4	10.6	0.97
Coronary artery disease (%)	29.6	42.4	0.06
Peripheral vascular disease (%)	16.0	18.8	0.59
Cerebral vascular disease (%)	15.8	15.3	0.77
Diabetes mellitus (%)	36.0	34.1	0.78

Abbreviation: GFR = glomerular filtration rate; s-alb = serum albumin; BMI = body mass index; MAMC = mid-arm muscle circumference; TSF = triceps skinfold; SGA = subjective global assessment
Expression of figures: n±SD–standard deviation

4.5 Discussion

The main goals of nutrition management in ESKD are to maintain optimal nutritional status, to preserve renal function and to achieve therapeutic targets. Findings of the current study indicated that patients presented to the pre-dialysis assessment clinic with high prevalence of suboptimal intake, nutrition abnormalities, malnutrition and parameters indicative of poor nutritional health. The magnitude of these nutritional issues increased as renal function deteriorated.

Our cohort was more advanced in age (65.7±13.6 years) and stages of CKD (mean GFR =17.3±6.5) compared with the majority of previous studies (mean age of 50–55 years and GFR of 20–55 mL/min/1.73m^2 except in one study).[85] In our study, nutritional status deteriorated as renal function decreased, in particular once GFR levels fell below 20 mL/min/1.73m^2; this is in line with the findings in the literature.[12, 85, 165] GFR levels at which symptoms emerged varied enormously among individuals; the prevalence increased dramatically once GFR fell below 15 mL/min/1.73m^2. However, we also found 45% of patients with a GFR of >20 mL/min/1.73m^2 experienced symptoms. Presence of symptoms was found in a patient with a GFR as early as 41.6 mL/min/1.73m^2, while some patients appeared fairly symptom-free with a GFR below 10 mL/min/1.73m^2.

Consistent with the literature,[11, 12, 85, 158, 160, 163, 165] spontaneous DPI decreased as GFR fell, with an average DPI of 1.18±0.42 g/kg IWB/d. The mean EI was comparable to that reported in the literature,[12, 161, 163, 165, 363] with a significant number of our patients consuming less energy than recommended.[205, 206, 310] Despite 76.2% of patients having an EI:REE ratio of less than 1.27 – the Goldberg cut-off indicating possible underreporting as described by other researchers,[163, 359] the suboptimal intake of our patients could largely be explained by the high prevalence of malnutrition accompanied by unintentional weight loss, muscle wasting, high symptom burden and physical inactivity. These observations were supported by a previous finding[112] that lean body mass (LBM), bone mineral content and basal EE were lower in patients with CKD (mean GFR 23.9±2.6 mL/min/1.73m^2) compared with pair-matched controls. This observation is further supported by a study that showed the commonly-used REE equations were found to over-predict REE in CKD patients.[364] Since no inflammatory marker, such as C reactive protein (CRP), was measured, the inflammation state of our patients was not known to interpret its effect on appetite, EI, REE, nutritional status, or its relationship with co-morbidities. Unfortunately, from observation, many of our

patients mistakenly perceived a low EI was an acceptable effect of aging on lower food intake and physical inactivity and failed to recognise the presence of uraemic symptoms. Even more confusing was that in the overweight/obese patients, a reduced intake could be a combination of intentional limiting of EI to control weight and unintentional reduction due to uraemia. Similar to a previous finding,[359] our overweight and obese patients had a significant lower EI than the healthy weight group. Malnutrition within the overweight/obese group was prevalent at 30.5%; this observation could not be ignored as being overweight and malnourished at the start of dialysis has been associated with high mortality risk.[317]

An optimal level of protein in the diet of 0.75–1.00 g/kg IBW/d[205] is recommended for this population to control uraemia and symptoms;[178, 184] most importantly, this must be accompanied by an adequate intake of energy to maintain nitrogen balance.[178, 205, 216] 37.9% of patients met the protein requirements but the majority (90.6%) did not meet energy requirements. On the other hand, 43.7% of patients consumed protein above this level but EI was poor. The undesirable combination of excess protein and low energy intakes has been associated with adverse parameters in patients with advanced CKD.[166, 365]

It appears that the significant protein intake reduction occurred after GFR fell below 20 mL/min/1.73m^2; this is in line with the findings that normalised protein catabolic rate (nPCR) dropped when creatinine clearance (CrCl) fell below 25 mL/min[11] and ended in a dramatic decline when CrCl reached 15 mL/min.[158] It is generally accepted that uraemia causes spontaneous reduction or self-limiting of DPI; however in our cohort, despite a total reduction of total energy or food intake, protein intake remained excessive in 61.2% of patients, even those with reported reduced appetite and symptoms. This could partly be explained by the high habitual protein intake of the average Australian adult as reported in the national dietary survey – almost twice the RDI level of 0.75 g/kg/d.[366, 367] Again, excess protein intake has been associated with

more rapid renal function deterioration and mortality even in early CKD,[368, 369] and increased uraemic toxins.[184] Therefore, timely intervention to optimise dietary intake is recommended.

Both the ADAT 5-point Likert scale appetite score and the combined "good appetite" vs. "reduced appetite" score were found to be useful in ranking energy and protein intake, and were useful in identifying adequate protein intake but not EI (see Section 4.7). These findings suggested subjective rating of appetite is insufficient to reflect adequate intake in a population with a gradual onset of symptoms; thus skilled diet history-taking and structured interview should form an essential part of nutritional assessment.

Abnormal vitamin and mineral status, including retention and deficiency, are common in patients with ESKD,[370, 371] and are associated with increased morbidity and mortality. Examples include low vitamin D levels and increased CVD risk,[372-374] folic acid deficiency relating to anaemia,[375] elevated homocysteine and increased CVD risk,[375] and iron deficiency relating to resistance to recombinant erythropoietin (rHuEPO) to correct anaemia.[376] Despite the "mean" intake of many nutrients appearing satisfactory, a significant percentage of patients did not meet the RDI of these nutrients (Table 4-4). The Lipid Lowering and Onset of Renal Disease (LORD) trial[163] baseline data suggested underreporting was responsible for the low levels of nutrient intake. However, we consider our results close to the true intake as our patients were more advanced in age (65.7±13.6 vs. 60.0±15.0 years) and in later stages of CKD (GFR 17.3±6.5 vs. 40.3±19.4 mL/min/1.73m^2) compared to those in the LORD study, and also had high symptom burden.

Obesity and diabetes in CKD stages 2–5 are strongly associated with hypovitaminosis D;[377] our cohort had high prevalence of obesity and suboptimal vitamin D intake, thus their vitamin D statuses were likely to be poor. However, further study is required to

confirm such deduction with estimates on sunlight exposure and blood vitamin D levels. Consumption of the core foods such as fruit and vegetables, the key contributors of antioxidants, phytochemicals, folates and dietary fibre, were poor in a large number of our patients. Thus, these patients were likely to have elevated levels of oxidative stress due to deficiency of these nutrients and antioxidants.[378] It was challenging to identify the duration and reason of such suboptimal intake, if these were a result of uraemia and/or long-term poor eating habits similar to that reported in national health surveys in the general population.[379, 380] An adequate fruit and vegetable consumption is recommended as it has an alkali-inducing effect that is comparable to sodium bicarbonate in decreasing markers of kidney injury.[381, 382] A high dietary fibre intake has also been associated with reduced risk of inflammation and mortality in patients with CKD.[383, 384] Moreover, the promising results of a prospective randomised study with a Mediterranean diet further convince healthy eating to improve dyslipidaemia, markers of inflammation and lipid peroxidation in stages 1–3 CKD patients.[385] Data collection for vitamin and mineral supplementation was incomplete for discussion. While some of these supplements are necessary to correct certain clinical conditions in ESKD, they cannot replace optimal intake of adequate energy, essential nutrients and food components from diet.

The majority of our patients were on a “free” diet prior to the initial clinic visit and presented with parameters indicative of poor nutritional health. The possible cause was a combination of advancing age, presence of uraemia and other symptoms, poor eating habits and self-induced inappropriate diet regimens. It is a common stigma in the renal community that dietary intervention in CKD implies restriction, which could cause malnutrition. Based on the evidence from the literature and results of the current study, for CKD patients to stay on a “free” diet or “free” from nutrition intervention is unlikely to achieve optimal nutrition; worse, this may even cause a missing diagnosis of

malnutrition and “self-induced” nutrition abnormality in these patients. All these factors will have carry-on effects after dialysis initiation and predict poor outcomes.

Malnutrition is common in this population, with 40.5% of the studied patients rated as malnourished, a result similar to those reported in the literature.[85] Nutrition requirements are indeed altered in ESKD and change over time. Although there is much debate about the timing of initiation and type of nutrition intervention in ESKD, before all the answers from high level of evidence are available, it appears logical to incorporate “healthy eating” explicitly with renal nutrition guidelines and recommendations to improve outcomes. The need for the other traditional and inseparable CKD nutrition management of sodium, potassium, phosphorous and fluid controls was also identified in this study, but was beyond the scope of discussion in this publication.

The main limitation of our study was the lack of data on inflammatory markers, such as CRP, which is known to be closely associated with malnutrition and is a marker of CVD.[74] It is worth noting that CRP did not associate with low fat stores, which in fact reflects poor EI.[164] Once again, this supports optimal EI being needed for optimal body composition.

In summary, this pre-dialysis assessment clinic provided a platform to identify patients at nutritional risk and to initiate nutrition intervention irrespective of future choice of dialysis or conservative care programs. The results of this study also point to the needs for earlier structured intervention to encourage “healthy eating” to prevent, and to manage, the complex nutritional abnormalities found in people with ESKD.

4.6 Conclusions

Patients presented to the current pre-dialysis assessment clinic with a high prevalence of abnormal nutrition parameters, including under- (malnutrition) and over-nutrition

(overweight and obesity), compounded with a dietary intake of undesirable quality and quantity, either voluntarily or involuntarily. While this clinic may provide an opportunity for nutrition intervention pre-dialysis, it appears that earlier referral for nutrition intervention is required. Further studies are needed to gauge how to effectively implement the complex and multifaceted aspects of nutrition management in ESKD.

Practical Application

There is a high prevalence of nutritional abnormalities in non-dialysis ESKD patients. The pre-dialysis assessment clinic provides a platform to assess the nutritional status of ESKD patients and to identify nutritional abnormalities for further intervention well before dialysis is required.

4.7 Supplement to Chapter 4: Evaluation of the self-rated appetite score and adequacy of energy and protein intakes in non-dialysis CKD patients

4.7.1 Introduction

Loss of appetite or anorexia is common in uraemic patients with ESKD,[97, 272] and is multi-factorial.[386] PEW is thought to link to defective central nervous system control of appetite[111] and subsequent reduction in dietary intake. Therefore, assessment of appetite is an essential part of the routine nutrition assessment. Furthermore, in HD patients, self-rating of appetite reflects inflammation state,[95] relates to poor QOL[387] and predicts hospitalisation.[96] Subjective assessment of appetite using the ADAT with a 5-point Likert scale has been used to screen patients for suboptimal intake and it also predicted the hospitalisation rate in patients on maintenance dialysis.[96, 238] The usefulness of this tool in non-dialysis CKD patients to measure adequacy of protein and energy intakes has yet to be examined.

4.7.2 Aim

The aim of this study was to examine the relationship between self-rated appetite score, and intake of energy and protein in a cohort of ESKD patients attending a pre-dialysis assessment clinic. We hypothesised that appetite score is effective in reflecting adequacy of energy and protein intakes.

4.7.3 Methods

This was a retrospective analysis of data from the nutrition assessment records of patients who attended the pre-dialysis assessment clinic (Chapter 4). As part of the routine nutrition assessment, patients were asked to rate their appetite according to the ADAT with a 5-point Likert scale:

Question: Overall, how would you describe your appetite?

(1) Very good
(2) Good
(3) Fair
(4) Poor
(5) Very poor

Dietary intake of patients was assessed by the dietitian(s) using a structured diet history method[242-244] which had been validated in a small sample of non-dialysis CKD patients.[245] In term of the interview structure of assessing dietary intake, the structured diet history method is similar to the 24-hour recall method, but it also takes into account the frequency of food consumption and food patterns. In our practice, patients were asked to give a detailed history of a "typical day's intake" of the week (last 7 days) with prompting, and assisted by measuring devices such as metric measuring cups and spoons and pictures showing food portion sizes. Of the 210 patients assessed, 206 patients had reliable diet intake records available for analysis. Subsequently, the diet history was analysed using a nutrients analysis software program (FoodWorks Professional Model 2009, Xyris, Brisbane, Australia) to estimate EI and DPI. In

addition, for easy comparison, appetite scores were grouped as (1) + (2) = “good” and (3) + (4) + (5) = “reduced appetite”. Fair appetite = (3) was grouped into “reduced appetite” as the patients’ usual appetite had been compromised. Energy and protein intake ≥25 kcal/kg IBW/d[310] and ≥0.75g/kg IBW/d[205] were considered to be adequate. The PPV of the appetite score in relation to the mean intakes of energy and protein were examined.

Statistical analyses included analysis of variance (ANOVA), *t*-tests and calculation of PPV using the 2x2 contingency table.[315] *P* values <0.05 were as considered to be statistically significant.

4.7.4 Results

As shown in Table 4-8, the appetite score was found useful in ranking both the EI and DPI. Patients’ self-rating of appetite according to the 5-point Likert scale – (1) Very good, (2) Good, (3) Fair, (4) Poor and (5) Very poor, correlated with an EI of 25.4±6.0, 24.2±6.8, 22.0±6.8, 19.4±6.2 and 14.9±1.8 kcal/kg IBW/d (*P* =0.002) respectively. The same applied for protein intake of 1.32±0.36, 1.17±0.45, 1.13±0.44, 0.86±0.25 and 0.57±0.18 g/kg IBW/d (*P* =0.001) respectively. The 5-point Likert scale correlated the incremental changes of both energy and protein intakes. For the combined scores of “good” and “reduced” appetite for protein and energy intakes, the rating showed statistical difference between the energy and protein intake of 24.7±6.5 vs. 21.2±6.7 kcal/ kg IBW/d (*P* =0.001) and 1.24±0.42 vs. 1.06±0.42g/kg IBW/d (*P* =0.006) respectively.

Table 4-8 Appetite score and intake of energy and protein

Appetite score (% of patients)	**1 Very good** (31.0%)	**2 Good** (39.0%)	**3 Fair** (23.3%)	**4 Poor** (5.7%)	**5 Very poor** (1.0%)	***P* value**
Energy intake (kcal/kg IBW/d)	25.4±6.0	24.2±6.8	22.0±6.8	19.4±6.2	14.9±1.8	0.002
Protein intake (g/kg IWB/d)	1.32±0.36	1.17±0.45	1.13±0.44	0.86±0.25	0.57±0.18	0.001
Combined appetite score	**Good** (70.0%)		**Reduced** (30.0%)			
Energy intake (kcal/kg IBW/d)	24.7±6.5		21.2±6.7			0.001
Protein intake (g/kg IWB/d)	1.24±0.42		1.06±0.42			0.006

Expression of figures: n±SD–standard deviation

When the PPVs were examined (Tables 4-9 and 4-10), the PPV of appetite score for EI was 0.41, which reflects 41% of patients rated a “good appetite” and consumed adequate energy, while the remainder (59%) rated “good appetite” but did not consume adequate energy. The PPV for protein intake was 0.92 reflecting 92% of patients rated a “good appetite” and consumed adequate protein and the remainder (8%) rated “good appetite” but did not consume adequate protein.

Table 4-9 Positive predictive value of appetite score for energy intake

		Energy intake*		**Total**
		Adequate	Inadequate	
Appetite	Good	59	85	144
	Reduced	18	44	62
	Total	77	129	206

* EI ≥25 kcal/kg IBW/d was considered to be adequate[310]

PPV = outcome occurred/total number of subjects tested

=59/144

=0.41 (95% CI: 0.36–0.45)

Table 4-10 Positive predictive value of appetite score for protein intake

		Protein intake*		**Total**
		Adequate	Inadequate	
Appetite	Good	132	12	144
	Reduced	48	14	62
	Total	180	26	206

* Protein intake ≥0.75 g/kg IBW/kg was considered to be adequate[205]

PPV = outcome occurred/total number of subjects tested

=132/144

=0.92 (95% CI: 0.88–0.95)

In summary, the ADAT, with a 5-point Likert scale, and the combined appetite score were found to be useful in ranking both energy and protein intakes with incremental changes. However, the appetite score was not useful in identifying adequate EI, whereas it was satisfactory in identifying adequate protein intake.

4.7.5 Discussion

Our results indicated the ADAT, with a 5-point Likert scale, was useful in ranking the intake of energy and protein; this is in line with the findings of a previous study with patients on HD.[96] In the current study with pre-dialysis CKD patients, despite the self-rated appetite scores being useful in ranking energy and protein intakes, the scores rated by patients were only related to adequate protein but not EI. A possible explanation is that the average Australian consumes more protein than recommended,[366, 367] so a "reduced" protein intake in uraemic patients could still be adequate or in excess, but this is not the same for total EI. During the gradual decline of kidney function, patients often fail to recognise the onset of uraemic symptoms, and may confuse a reduced appetite and decreased dietary intake with the effects of aging, especially in elderly patients. The possibility of underreporting of EI was discussed in the body of Chapter 4. The diet interview or structured diet history used in the current study was validated against other dietary methods such as a 3–7 day food record.[243, 245] It is known that many diet estimation methods underestimate EI by approximately 20% when compared to the estimated EE in the non-renal disease population.[243] For reasons previously explained, a number of factors, including altered EE in uraemia, loss of muscle mass, high symptom burden, self-imposed dietary restriction and low PA level, all could contribute to the suboptimal EI in our patients.

Based on our findings, in studies using a self-rated appetite in patients with stage 5 pre-dialysis ESKD (mean GFR 7±2 mL/min/m^2) and on a HD program (dialysis vintage 12±2 months), it was not surprising to see results that poor appetite rating (as part of the subjective global assessment component) was not associated with mortality risk in the 12-month follow up.[388] This was possibly explained in the nature of subjective rating, which does not necessarily reflect actual dietary intake and duration. In addition, any subsequent nutrition intervention or changes in clinical conditions that may affect mortality were not considered in the analyses. Interestingly, not all patients' appetite rating improved after dialysis started; and some even got worse. Furthermore, in the pre-dialysis ESKD group, even though the good appetite group had a significantly lower level of CRP compared to the poor appetite group, 3.1 (1.4–9.5) vs. 6.0 (2.2–15.5) mg/L, *P* <0.05, the prevalence of malnutrition was the same, at 50% in both groups. Contrary to previous findings, poor appetite and high CRP levels did not predict mortality risk.[95] Again, the actual intake of energy and protein[15] and nutritional status[15, 346, 348] appear to be more superior to appetite rating alone in predicting mortality risk. The cause of poor appetite could be multifactorial in patients with CKD, such as uraemia and/or inflammation,[97, 386] which could explain the inconsistent findings. 62.4% of our patients were overweight or obese, so perhaps some of these patients had reduced total caloric intake in an attempt to lose weight. However, EI intake <25 kcal/kg IBW/d was still considered to be inadequate.[178, 310] In our pre-dialysis cohort, 23.0% patients reported poor appetite but still consumed higher than RDI levels of protein (0.75g/kgIBW/d),[176] and possibly accumulated high levels of uraemic toxins while EI remained poor.

To our knowledge, no previous study has analysed the PPVs of appetite score and dietary intakes of energy and protein in patients with non-dialysis CKD.

4.7.6 Conclusions

While the self-rated appetite scores were useful in ranking energy and protein intakes, subjective reporting of a good appetite was likely to associate with adequate protein intake but not EI. This means a self-rated “good appetite” does not always equate to adequate intake in non-dialysis ESKD patients with high levels of uraemic complications. Therefore skilled dietary assessment by a dietitian should form part of the routine care for managing patients with ESKD.

Implications for clinical practice:

Self-rated “good” appetite score does not necessary reflect adequate energy or protein intake. Therefore, dietary intake assessment by a dietitian should form part of the routine nutrition care in patients with ESKD.

Chapter 5 Nutritional Characteristics of Patients at Enrolment to the Pre-Dialysis Assessment Clinic over a Ten-Year Study Period

This chapter is written in a format intended for submission to the *Journal of Renal Nutrition*, the official journal of the Council on Renal Nutrition of the National Kidney Foundation, USA.

Title: The change in nutrition profile and preference for renal replacement therapy of patients at enrolment to the multidisciplinary pre-dialysis assessment clinic between 2002–2012.

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Abstract

Aim: Pre-dialysis management is important for the timely management of patients with end stage kidney disease (ESKD). We investigated the trend of clinical and nutritional characteristics of patients enrolled in a pre-dialysis assessment clinic of our renal unit over a 10-year study period.

Methods: Data were extracted for analysis from the clinical and nutrition records of patients at enrolment to the pre-dialysis clinic from April 2002 to March 2012. Parameters included: demographics, such as age and gender; co-morbidities; and nutritional data, including body mass index (BMI), serum albumin (s-albumin) and subjective global assessment (SGA). Data were also divided into two 5-year periods for comparison, namely April 2002 to March 2017 vs. April 2007 to March 2012.

Results: Records of 501 patients were examined. The mean age was 66.0±14.7 years with a mean glomerular filtration rate (GFR) of 20.2±8.6 mL/min/1.73m^2, and 60.1% were male. 40.1% of patients were rated as overweight and 41.1% were malnourished. When comparing the two study periods, patients were enrolled to the clinic at an earlier point in the latter period, with a higher GFR: 16.7±6.7 vs. 22.1±9.1 mL/min/1.73m^2 (*P* <0.0001). The prevalence of obesity and diabetes were significantly higher in the second study period, being 32.0% vs. 44.7% (*P* =0.01) and 33.0% vs. 51.4% (*P* <0.0001) respectively. However, the malnutrition rate scored by SGA remained high at 39.7% vs. 42.0% (*P* =0.64), despite earlier referral. Patients who preferred a conservative or no-dialysis pathway were significantly more advanced in age (77.3 vs. 63.9 years, *P* <0.0001) and with a higher prevalence of malnutrition (64.6 vs. 36.8%, *P* <0.0001).

Conclusions: A significant increase in the prevalence of obesity and diabetes over the 10-year study period was observed. There was no significant difference in the

prevalence of malnutrition, which remained high despite an increase in patients who were enrolled at a high level of GFR.

5.1 Introduction

Chronic kidney disease (CKD) has reached epidemic proportions in Australia[4-6] and worldwide.[1, 2] Approximately 11.4% of the Australian population has stage 3 to 5 CKD with a dramatic increase in the incidence of end stage kidney disease (ESKD) (GFR <15 mL/min/1.73m^2) due to an aging population and growing prevalence of diabetes.[6, 389, 390] ESKD imposes a tremendous clinical and societal burden and is associated with high morbidity, mortality and hospitalisation. Inevitably many people with CKD progress to ESKD and require dialysis to sustain life. There is ample evidence showing that malnutrition and other nutrition abnormalities present at the initiation of dialysis are associated with adverse outcomes.[13-15, 346, 348] Furthermore, the benefits of elderly patients and patients with a high number of co-morbidities commencing dialysis programs have been questionable.[16] In light of these findings, a multidisciplinary and multifaceted pre-dialysis program, including nutrition assessment and education, may provide a platform to identify patients for early intervention,[260] such as those at nutritional risk, including malnutrition and overweight/obesity. The majority of nutritional studies in patients with ESKD have been focused on those who have already participated in a renal replacement program (RRT), namely dialysis and transplantation; limited information is available regarding patients in the pre-dialysis stage.

The prevalence trend of various clinical parameters in stage 4 to 5 non-dialysis CKD patients over time has seldom been studied; in particular, to see if it mirrors the trend of obesity[124, 125] and diabetic epidemics[391] globally and those reported in the Australian Diabetes, Obesity and Lifestyle Study (AusDiab).[389, 392] This knowledge is very important as obesity and diabetes mellitus (DM) are linked to disease progression and

cardiovascular disease,[29] and cause premature mortality in patients with ESKD.[393] Tto evaluate current practices and to formulate strategic planning of a future pre-dialysis assessment clinic, it is useful to know the trends of clinical and nutrition characteristics of people enrolled in a pre-dialysis assessment clinic over time. Another important question is, as the clinic structure has evolved over time, have patients been referred earlier? If that is the case, was the prevalence of nutrition abnormalities lower?

5.2 Aim

The aim of this study was to examine the prevalence and trend of various demographic, clinical and nutritional characteristics of ESKD patients at enrolment in an outpatient pre-dialysis clinic over a 10-year study period from April 2002 to March 2012. Comparison of these parameters were made over two 5-year periods, namely from April 2002 to March 2007 and from April 2007 to March 2012. There was a particular focus on age and the levels of GFR at which patients were referred, as well as the prevalence of nutrition and related abnormalities, such as obesity and malnutrition. In addition, the relationship of these parameters and the initial choice of RRT or conservative care by patients was also examined.

5.3 Methods

This retrospective study examined clinical and nutrition records of all patients enrolled in the multidisciplinary outpatient pre-dialysis assessment clinic at the St. George Hospital, Sydney, Australia established in April 2002 and continuing through to March 2012. Patients referred by nephrologists to this clinic were predominantly in CKD stages 4 and 5 (GFR <30 mL/min/1.73m^2). As part of routine care, patients and their carers were seen by a clinical nurse consultant, pharmacist, social worker and dietitian for discipline-specific assessment and education. Patients excluded from analysis were those who were referred to the pre-dialysis assessment team during acute hospital admission and expected to start dialysis within the next 1–2 months, and those missed

the assessment by the dietitian due to reasons such as dietitian was not available to the clinic session, or patients were unable to be properly assessed due to language barrier and patient's lack of interest for nutrition assessment etc

Demographic, clinical and nutritional data collected were: age; gender; race; smoking habits; and presence of co-morbidities, such as coronary artery disease (CAD), cerebral vascular disease (CVD), DM, chronic lung disease (CLD) or peripheral vascular disease (PVD). Ex- and current smokers were combined as having a positive smoking history while the presence of co-morbidity as "yes" or "suspected" were combined as "presence of" for analysis.

Nutritional data included for analyses included anthropometric measures, e.g., height (m), oedema-free body weight (kg), BMI [weight÷height^2 (kg/m^2)] and weight history. The clinical practice guidelines[205] defined a healthy weight range as a BMI of 22–26 kg/m^2; therefore a BMI ≥26 kg/m^2 was treated as overweight. Prevalence of renal-specific BMI categories[205, 310] were also examined with undernourished, ideal range, overweight and obese defined as BMI <23, 23–26, 26–30 and >30 kg/m^2 respectively. Pathology results included serum-albumin (s-albumin) and serum creatinine; GFR was calculated using the Cockcroft-Gault equation.[300] Approximately 50% of the blood tests were analysed by private providers instead of the hospital-based laboratory; thus, different analytical methods for s-albumin and reference range. Therefore, for s-albumin levels, both actual figures and whether they were below or within reference range were also recorded for analysis. The renal dietitian(s) (mainly the author MC) also performed the subjective global assessment (SGA),[149] which categorises patients as A = well nourished, B = mild-moderately and C = severely malnourished based on the patient's medical history and physical examination. The combined score of B or C was used as "malnourished". The prevalence of combined malnutrition (classified by SGA score B and C) and BMI (<26 kg/m^2 vs. ≥26 kg/m^2) was also examined. The

difference of these parameters over the two 5-year periods, namely from April 2002 to March 2007 and from April 2003 to March 2012, were compared to examine the trend of patient characteristics over time. All patients were seen by the clinical nurse consultant for options regarding a future RRT program or to be maintained on a conservative pathway. Relationships between nutrition factors and "initial" treatment option, such as dialysis modality or conservative care pathway, were also explored.

All tests were performed using the statistical software IBM© SPSS© Statistics version 20. Continuous variables were expressed as mean ± standard deviation for normally distributed data. Comparisons between groups were performed using unpaired sample *t*-tests, whereas categorical variables were compared using the χ^2 test. *P* values <0.05 were regarded as statistically significant.

The study was approved by the ethics committee of the South Eastern Sydney and Illawarra Area Health Service, NSW, Australia.

5.4 Results

A total of 552 patients were referred to the pre-dialysis assessment team for education during the study period. Of these, 520 attended the outpatient pre-dialysis assessment clinic and data for 501 patients were available for inclusion in analyses. The demographics and co-morbidities are summarised in Table 5-1, and Table 5-2 summaries the clinical and nutritional parameters.

Our cohort consisted of 60.1% male patients with a mean age of 66.0±14.7 years; mean GFR was 20.2±8.6 mL/min/1.73m^2. The leading cause of ESKD was diabetic nephropathy (28.7%), followed by renovascular disease/hypertensive nephrosclerosis (19.6%), chronic glomerulonephritis (13.2%), IgA nephropathy (7.2%), adult polycystic kidney disease (5.8%), reflux nephropathy/congenital abnormality (3.8%), analgesic nephropathy (2.4%) and other miscellaneous causes (19.6%). There was no statistical

difference between male and female patients for all demographic and co-morbidity data, except men had a significantly higher prevalence of positive smoking history than women (56.2% vs. 31.0%, χ^2 =24.4, *P* <0.0001) and presence of CAD (37.0% vs. 28.0%, χ^2 =4.4, *P* =0.04).

Table 5-1 Demographic data and co-morbidities

Parameters	**All n =501 *(n missing)***	**Male n =301 (60.1%)**	**Female n =200 (39.9%)**	***P* value**
Age (year)	66.0±14.7	66.7±14.4	65.0±15.1	0.22
Age >65 years (%)	62.1	62.8	61.0	0.69
Age >75 years (%)	30.7	33.2	27.0	0.14
Race (% Caucasian)	80.8	80.4	81.5	0.76
Smoking (% positive history)	46.2 *(n =103)*	56.2	31.0	<0.0001
Co-morbidities				
Chronic lung disease (%)	10.4 *(n =3)*	8.7	13.1	0.11
Coronary artery disease (%)	33.4 *(n =1)*	37.0	28.0	0.04
Peripheral vascular disease (%)	17.2 *(n =2)*	18.7	15.1	0.30
Cerebral vascular disease (%)	14.8 *(n =2)*	15.3	14.1	0.70
Diabetes mellitus (%)	44.9	47.2	41.5	0.21

Expression of figures: n±SD–standard deviation

The BMI distribution was 15.7%, 18.4%, 26.2% and 39.7% for underweight (BMI <23 kg/m^2), healthy weight range (BMI 23–26 kg/m^2), overweight (BMI 26–30 kg/m^2) and obese (BMI ≥30 kg/m^2) respectively. The prevalence of CAD was higher in the overweight/obese (BMI ≥26 kg/m^2) group than the BMI <26 kg/m^2 group (38.1% vs. 23.6%, χ^2 =10.2, *P* =0.001). Similarly, this applied to the prevalence of DM (52.8% vs. 28.9%, χ^2 =25.2, *P* <0.0001). When the relationships of obesity (BMI >30 kg/m^2) and CAD or DM were examined, prominent effects continued to apply with 39.2% vs. 29.1%, χ^2 =5.4, *P* =0.02 and 60.8% vs. 33.8%, χ^2 =34.4, *P* <0.0001, respectively, compared with the non-obese (BMI ≤30 kg/m^2) patients.

A high prevalence of malnutrition was observed in 41.1% of the whole cohort. 20.0% and 11.0% of patients were classified as malnourished and overweight (BMI >26 kg/m^2), and malnourished and obese (BMI >30 kg/m^2) respectively. Within the malnourished group, 48.9% of patients were overweight/obese (BMI >26 kg/m^2) and within the overweight/obese group, 30.4% were malnourished. More women were rated as malnourished compared to men (47.2% vs. 36.9%, χ^2 =4.5, *P* =0.04), and there was also a trend of higher prevalence of combined malnutrition and overweight/obese (24.4% vs. 17.1%, χ^2 =3.5, *P* =0.06).

Table 5-2 Clinical and nutritional parameters

Parameters	**All n =501 *(n missing)***	**Male n =301 (60.1%)**	**Female n =200 (39.9%)**	***P* value**
Serum creatinine (μmol/L)	0.346±0.121 *(n =2)*	0.364±0.123	0.318±0.115	<0.0001
GFR_{CG} (mL/min/1.73m^2)	20.2±8.6 *(n =18)*	20.0±8.8	20.3±8.4	0.47
CKD stages, 2:3:4:5 (%)	1:12:58:29 *(n =18)*	1:10:59:30	0:14:57:29	0.37
Nutritional parameters				
Serum albumin (g/L)	35.2±6.4 *(n =11)*	35.4±6.4	35.3±6.6	0.31
Serum albumin < reference range (%)	32.4 *(n =11)*	29.7	36.6	0.11
BMI (kg/m^2)	29.1±6.5 *(n =17)*	28.8±5.9	29.4±7.3	0.40
BMI <23 kg/m^2, underweight (%)	13.7 *(n =17)*	18.7	15.7	0.15
BMI >26 kg/m^2, overweight/obese (%)	65.6 *(n =17)*	65.8	65.7	0.97
BMI >30 kg/m^2, obese (%)	40.1 *(n =17)*	41.2	38.3	0.53
Malnutrition (SGA B or C)	41.1 *(n =62)*	36.9	47.2	0.04
Malnourished + BMI >26 kg/m^2 (%)	20.0 *(n =62)*	17.1	24.4	0.06
Malnourished + BMI >30 kg/m^2 (%)	11.0 *(n =62)*	9.2	13.6	0.14

n = total sample size; n missing = missing data, Expression of figures: n±SD–standard deviation

The total number of patients (n =325) who attended in the second 5-year period was almost twice the number of the first period (n =176), reflecting the increased demand of services (Table 5-3). Over the 10-year study period, patients enrolled to the clinic

earlier or at higher levels of GFR, with a significant increase of GFR: 16.7±6.7 vs. 22.1±9.1 mL/min/1.73m^2, *P* <0.0001 from the first to second 5-year period (Figure 5-1). The latter period also had fewer patients in CKD stage 5 (41.4% vs. 23%, χ^2 =18.1, *P* <0.0001). There was no significant change in mean age of patients with predominately elderly patients older than 65 years of age across the two periods. There was a significant increase in the number and prevalence of patients with diabetic nephropathy (20.5% vs. 33.2%, χ^2 =9.1, *P* =0.003) that corresponded to an increase in the prevalence of DM (33.0% vs. 51.4%, χ^2 =15.7, *P* <0.0001). Despite the number of patients with glomerulonephritis remaining constant, it became less prevalent in the second period (18.8% vs. 10.2%, χ^2 =7.4, *P* =0.007), due the growth of patients with diabetic nephropathy. Figure 5-2 shows the prevalence of diabetes, obesity and malnutrition over the two 5-year study periods. While the prevalence of overweight/obesity (BMI >26.0 kg/m^2) appeared stable (*P* =0.16), the prevalence of obesity increased enormously (32.0% vs. 44.7%, χ^2 =7.5, *P* =0.01). The prevalence of obesity-related causes of ESKD, such as diabetic nephropathy, increased significantly over the two study periods, whereas renovascular disease/hypertensive nephrosclerosis remained similar (*P* =0.31). Despite patients being enrolled in the clinic earlier, the prevalence of malnutrition remained high (39.7% vs. 42.0%, *P* =0.64). Although there was no statistical difference between the prevalence of malnutrition among the two periods, the total number of patients rated as malnourished increased substantially (n =174 vs. 265) due to the increase in clinic enrolment (Figure 5-2).

Table 5-3 Comparison of demographic, clinical and nutritional parameters over the two 5-year study periods

Parameters *(n missing)*	**Time period** *(data available per parameter)*		***P* value**
	April 2002 to March 2007	**April 2007 to March 2012**	
Number	n =176	n =325	
Demographics			
Age (year)	65.2±13.8	66.4±15.2	0.39
Gender (% male)	61.9	59.1	0.53
Race(% Caucasian)	84.1	79.1	0.17
Clinical and co-morbidities			
Serum creatinine (μmol/L) *(n =2)*	0.399±0.125	0.318±0.111	<0.0001
GFR_{CG} (mL/min/1.73m^2) *(n =18)*	16.7±6.7	22.1±9.1	<0.0001
CKD stage 5 (%) *(n =18)*	41.4	23.0	<0.0001
Smoking, positive history (%) *(n =103)*	55.4	52.7%	0.60
Coronary artery disease (%) *(n =1)*	36.6	31.7	0.27
Diabetes mellitus (%)	33.0	51.4	<0.0001
Cause of ESKD			
Chronic glomerulonephritis (%)	18.8	10.2	0.007
Diabetic nephropathy (%)	20.5	33.2	0.003
Renovascular disease/ hypertensive nephrosclerosis (%)	21.6	17.8	0.31
Nutritional parameters			
s-albumin (g/L) *(n =11)*	34.5±5.9	35.5±6.6	0.10
s-albumin < reference range (%) *(n =11)*	37.4	29.7	0.09
BMI (kg/m^2) *(n =17)*	28.1±5.9	29.6±6.8	0.01
BMI <23 kg/m^2 (%) *(n =17)*	17.7	14.6	0.36
BMI >26 kg/m^2 (%) *(n =17)*	61.7	68.0	0.16
BMI >30 kg/m^2 (%) *(n =17)*	32.0	44.7	0.01
Malnutrition (SGA B or C) (%) *(n =61)*	39.7	42.0	0.64

n =total data available per parameter
Expression of figures: n±SD–standard deviation
Remark: Chinese (6.0%), Egyptian (1.7%), Indian (2.2%), Maori / New Zealander (2.2%), Pilipino (0.9%), Others (1.3%)

Figure 5-1 The trend of patients' GFR levels at enrolment in the pre-dialysis assessment clinic over the 10-year study period

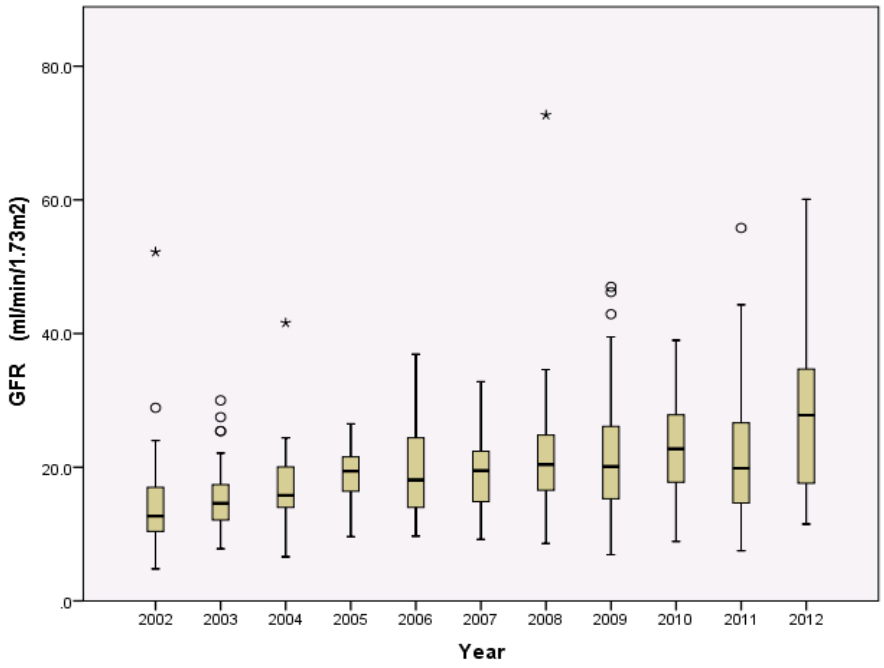

Figure 5-2 Comparison of the prevalence of diabetes, obesity and malnutrition over the two 5-year study periods

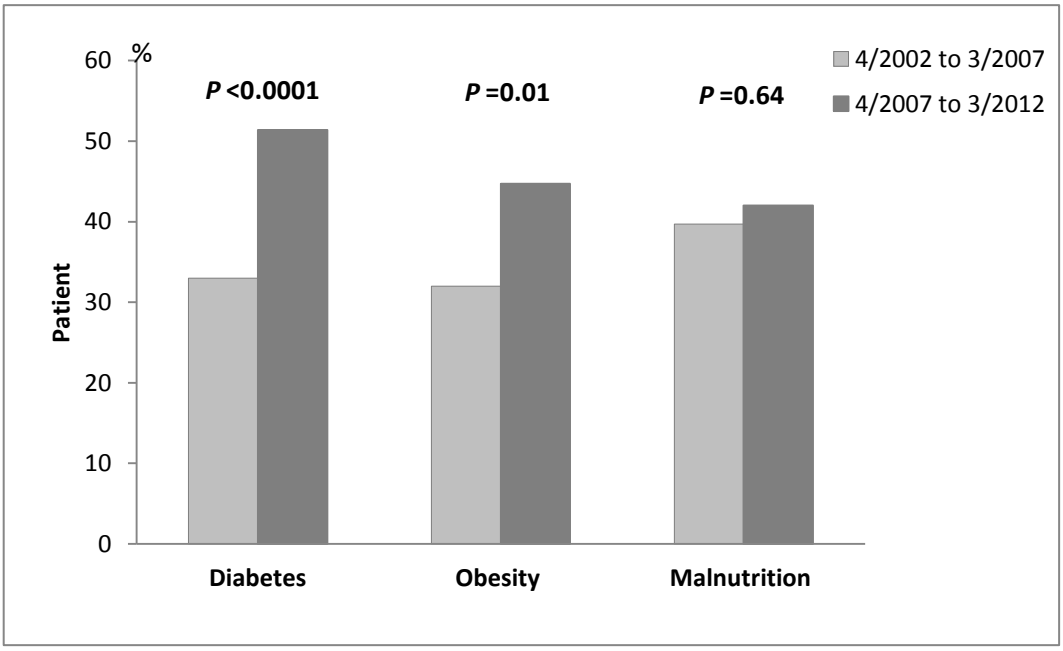

Table 5-4 Comparison of patients' initial choice for future RRT treatment over the two 5-year study periods

Study period / Treatment		% total n =501	4/2002 to 3/2007 (n =176)	4/2007 to 3/2012 (n =325)	χ^2	*P* value*
Non-RRT		14.8	15.3	14.5	0.07	0.79
RRT	PD (home)	47.7	39.2	52.3	7.9	0.01
	HD (Home)	13.6	21.0	9.5	12.8	<0.0001
	HD (hospital)	18,2	19.3	17.6	0.24	0.62
	Early TP	3.8	3.4	4.0	0.11	0.74
Others (unsure)		1.9	1.8	2.2	0.12	0.73

* *P* value between the two 5-year study periods of 4/2002 to 3/2007 and 8.2007 to 3/2012
Abbreviation: RRT = renal replacement therapy; PD = peritoneal dialysis; HD = haemodialysis; TP = transplant

Table 5-4 shows that preferences for the future treatment options changed significantly over time (*P* =0.008). A preference for home dialysis therapy – namely PD and home HD – remained high, with PD becoming the first choice, increasing from 39.2% in the first period to 52.3% in second period (*P* <0.01). This was accompanied by a downward shift of preference to home HD, decreasing from 21.0% to 9.5% (*P* <0.0001).

The proportion of patients preferring a conservative or no-RRT pathway remained stable (15.3% vs. 14.5%). This conservative group of patients, when compared to all other patients combined, were older (77.3±7.0 vs. 63.9±14.7 years, *P* <0.0001), had lower levels of GFR (17.5±8.3 vs. 20.7±8.6 mL/min/1.73m^2, *P* =0.004) and a higher prevalence of malnutrition (64.6% vs. 39.6%, χ^2 =17.6, *P* <0.0001).

Within the whole cohort, there was no statistical difference for the stages of CKD, comorbidities, s-albumin or BMI (Table 5-5). Among the patients who chose to start

dialysis, patients who preferred hospital dialysis (HD) were older (68.7±11.5 vs. 64.0±14.2 years, *P* <0.0001), had a higher prevalence of CAD (49.5% vs. 29.0%, χ^2=13.2, *P* <0.0001), DM (60.4% vs. 42.0%, χ^2 =9.6, *P*=0.003), and malnutrition (52.1% vs. 32.7%, χ^2 =9.0, *P* =0.003) compared to those preferred home dialysis (PD and HD). The two most elderly groups were those preferred conservative pathway and hospital dialysis, apart from age (77.3±7.0 vs. 68.6±11.5 years, *P* <0.0001) and BMI (28.1±5.9 vs. 30.3±6.8 kg/m^2, *P* =0.04), there was no statistical difference for all other variables including the high prevalence of malnutrition (51.2 % vs. 64.6%, χ^2 =2.6, *P* =0.11).

In summary, the total number of patients enrolled in the clinic almost doubled over the two 5-year observation periods. Diabetic nephropathy remained the leading cause of ESKD with an increase in prevalence over time. Prevalence of obesity and diabetes increased significantly during the study period, whereas the prevalence of malnutrition remained constant but with an increase in total number reflecting larger numbers enrolled in the clinic in the second period. Demographic and nutritional parameters were found to be closely associated with the patients' choice of treatment options, with patients who preferred a conservative pathway (or no-RRT) being more advanced in age with a higher prevalence of malnutrition; this pattern is closely followed by those opting for a hospital dialysis program.

Table 5-5 Demographic, clinical and nutritional factors associated with future choice of RRT or conservative care (no-RRT)

n =501 *(n missing)*	No-RRT	Renal replacement program (RRT)				Others (unsure)	*P* value*
		PD	Home HD	Hospital HD	Early TP		
n (% total)	74 (14.8)	239 (47.7)	68 (13.6)	91 (18.2)	19 (3.8)	10 (1.9)	-
Age (yr)	77.3±7.0†	65.6±14.3	58.6±12.7	68.6±11.5	41.1±16.3	68.3±14.7	n/a
Age >65 yr (%)	91.9†	61.5	32.4	73.6	5.3	60.0	<0.0001
Age >75 yr (%)	71.6†	27.2	5.9	28.6	0.0	60.0	<0.0001
Gender (% male)	55.4	63.6	61.8	54.9	47.4	70.0	0.46
Creatinine (µmol/L) *(n =2)*	0.351±0.125	0.349±0.130	0.357±0.115	0.338±0.109	0.304±0.100	0.336±0.115	n/a
GFR (mL/min/1.73m^2) *(n =18)*	17.5±8.4‡	20.3±8.8	21.2±6.6	19.7±7.2	29.7±13.1	18.9±7.6	n/a
CKD stage 5 (%) *(n =18)*	42.3	30.3	16.4	29.9	11.1	44.4	0.01
CAD (%) *(n =18)*	35.6	32.2	17.6	49.5	10.5	50	<0.0001
DM (%)	47.3	46.4	26.5	60.4	10.5	40	<0.0001
BMI (kg/m^2) *(n =18)*	28.1±5.9	28.7±6.1	30.1±8.3	30.2±6.8	29.2±6.0	27.0±4.9	n/a
s-alb (g/L) *(n =17)*	34.5±6.6	35.1±6.7	36.8±5.6	33.9±6.5	37.4±4.8	36.4±5.8	n/a
s-alb < ref. (%) *(n =17)*	37.5	31.3	25.4	40.0	15.8	33.3	0.20
Malnourished (%) *(n =62)*	64.6*	34.3	27.7	51.9	33.3	42.9	<0.0001

Abbreviation: GFR = glomerular filtration rate in mL/min/1.73m^2; s-alb = serum albumin
no-RRT group vs. the combined RRT group (PD + home HD, Hospital PD and early transplant)
**P* value for categorical variables, †*P* <0.0001, ‡*P*=0.004
Expression of figures: n±SD–standard deviation

5.5 Discussion

The current study indicated a substantial growth of enrolment of ESKD patients to the pre-dialysis assessment clinic over a 10-year study period. This reflected the increased need of patients considering dialysis over time in our unit similar to the national Australian statistics.[4, 5] As the clinic became more established, patients were referred by nephrologists significantly earlier or at higher levels of GFR. Even though the mean age at enrolment remained fairly stable at 66.0±14.7 years, there was a significant growth of patients with obesity and diabetes, which paralleled the global obesity epidemic.[124, 125] These trends were also associated with an increase in the prevalence of diabetic nephropathy, which remained the leading cause of ESKD in our cohort. These observations were in agreement with analysis of the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) data, that diabetic nephropathy accounted for a substantial increase in incident dialysis patients between 1990 and 2009.[394] The mean GFR of those incident dialysis patients was 8.2 mL/min1.73m^2 while patients enrolled in our pre-dialysis clinic had a mean GFR of 20.2±8.6 mL/min/1.73m^2, that reflected similar characteristics well before dialysis was required.

Overweight and obese patients have metabolic derangements that compound on the effect of uraemia and related complications to accelerate disease progression,[138, 393] and cardiovascular events.[29] The substantial growth of patients with obesity may also lead to high prevalence of obese patients starting dialysis, and subsequently transplantation, similar to a study from the United States.[395] Although there have been many debates on the “obesity paradox”,[128, 129] which supports the survival advantage of obesity in dialysis patients, other research has found obesity was associated with high mortality risk.[133] In light of the negative effects of obesity on disease progression and cardiovascular events in the pre-dialysis stage, structured weight reduction intervention through diet[207, 396, 397] and exercise[398, 399] should be considered to optimise body weight

and body composition. Indeed, muscle mass has been reported to be the main determinant of survival over BMI alone in dialysis patients.[15, 143, 351, 356]

Despite patients being referred to the clinic earlier or at higher levels of GFR by the nephrologists over time, the prevalence of malnutrition remained stable and high at 41.4% in the second period. Malnutrition at initiation of dialysis is an independent predictor of mortality, morbidity and hospitalisation,[13, 14, 156, 317, 346, 348] and the same applies to non-dialysis CKD patients well before dialysis is required.[98] In our cohort, approximately 20.0% of patients were rated as malnourished and overweight (SGA B and C + BMI ≥26 kg/m^2); such observation at the initiation of dialysis has been shown to associate with high mortality risk compared to other patients.[317] Early structured nutrition intervention to malnourished patients, with or without presence of overweight/obesity, should be implemented before dialysis starts.[363] A recent observational study revealed pre-dialysis dietitian care for more than 12 months independently associated with higher s-albumin and lower total cholesterol levels at the start of dialysis; and lower 1-year mortality after initiation of dialysis.[400] In view of the complex nutrition requirements of ESKD patients, early nutrition intervention is recommended.

A Canadian study reported that timely referral of patients at CKD stage 4 to the multidisciplinary renal management clinic (RMC) resulted in significant non-progression or improved renal function, leading to delayed initiation of dialysis compared to those referred late in stage 5.[264] Similar advantages of multidisciplinary pre-dialysis programs were also reported elsewhere.[262, 263, 265, 267] The major outcome of our clinic was that enrolling patients in the clinic at an earlier stage of CKD or higher GFR may provide a window of opportunity to improve outcomes. The structure of our clinic was different from the Canadian and other studies as a nephrologist or medical officer made the referral but did not attend the clinic. Secondly, our clinic was almost a “one-off” assessment by various health professionals, with further intervention arranged for

patients if required. Due to limited staffing resources, the nature of the clinic and limited post-clinic intervention, it was uncertain if comparable outcomes were achieved. Further study is needed to examine the outcomes of our patients. Our study raised the issue of growing demand on nutrition intervention due to an increase in patient numbers and a higher prevalence of nutritional abnormalities. There were other substantial needs for nutrition interventions not examined in this study, such as hypertension, poorly-controlled diabetes, hyperkalaemia and hyperphosphataemia, etc. This was compounded by the fact that our patients were more advanced in age and thus required additional attention for age-related nutritional health issues, such as sarcopenia, chewing and swallowing problems and food provision. Furthermore, attendance at this pre-dialysis clinic was not mandatory for all ESKD patients in our unit, and the results cannot be generalised to those who did not attend the clinic. Undoubtedly, a substantial number of patients waiting to start dialysis or planning to be maintained on the conservative pathway were at severe nutritional risk similar to reports in the literature.[239, 401]

From our understanding, this study was the first to examine the relationship between nutritional status and future choice of ESKD management including, conservative management or no-RRT. The proportion of patients who chose to start a home dialysis (HD or PD) program remained steady over time, similar to the ANZDATA report[5] on new dialysis patients. However, the rate of preferring PD significantly increased (39.2% vs. 52.9%, χ^2=7.9, *P* =0.01) and was accompanied by a decline in home HD (21.0% vs. 9.5%, χ^2 =12.8, *P* <0.0001) over time. This may have been because automated PD (APD) became more readily available to patients over the last few years. APD is a machine-operated PD, which is simpler to perform compared to the traditional manually-operated continuous ambulatory PD (CAPD); it costs less and reportedly improves quality of life of patients with ESKD. Our result aligns with the trend of more

patients starting APD than CAPD, as previously reported for the period of 1999 and 2008.[5, 402]

It is not surprising that those patients who preferred conservative management were more advanced in age, had lower levels of GFR and higher prevalence of malnutrition. The general understanding is that in elderly patients there is no significant survival advantage in starting dialysis compared with staying in conservative care, especially in those with multiple co-morbidities.[16, 403, 404] Since malnutrition is one of the major determinants of survival in this population,[401] nutrition intervention should be provided to improve the outcomes of these patients. For patients who planned future dialysis, those who preferred hospital dialysis were older and had higher prevalence of CAD, DM and malnutrition, all of which require more intense nutrition intervention. Studies are needed to explore if prevention or intervention of malnutrition plays a role to move these patients to home dialysis programs, and/or to delay the start of dialysis, as both strategies would help reduce health care costs.

The strength of this study was the long study period, with a reasonable sample size that allowed meaningful comparison of the change in characteristics of these patients over time. The major limitations were the retrospective nature of the study with missing data and lack of measure of inflammation, e.g., C reactive protein (CRP), which is closely linked to nutritional status. In spite of these limitations, the current study provides invaluable baseline information of a cohort of patients who enrolled in a pre-dialysis clinic over a 10-year period.

5.6 Conclusions

The number of patients enrolled in our multidisciplinary clinic doubled in the second 5-year period over the 10-year observation. The leading cause of ESKD remained diabetic nephropathy, with an increase in prevalence overtime. Prevalence of obesity

and diabetes increased significantly, mirroring the obesity and diabetes epidemics in the general population; malnutrition rate remained constant but with an increase in total number reflecting larger numbers enrolled in the clinic in the second period. Demographic and nutritional parameters were found to be closely related to the patients' choice of future treatment options, especially in patients who preferred a conservative pathway followed by hospital dialysis, those patients being more advanced in age with a higher prevalence of malnutrition. Therefore, nutrition intervention should be considered in pre-dialysis groups, including elderly patients who have chosen conservative or hospital-dependent dialysis.

Implications for clinical practice:

The number of patients with nutrition abnormalities requiring nutrition intervention has grown exponentially, supporting the need of structured nutrition care process by dietitian including assessment and intervention in the pre-dialysis CKD stages.

Chapter 6 Thesis Conclusions

Nutrition abnormalities are common in patients with CKD and are associated with poor clinical outcomes and QOL. During the course of decline of renal function these nutritional problems emerge and change in nature and magnitude through to dialysis and transplantation. The findings presented in this thesis focused on the examination of nutritional abnormalities in ESKD or CKD stages 4 to 5 before, and at the start of dialysis. The studies revealed the prevalence and prognostic significance of these nutritional abnormalities, which are independently associated with mortality risks. One of the major strengths of this thesis was the naturalistic study design so that all patients of the defined treatment or program were included in the observation; in contrast to the majority of the published data there was therefore no experimental selection bias. These are representative data of ESKD patients of a typical Australian renal unit setting, which was seldom examined previously. Moreover, the major strength of this thesis has been the continuous research for better practice through a series of clinical, practice-based and epidemiological studies.

The primary research question of the thesis was: “Is nutrition management good enough only when it starts at or near dialysis initiation?” and how can we do better to improve work practice and patient outcomes.

6.1 Summary of findings

The first part of the thesis began with the examination of demographic, clinical and nutritional characteristics of patients at commencement of dialysis, and a number of parameters were found to be independently associated with high mortality risks. The preliminary analysis two years after the initial data collection indicated an unfavourable outcome of malnourished patients; therefore a pre-dialysis assessment clinic was

established to provide education pre-dialysis. The nutritional characteristics of this clinic were examined. A summary of the findings is listed below:

1. A high prevalence of nutritional abnormalities presented at the initiation of dialysis was observed and associated with high mortality risk over the 10-year observation period. Older age (>65 years), presence of PVD, reduced s-albumin and malnutrition (SGA score B and C) independently predicted mortality over the 10-year study period (*P* <0.0001, *P* <0.0001, *P* =0.01 and *P* =0.02 respectively). Furthermore, in contrast to the current understanding of the "obesity paradox", overweight/obese was not found to be protective to mortality risk. In fact, when combined with malnutrition, it was associated with the highest mortality risk compared to other combinations of BMI < or >26 kg/m^2 and SGA categories. In addition, GFR levels at which dialysis started did not associate with mortality, indicating that with sound clinical practice and judgement, including nutrition, dialysis can be started at lower levels of GFR.
2. High prevalence of nutritional abnormalities was observed in the initial assessment of patients who attended the pre-dialysis clinic. The mean GFR of this cohort was 17.0±6.3 mL/min/1.73m^2; prevalence of malnutrition and overweight/obesity was 40.5% and 62.4% respectively. The dietary intake of protein and energy positively correlated with GFR; in other words, as renal function declined, dietary intake decreased. Furthermore, the prevalence of malnutrition, muscle wasting measured by MAMC and presence of symptoms increased as GFR decreased. Self-imposed restrictive diet and poor eating habits also contributed to abnormal nutrition in this cohort.
3. Self-rated appetite scores were found useful in ranking energy and protein intakes but subjective reporting of a good appetite was likely to associate with adequate protein intake, not energy intake.

4. Over the 10-year period from April 2002 to March 2012, patients were enrolled in the pre-dialysis assessment clinic at an earlier point in the second 5-year period. GFR was 16.7±6.7 vs. 22.1±9.1 mL/min/1.73m^2 (*P* <0.0001) in the first and second periods respectively. Despite earlier referral, malnutrition rate scored by SGA remained high at 39.7% vs. 42.0% (*P* =0.62). In addition, the total number of patients who attended the clinic doubled, reflecting the need for additional service provision to treat malnutrition.
5. There was a significant increase in the prevalence of obesity and diabetes over the 10-year study period, which mirrored epidemics in the general population.
6. Patients who preferred a conservative (or no dialysis) pathway or hospital-based dialysis were more advanced in age and had a higher prevalence of co-morbidities and nutrition abnormalities, including malnutrition.

6.2 Summary of findings to address research question and hypothesis

The global research question of this thesis was "Is nutrition management good enough only when it starts at or near dialysis initiation?" and the aim was to examine the relationships between nutritional factors and clinical outcomes in people with ESKD.

Hypothesis 1: nutritional abnormalities at the initiation of dialysis would be associated with high mortality risk.

Addressing Hypothesis1 (chapter 3): The results support the hypothesis that nutritional abnormalities presented at the initiation of dialysis are associated with high mortality risk over a 10-year observation period.

There were a number of additional significant findings. a) In contrast to the current understanding of the "obesity paradox", overweight/obese was not found to be protective to mortality risk. In fact, when combined with malnutrition, it was associated with the highest mortality risk compared to other combinations of BMI < or >26 kg/m^2

and SGA categories. b) GFR levels at which dialysis started did not associate with mortality, indicating that with sound clinical practice and judgement, dialysis can be started at lower levels of GFR.

Hypothesis 2: abnormal nutrition would be prevalent in advanced CKD before dialysis was required.

Addressing Hypothesis 2 (Chapter 4): High prevalence of nutritional abnormalities was observed in the initial assessment of patients who attended the pre-dialysis clinic. This supports hypothesis 2.

The mean GFR of this cohort was 17.0±6.0 mL/min/1.73m^2; and prevalence of malnutrition and overweight/obesity was 40.5% and 62.5% respectively. The dietary intake of protein and energy positively correlated with GFR; in the other words, as renal function declined, dietary intake decreased. Furthermore, the prevalence of malnutrition, muscle wasting measured by mid-arm muscle circumference and presence of symptoms increased as GFR decreased. Self- imposed restrictive diet and poor eating habits also contributed to abnormal nutrition.

Hypothesis 3: the subjective rating of a good appetite using the ADAT appetite score[238, 299] would be useful in reflecting adequate intakes of protein and energy.

Addressing Hypothesis 3 (Chapter4): The results of this study did not entirely support hypothesis 3. The results indicated self-reported appetite scores were useful in ranking energy and protein intakes, but subjective reporting of a good appetite was only likely to associate with adequate protein intake, not energy intake.

Hypothesis 4: as the clinic became more established over the 10-year study period, patients with ESKD would be referred to the clinic earlier (or at higher levels of GFR) for management. Hopefully, less malnourished patients would be presented to the clinic in the second half of the study period.

Addressing Hypothesis 4 (Chapter 5): Initially the results support hypothesis 4: over the 10-year observation, patients were enrolled at the clinic at an earlier point in the second five-year period, with GFR being 13.2±4.5 vs 17.1±5.5 mL/min/1.73m^2 (*P* <0.0001) respectively. However, despite the earlier referral, malnutrition rate scored by SGA remained high at 39.7% vs 42.0% (*P* =0.62). Therefore, overall the results refute hypothesis 4. In addition, the total number of patients who attended the clinic doubled, reflecting the need for additional service provision to treat malnutrition.

Hypothesis 5: in view of the obesity epidemic, there would be a higher prevalence of overweight and obese patients between the first and second half of the study period.

Addressing Hypothesis 5 (Chapter 5): The results support hypothesis 5: there was a significant increase in the prevalence of obesity and diabetes over the 10-year study period, which mirrored the obesity and diabetes epidemic in the general population.

Hypothesis 6: nutritional status would be associated with the future choice of RRT

Addressing Hypothesis 5 (Chapter 5): The results support hypothesis 6: Patients who preferred a conservative (or no dialysis) pathway or hospital-based dialysis were more advanced in age and had a higher prevalence of co-morbidities and nutrition abnormalities, including malnutrition.

To answer the global research question of this thesis “Is nutrition management good enough only when it starts at or near dialysis initiation?, the answer is NO. To improve health outcomes of patients with ESKD, structured nutrition management should be implemented well before dialysis is required and even before the pre-dialysis stage.

6.3 Strengths and limitations

The naturalistic approach of these retrospective studies allowed the data of all patients to be included for analysis. From our experience with nutrition research, not all

patients were willing to consent to participate in studies, especially the older and frail patients. The sample sizes were powerful enough for analysis to answer the research questions that were proposed. The other major strength of our studies was the extended observation period that allowed the long-term effects of nutritional factors on mortality to be examined. Most importantly, this thesis built upon the research in practice framework to translate research evidence to aim for practice improvement. It involved a series of clinical science, practice-related research, epidemiological study that have led to a change of work place culture and practice, such as establishment of a pre-dialysis clinic and earlier referral to the clinic over time, which were subjected to continuous evaluation and improvement.

The major limitation, like all retrospective studies, is that we could only draw associations between the study factors and outcomes, but could not surmise causal relationships. Similar to the shortcomings of epidemiological studies, we may have missed important confounding factors that could affect the results. For example, we could not examine inflammation in our analyses, as the commonly-used inflammatory marker CRP was not routinely measured in our cohort of patients. Despite this limitation, we were able to collect a wide range of nutritional data typically measured in nutritional assessment as recommended by the clinical practice guidelines.[205, 216] These measures included anthropometry (weight, height, BMI, weight history, TSF and MAMC), biochemistry (s-albumin), clinical signs and symptoms (appetite, nausea and taste change/aversion), dietary intake using the structured diet history method with sufficient details for computer analysis, and the global assessment score – SGA. Although the results of these studies could not infer any causality, this information may help complement the limitations of RCT[275, 405] for clinicians to deduce good clinical practice in the absence of high level evidence, or to formulate a further intervention study. The prevalence data was useful to help plan service provision.

In addition, there are many unique features of our studies; to our knowledge, at the planning stage of our studies the following aspects had never, or seldom, been studied by other researchers.

In Study I, we only included patients who had started dialysis after a gradual decline of renal function. Therefore we excluded factors that may affect the nutritional state other than chronic uraemia, e.g., AKI and ex-transplantation. We also examined the combination of malnutrition and overweight/obesity factors, and showed the detrimental effects of such a combination. Furthermore, if patients were maintained as clinically sound, including optimal nutritional status with limited symptoms (as part of the SGA score), we found there is no need to consider early initiation of dialysis, which imposes tremendous heath, social and economic burden. Approximately $50,000 to $80,000 per year is required to maintain a patient on dialysis, depending on treatment modality and setting.[4] However, data was excluded from analysis for 50% of the total participants who started dialysis because of other reasons, such as AKI; many of whom still required long-term dialysis. The relationship between the baseline nutritional factors and outcome of these patients could be very different and a separate analysis is required.

The comprehensive cross-sectional analysis of nutritional status and dietary intake encompassed by Study II of the study was seldom performed in the literature. We not only considered the typical energy and protein intake, but also included other micronutrients and consumption of core foods, such as fruit and vegetables. The relationships between intake, appetite and symptoms have seldom been explored before. For clinical importance, we found self-rated appetite did not equate to adequate intake, especially energy intake; therefore structured dietary intake assessment by a dietitian should be an essential part of nutrition care in patients with ESKD. However, these results were generated by analysis of a referred population of patients with CKD

stages 4 to 5, and therefore cannot be generalised to patients who were not referred to the clinic at other CKD stages.

6.4 Latest evidence since the initial literature review

The latest evidence in the literature was included in the discussion sections of each chapter. At the time of submission of this thesis, to the best of the PhD candidate's knowledge the research findings summarised in Section 6.1 of this thesis were considered to be novel, and there is no major contradiction to the current understanding in the field of renal nutrition. Therefore, the current findings support the direction of future research proposed in Section 6.6.

6.5 Conclusions

In conclusion, nutritional factors, along with Older age (>65 years) and co-morbidities, independently predict mortality. Nutrition abnormalities emerge well before dialysis is required; therefore an early continuum of structured nutritional care in patients with ESKD is recommended.

To answer the question "Is nutrition management good enough only when it starts at or near dialysis initiation?" the answer is NO.

To improve health outcomes of patients with ESKD, structured nutrition management should be implemented well before dialysis is required and even before the pre-dialysis stage. However, the efficacy, cost-effectiveness and best model of care are yet to be determined.

6.6 Implications for clinical practice

The results of these studies revealed poor outcomes associated with nutritional abnormality in ESKD from pre-dialysis stage or during dialysis. There is growing

evidence to support the benefit of various nutrition interventions involving a dietitian,[257, 363, 397] this includes pre-dialysis intervention on the favourable outcome one year after dialysis started;[400] therefore, timely structured nutrition care involving a dietitian is strongly recommended. The results of our study and the literature suggest intervention should start no later than CKD stage 3b, or when GFR falls <45 mL/min/1.73m^2 or even earlier, as recommended by the newly-developed CARI guidelines for CKD stages 1 to 3 (early CKD)[83] – of which the PhD candidate is the principal-author. A structured nutrition care process should be under the framework of medical nutrition therapy (MNT),[221] which includes: a) timely referral to a dietitian; b) nutritional assessment; c) nutrition intervention and dietary prescription; and d) implementation and monitoring with defined frequency and duration:

In addition:

1. Judging from the varied combination of nutritional abnormalities, an individualised treatment plan should be implemented.
2. During clinical and nutritional assessment, a detailed intake assessment should be performed in addition to the patient's subjective reporting of appetite.
3. In addition to the traditional clinical and nutritional parameters, patient-centred outcomes, such as QOL, symptom control and satisfaction, are also important treatment outcome measures to be assessed longitudinally.

Regular quality assurance activity is important to evaluate the system outcomes.

6.7 Direction of future research

A number of research initiatives are proposed based on the current literature and findings from the research in this thesis, which represent the knowledge gap to be filled to improve the outcomes of patients with ESKD.

1. To examine the logistics and effect of nutrition intervention, especially when insufficient renal dietitian staffing levels are thought to affect outcomes. This could be achieved through further analysis of existing data on the pattern of nutrition intervention from various time points, such as after initial pre-dialysis clinic attendance and after commencement of dialysis. These data points also serve to examine the change of nutritional status from the time of pre-dialysis clinic attendance to time of initiation of dialysis.
2. To plan and conduct RCTs of nutrition intervention in pre-dialysis CKD patients with targeted criteria and outcome measures, for example:

   i. Integrated nutrition and exercise intervention, as these two factors are closely linked in the energy and metabolic pathway, especially in the PEW pathway and lipid metabolism in ESKD. The combined intervention could have escalating effects.
   ii. Weight reduction through caloric restriction and exercise in overweight and obese patients. Suggested outcome measures are change in BW, waist circumference body compositions, blood pressure and possible reduction in antihypertensive medications used, and parameters of metabolic syndrome, e.g., the homeostatic model assessment (HOMA) index and fasting serum lipids.
   iii. Nutritional support in malnourished patients, through a combination of dietary counselling and education regarding diet plans, food fortifications and use of oral nutrition supplements that suit the need of individual patients. Suggested outcome measures are: improvement in SGA score (either the 7-point scale version[149] or patient-generated – PG-SGA); QOL using a validated questionnaire (e.g., SF-36);[254, 406] change in anthropometric measures and body composition, blood nutritional and inflammation markers, e.g., s-albumin and CRP; improvement in symptoms; dietary intake of energy and protein; and function

capacity measured using hand-grip strength[407] and a physical activity questionnaire.

iv. Nutrition intervention in elderly patients on conservative care based on the current recommendations for nutrition prescription. Outcome measures should focus on symptom control and QOL measured. Survival analysis could be performed as a long-term outcome measure.

3. To formulate the “ideal diet” for patients with stage 4 to 5 CKD through dietetic modelling. This means in addition to the current recommendations for energy, protein, sodium, potassium, phosphorous and other vitamin and minerals, dietary patterns should also be considered in view of the known reno- and cardioprotective properties of fruit, vegetables, oily fish and a Mediterranean-style diet.

4. To design and validate sensitive assessment tools to evaluate the effect of nutrition intervention. This could be symptom scoring that responds to change of intake and nutritional status.

5. To perform a cost-benefit analysis of structured nutrition intervention to examine if the benefits outweigh the implementation costs. Time-saving devices based on technological innovation – such as patient record and appointment tracking, communication, video conferencing and telecommunication using personal computer – should be explored to reduce appointment and travelling time.

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Appendices

Appendix A Renal medication list for dietitians

ANTIHYPERTENSIVES	DIURETICS	IMMUNOSUPPRESSANTS
ACE Inhibitors *(increase K)* Captopril Enalapril Fosinopril Lisinopril Perindopril Quinapril Ramipril Trandolapril	**Loop Diuretics** *(decrease K)* Frusemide Bumetanide Ethacrynic acid Indapamide **Thiazides** ***(decrease K)*** Hydrochlorothiazide Chlorthalidone Bendrofluazide	**Calcineurin Inhibitors** Tacrolimus (hyperglycaemia) Cyclosporin **MTOR Inhibitors** Sirolimus (hyperlipidaemia) Everolimus (hyperlipidaemia) *All above may cause electrolyte disturbances*
Angiotensin 2 Blockers *(increases K)* Irbesartan Candesartan Telmisartan Eprosartan Losartan	**Potassium Sparing Diuretics** *(increase K)* *Spironolactone* *Amiloride* Triamterene	Mycophenolate Azathioprine Prednisolone *(decreases K)*
Beta Blockers	**PHOSPHATE BINDERS**	**VITAMINS & MINERALS**
Atenolol Bisoprolol Carvedilol Metoprolol Pindolol Propranolol	Aluminium *(Alutabs)* Calcium *(Caltrate, Cal 600, Calsup, Titralac)* Lanthanum *(Fosrenol)* Magnesium combinations *(Mylanta, Gastrogel, Gastrobrom)* Sevelamer *(Renagel)*	Calcitriol *(Vitamin D)* Paricalcitol *(Vitamin D analogue)* Cinacalcet *(Sensipar)* – Calcimimetic Folic Acid Ferrous sulphate Vitamin B group + C
Calcium Channel Blockers	**ERYTHROPOIETIN**	**RENAL MISCELLANEOUS**
Amlodipine Felodipine Lercanidipine Nifedipine Diltiazem Verapamil	Darbepoetin (*Aranesp)* Epoetin *(Eprex)* Epoetin Beta *(NeoRecormon)*	**Bis-Phosphonates** Alendronate Risedronate Pamidronate Sodium Bicarbonate Allopurinol Colchicine
Vasodilators	**DIABETES**	**LIPID-LOWERING AGENTS**
Prazosin Hydralazine Minoxidil **Centrally-acting** Clonidine Moxonidine Methyldopa	**Sulphonylureas** *(hypoglycaemia)* ***Glimepiride*** Glibenclamide Glipizide Gliclazide **Biguanides** ***Metformin (lactic acidosis)***	**HMG CoA Reductase Inhibitors** ***Atorvastatin*** Fluvastatin Pravastatin Rosuvastatin Simvastatin **Other Agents** Gemfibrozil Fenofibrate Ezetimibe

NB: This is not an exhaustive list. Many anti-hypertensive medications come in a combined form with a diuretic. Compiled by Ms J Tierney, Deputy Director of Pharmacy, The St. George Hospital, updated 2007.

Appendix B Preliminary analysis of the pre-dialysis assessment clinic

Proceeding of Australian and New Zealand Society of Nephrology, 40th Annual Scientific Meeting, poster 146. *Nephrology*; **9** (Suppl.), A1–A43, 2004.

NUTRITION MANAGEMENT IN PRE-DIALYSIS ASSESSMENT CLINIC – 18 MONTHS EXPERIENCE

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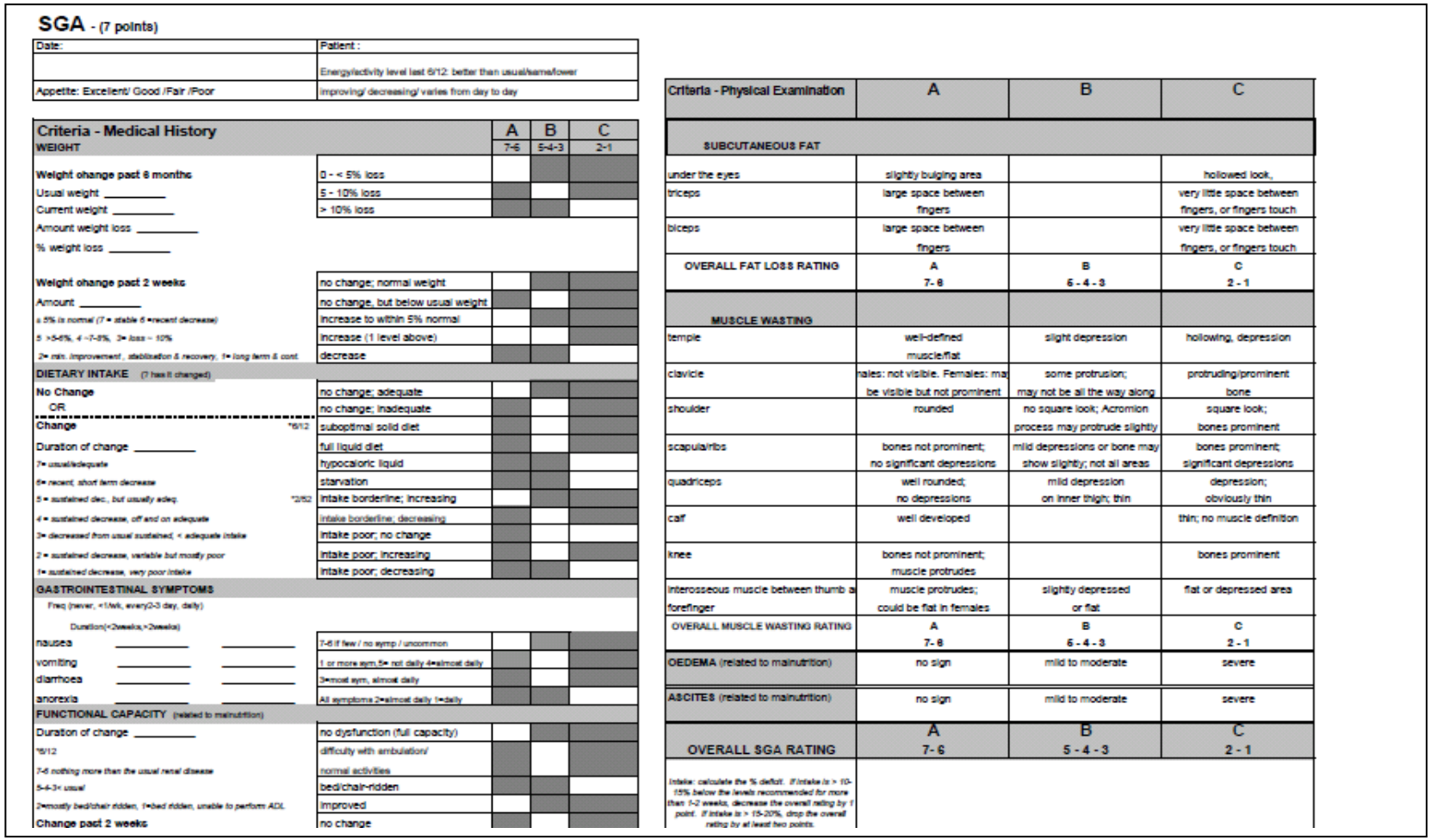
Background: One of the nutrition goals in renal medicine is to prevent malnutrition which predicts morbidity and mortality. Between 8/00 and 6/02, assessment of 97 new dialysis patients with progressive ESRF indicated a high prevalence of malnutrition using Subjective Global Assessment (SGA B:C =41%:14%) and 56% of patients had low serum albumin. Less than 30% of these patients received nutrition intervention in the pre-dialysis stage. A multidisciplinary pre-dialysis assessment clinic was then established, in which the dietitian became responsible for the nutrition assessment and intervention of patients with GFR <25 mL/min based on clinical practice guidelines (e.g., CARI and K/DOQI) and agreed department protocols.
Methods: Clinical characteristics of these patients and evaluation of the nutrition component of the pre-dialysis clinic are described.
Results: 77 patients (49M:28F, age 67.0±14 year) attended the clinic between 4/02 and 10/03. Mean GFR was 14.4±5.6 mL/min/1.73m^2 (range 4.8–30.0). 54.6% of these patients were malnourished (SGA B:C =46.8%:7.8%) well before dialysis was required and 18.2% experienced >5% unplanned weight loss in the previous 6 months. Computerised nutrition intake analysis indicated suboptimal intake of protein (26.0% of patients <0.75 g/kg IBW/d – Australian RDI; 13.7% of patients <0.6 g/kg IBW/d) and energy (72.6% of patients <30–35 kcal/kg IBW/d). 30/51(58.8%) of patients reported a good appetite but estimated protein and/or energy intake was suboptimal. Factors identified for suboptimal intake included nausea/taste aversion (53.3%) and self-imposed dietary restrictions (19.7%). Only 39.0% of patients had physician referral for nutrition intervention. After the initial evaluation at 6 months, 'blanket referral' for nutrition intervention was established. Preliminary data indicated ~91% of recent clinic patients and >70% of new dialysis patients with progressive ESRF were assessed and/or received intervention by the dietitian.
Conclusions: Pre-dialysis assessment clinic allows a systematic approach of nutrition management to patients with advanced renal failure and is sustainable.

Appendix C Subjective Global Assessment (SGA) tool – 7-point scale



SGA - (7 points)

Date:	Patient :
	Energy/activity level last 6/12: better than usual/same/lower
Appetite: Excellent/ Good /Fair /Poor	improving/ decreasing/ varies from day to day

Criteria - Medical History		A	B	C
WEIGHT		7-6	5-4-3	2-1
Weight change past 6 months	0 - < 5% loss			
Usual weight _____	5 - 10% loss			
Current weight _____	> 10% loss			
Amount weight loss _____				
% weight loss _____				
Weight change past 2 weeks	no change; normal weight			
Amount _____	no change, but below usual weight			
± 5% is normal (7 = stable 6 =recent decrease)	increase to within 5% normal			
5 =5-6%, 4 =7-8%, 3= loss ~ 10%	increase (1 level above)			
2= min. improvement , stabilisation & recovery, 1= long term & cont.	decrease			
DIETARY INTAKE (7 has it changed)				
No Change	no change; adequate			
OR	no change; inadequate			
Change **6/12*	suboptimal solid diet			
Duration of change _____	full liquid diet			
7= usual/adequate	hypocaloric liquid			
6= recent, short term decrease	starvation			
*5 = sustained dec., but usually adeq. *2/52*	intake borderline; increasing			
4 = sustained decrease, off and on adequate	intake borderline; decreasing			
3= decreased from usual sustained; < adequate intake	intake poor; no change			
2 = sustained decrease, variable but mostly poor	intake poor; increasing			
1= sustained decrease, very poor intake	intake poor; decreasing			
GASTROINTESTINAL SYMPTOMS				
Freq (never, <1/wk, every2-3 day, daily)				
Duration(<2weeks,>2weeks)				
nausea _____ _____	7-6 if few / no symp / uncommon			
vomiting _____ _____	1 or more sym,5= not daily 4=almost daily			
diarrhoea _____ _____	3=most sym, almost daily			
anorexia _____ _____	All symptoms 2=almost daily 1=daily			
FUNCTIONAL CAPACITY (related to malnutrition)				
Duration of change _____	no dysfunction (full capacity)			
**6/12*	difficulty with ambulation/ normal activities			
7-6 nothing more than the usual renal disease	bed/chair-ridden			
5-4-3= usual	improved			
2=mostly bed/chair ridden, 1=bed ridden, unable to perform ADL	no change			
Change past 2 weeks				

Criteria - Physical Examination	A	B	C
SUBCUTANEOUS FAT			
under the eyes	slightly bulging area		hollowed look,
triceps	large space between fingers		very little space between fingers, or fingers touch
biceps	large space between fingers		very little space between fingers, or fingers touch
OVERALL FAT LOSS RATING	A 7- 6	B 5 - 4 - 3	C 2 - 1
MUSCLE WASTING			
temple	well-defined muscle/flat	slight depression	hollowing, depression
clavicle	nales: not visible. Females: may be visible but not prominent	some protrusion; may not be all the way along	protruding/prominent bone
shoulder	rounded	no square look; Acromion process may protrude slightly	square look; bones prominent
scapula/ribs	bones not prominent; no significant depressions	mild depressions or bone may show slightly; not all areas	bones prominent; significant depressions
quadriceps	well rounded; no depressions	mild depression on inner thigh; thin	depression; obviously thin
calf	well developed		thin; no muscle definition
knee	bones not prominent; muscle protrudes		bones prominent
interosseous muscle between thumb a forefinger	muscle protrudes; could be flat in females	slightly depressed or flat	flat or depressed area
OVERALL MUSCLE WASTING RATING	A 7- 6	B 5 - 4 - 3	C 2 - 1
OEDEMA (related to malnutrition)	no sign	mild to moderate	severe
ASCITES (related to malnutrition)	no sign	mild to moderate	severe
OVERALL SGA RATING	A 7- 6	B 5 - 4 - 3	C 2 - 1
Intake: calculate the % deficit. If intake is > 10-15% below the levels recommended for more than 1-2 weeks, decrease the overall rating by 1 point. If intake is > 15-20%, drop the overall rating by at least two points.			

Appendix D Ethics approval letter for Study I

Ethics approval letter, reference number: 03/115 Chan

SOUTH EAST HEALTH
HUMAN RESEARCH ETHICS COMMITTEE
SOUTHERN SECTION

22nd August 2003

Ms M Chan
Dept of Nutrition & Dietetics
St George Hospital

Dear Ms Chan,

RE: Nutritional status at commencement of dialysis and outcomes (03/115 Chan)

Thank you for your letter dated 6th August 2003, containing the Committee's requirements. As you have now fulfilled all necessary conditions I hereby notify you that, at its meeting held on the 29th July 2003, the South East Health Human Research Ethics Committee - Southern Section agreed to approve: -

Nutritional status at commencement of dialysis and outcomes (03/115 Chan)

The Committee requires a brief six month progress report on research it has approved and yearly reports thereafter. **(Estimated duration of the project is 5 years).**

These reports should: -

Be accompanied by abstracts of any articles or publications (if any) arising out of the study.

Confirm security of records.

Confirm compliance with approved consent procedures and documentation.

SEH HREC SS
St George Hospital
Gray St.,
KOGARAH 2217

TEL 9350 2481
FAX 9350 3968
Email: leriasd@sesahs.nsw.gov.au
South Eastern Sydney Area Health Service

The investigator should also report immediately to the Ethics Committee anything, which might affect ethical acceptance of the protocol, including: -

Adverse events on subjects.

Proposed changes in the protocol.

Unforeseen events that might affect continued ethical acceptability of the project.

Please note that the Committee has given approval for you to conduct this study up to the estimated completion dated of **September 2008**. If your study is not completed by this date, you will need to apply for an extension along with your final progress report. Failure to do so may result in withdrawal of the Committee's approval for this study after this date.

I look forward to placing your first report before the Committee and wish you well in this study.

Yours sincerely,

Doukessa Lerias
Coordinator
South East Health Human Research Ethics Committee -
Southern Section

Appendix E Ethics Approval letter for Study II

Ethics approval letter I, reference number: 03/134 Chan

SOUTH EAST HEALTH
HUMAN RESEARCH ETHICS COMMITTEE
SOUTHERN SECTION

5th September 2003

Ms M Chan
Dept of Nutrition & Dietetics
St George Hospital

Dear Ms Chan,

RE: Pre-dialysis nutrition management audit (03/134 Chan)

Thank you for your application dated August 2003. As you have now fulfilled all necessary conditions I hereby notify you that, at its meeting held on the 26th August 2003, the South East Health Human Research Ethics Committee - Southern Section agreed to approve: -

Pre-dialysis nutrition management audits (03/134 Chan)

The Committee requires a brief six month progress report on research it has approved and yearly reports thereafter. **(Estimated duration of the project is 5 years).**

These reports should: -

Be accompanied by abstracts of any articles or publications (if any) arising out of the study.

Confirm security of records.

Confirm compliance with approved consent procedures and documentation.

SEH HREC SS
St George Hospital
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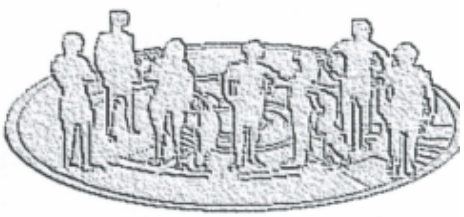

The investigator should also report immediately to the Ethics Committee anything, which might affect ethical acceptance of the protocol, including: -

Adverse events on subjects.

Proposed changes in the protocol.

Unforeseen events that might affect continued ethical acceptability of the project.

Please note that the Committee has given approval for you to conduct this study up to the estimated completion dated of **September 2008**. If your study is not completed by this date, you will need to apply for an extension along with your final progress report. Failure to do so may result in withdrawal of the Committee's approval for this study after this date.

I look forward to placing your first report before the Committee and wish you well in this study.

Yours sincerely,

Doukessa Lerias
Coordinator
South East Health Human Research Ethics Committee -
Southern Section

Ethics approval letter 2, reference number: LNR/12/STG/104, LNRSSA/12/SGA/105

Health
South Eastern Sydney
Local Health District

24 July 2012

Ms Maria Chan
Nutrition and Dietetics
St George Hospital
Gray Street
KOGARAH NSW 2217

Dear Ms Chan

HREC reference number: LNR/12/STG/104
SSA reference number: LNRSSA/12/STG/105
Project title: Nutritional characteristics of patients at enrolment to the pre-dialysis assessment clinic – a retrospective review to determine parameters

Thank you for submitting a Low and Negligible Risk Research – New South Wales, Site Specific Assessment (SSA) Form for governance review on 19 July 2012.

Please quote the above SSA reference number in all correspondence to the Research Governance Officer.

The following definitions have been given to classify research conducted under this application type:
Low risk research
The National Statement on Ethical Conduct in Human Research 2007 describes research as "low risk", where the only foreseeable risk is one of discomfort. Discomforts may include minor side-effects of medication, discomforts related to measuring blood pressure or anxiety induced by an interview. Where the risk, even if unlikely, is more serious than discomfort, the research is not low risk.

Negligible risk research
The National Statement on Ethical Conduct in Human Research 2007 describes research as "negligible risk" where there is no foreseeable risk of harm or discomfort; and any foreseeable risk is not more than inconvenience to the participants. Inconvenience is the least form of harm that is possible for human participants in research. The most common examples of inconvenience in human research are filling in a form, participating in a survey or giving up time to participate in a research activity. Where the risk, even if unlikely, is more than inconvenience, the research is not negligible risk.

The following documents were submitted for consideration and entered into AURED:

Document	Details	Date
SSA LNR Form	AU/7/CEDD014	23/06/2012
HREC Approval Letter		28/06/2012

SESLHD Research Support Office
St George & Sutherland Hospitals & Health Services
Level 3, James Laws House
St George Public Hospital
Gray Street, KOGARAH NSW 2217
CentralEthics@sesiahs.health.nsw.gov.au
Telephone: 612 91132027 Facsimile: 612 91133960

I am pleased to inform you that authorisation has been granted by the Chief Executive (or delegate) for this project to take place at the following site/s:

☐ **St George Hospital & Health Service**

Authorisation is conditional on ethical and scientific approval of the project, which has been granted in line with Policy Directive PD2010_055 *Research - Ethical and scientific review of human research in NSW Public Health Organisations*.

You are required to provide the Research Support Office with the following details (where applicable) at your earliest convenience:

1. Project commencement date
2. Proposed amendments to the research protocol or personnel which may affect the ongoing site acceptability of the project - these may include budget, risk, staffing and infrastructure issues
3. All authorised documentation from the approving HREC

Yours faithfully

Lisa Stanton
Research Governance Officer
St George / Sutherland Hospitals and Health Services

Appendix F Appetite & Diet Assessment Tool (ADAT) 5-point Likert scale

Question: Overall, how would you describe your appetite?

(1) Very good

(2) Good

(3) Fair

(4) Poor

(5) Very poor

Appendix G Audit checklist

Nutritional assessment		**Demographic**	
(A) Anthropometry			Age
	Weight		Gender
	weight history		Race
	Height	**Clinical data**	
	Triceps skinfold		Cause of kidney failure
	Mid-Arm circumference		Co-morbidities, presence of:
(B) Biochemistry /blood results			Coronary artery disease
	Serum creatinine		Chronic lung disease
	Serum albumin		Cerebral vascular disease
(C) Clinical signs and symptoms			Peripheral vascular disease
	Appetite score – appendix F		Diabetes Mellitus
	Presence of nausea		Smoking habits
	Presence of taste change	**Future treatment option**	
(D) Dietary intake assessment			Conservative care
	Diet history		Haemodialysis(home/hospital)
	Nutrient analyses		Peritoneal dialysis
(E) Exercise and Physical activity			Transplantation
Others			
	Subjective Global Assessment		

Appendix H Sample structured diet history interview sheet

- Introduce self to the participant
- Read out: The following interview aims to assess your usual intake on a 'typical day". Please consider all the questions I ask you carefully and answer as honestly as possibility, to the best of your ability.
- Sample questions for Breakfast:
    - Do you have breakfast? Do you always have breakfast?
    - What do you eat for breakfast?
    - Do you eat bread?
    - How many slices would you have?
    - Do you have anything spread on it such as margarine, butter, jam or vegemite? Salted or unsalted? Amount?
    - How many times per week would you say you had this for breakfast?

Meal time	**Food consumed**	**Serving size**	**Frequency**	**Specific information / cooking methods (including brand name, oil used)**	**Did you finish the meal?**
Breakfast	Cereal: Milk/Juice: Extra (yoghurt, fruit, sugar): Bread/toast/buns/rolls: Spread (margarine, butter. Jam, honey, vegemite, others), salted or unsalted				

Meal time	Food consumed	Serving size	Frequency	Specific information / cooking methods (including brand name, oil used)	Did you finish the meal?
Breakfast continued	Extras (cheese, tomato, ham): Hot food (eggs, bacon, sausages, baked beans, pancakes): Condiments(i.e. maple syrup, tomato sauce, salt, pepper) Drinks (tea, coffee, juice, other): Added to drinks (milk, sugar, lemon): *Do you eat these foods everyday? If not, what do you usually eat on other days and how often?* *Weekend variation:*				