Effect of fruit and vegetable intake on the progression of kidney failure in adults with chronic kidney disease: A systematic review

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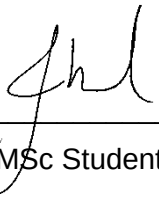
PREFACE

This dissertation is written in article format and consists of the following four chapters: Chapter 1 is an introduction to the topic. Chapter 2 is a detailed literature review on the topic. Chapter 3 entails an article prepared for submission to the Journal of Renal Nutrition titled: “Effect of fruit and vegetable intake on the progression of kidney failure in adults with chronic kidney disease: A systematic review” written according to the author’s instructions of the journal by Jacomie Nel, MSc student. Dr Robin Dolman and Dr Martani Lombard are the co-authors of the article. Chapter 4 is a narrative systematic review following the findings of the systematic review. The article is also prepared for submission to the Journal of Renal Nutrition and is titled: “Dietary patterns and progression of kidney failure and mortality in adults with chronic kidney disease: A narrative systematic review.” Chapter 5 consists of a general discussion of the findings of the study together with recommendations and conclusion.

I hereby declare that I, Jacomie Nel, planned, researched and wrote this dissertation at the Centre of Excellence for Nutrition at the North-West University under the guidance and supervision of Dr Robin Dolman and Dr Martani Lombard.



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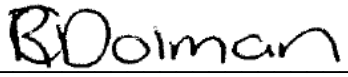
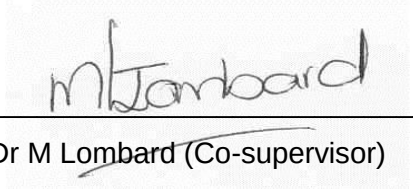


Dr R Dolman (Supervisor)



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ABSTRACT

Background: Dietary intervention has been a significant part of chronic kidney disease (CKD) treatment with the emphasis on reducing protein, sodium, phosphorus, and potassium intake, limiting fruit and vegetable consumption. These dietary recommendations are very restrictive and difficult to comply with. Recent evidence shows that fruit and vegetable intake might be a cost-effective and acceptable management option for patients with CKD and that overall healthy dietary patterns rich in fruit and vegetables may improve clinical outcomes of these patients. The aim of the current study was therefore to perform a systematic review that investigated the effect of various fruit and vegetables on specified clinical outcomes of patients with CKD.

Methods: Two systematic reviews were performed. The first aimed to investigate the effect of fruit and vegetable intake on clinical outcomes of patients with CKD, especially on estimated Glomerular Filtration Rate (eGFR). Randomised controlled trials (RCTs) of the effect of fruit and vegetable intake on blood pressure, metabolic acidosis and eGFR in adult patients with CKD (eGFR <60 ml/min/1.73m^2) published before April 2019 were included. Control groups received usual care. The aim of the second narrative systematic review was to investigate the effect of dietary patterns on clinical outcomes of patients with CKD, especially the progression of kidney failure. Cohort studies with an adult population with CKD not receiving dialysis, published before July 2019, were included. The searches for both studies were systematically performed on EBSCO Host, Google Scholar, MedLine, Pubmed, Science Direct, Scopus and The Web of Science on studies and The Cochrane Central Register of Controlled Trials using keywords and MeSh terms.

Results: Two studies with a total of 143 participants were included in the systematic review of RCTs. The eGFR of the fruit and vegetable group in the first study was the same as that of the group receiving oral sodium bicarbonate ($NaHCO_3$) after one year (Goraya *et al*., 2013). The eGFR was also significantly higher in the fruit and vegetable group when compared with usual care. The included studies found a significant reduction in body weight, systolic blood pressure and potential renal acid load (PRAL) when compared to baseline and to control group, and significant improvement in plasma total carbon dioxide (TCO_2) in the fruit and vegetable group when compared to baseline. Fruit and vegetable intake had no effect on plasma potassium when compared to baseline and/or to the control group in both the studies included. Five observational studies with a total of 8 649 participants were included in the narrative systematic review of cohort studies. Four of the included studies found that a higher plant-based dietary pattern and intake of fruit and vegetable reduce all-cause mortality in patients with CKD when compared with the lowest quintile intake.

Conclusion: Fruit and vegetables are just as effective in delaying the progression of kidney failure as $NaHCO_3$ in CKD patients with metabolic acidosis, without producing hyperkalaemia. Dietary patterns rich in fruit and vegetables are associated with lower mortality rates in patients with CKD, but further well-designed trials with clearly defined portion sizes and quantities of fruit and vegetable intake or dietary pattern are needed.

Keywords: Chronic kidney disease, dietary patterns, fruit intake, vegetable intake, metabolic acidosis, GFR

LIST OF ABBREVIATIONS

AA	Amino acids
ACR	Albumin to creatinine ratio
AER	Albumin excretion rate
AKI	Acute kidney injury
AV	Arterio-venous
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CARE	Cholesterol and Recurrent Events study
CGA	Albuminuria category
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence Interval
CKD	Chronic kidney disease
CRIC	Chronic Renal Insufficiency Cohort
CRISIS	Chronic Renal Insufficiently Standards Implementation Study
CRP	C-reactive protein
CRS	Cardio-renal syndrome
CVA	Cardiovascular accident
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension

DHQ	Dietary History Questionnaire
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
ET	Endothelin
FGF23	Fibroblast growth factor 23
GI	Gastrointestinal
HD	Haemodialysis
HIV	Human immunodeficiency virus
HPT	Hypertension
IHD	Ischaemic heart disease
JBI	Joanna Briggs Institute
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LVH	Left ventricle hypertrophy
MDRD	Modification of Diet in Renal Disease study
MI	Myocardial infarction
MNT	Medical Nutrition Therapy
M.Sc.	Master of Sciences
$NaHCO_3$	Oral Sodium Bicarbonate
NH_4^+	Ammonium
NCD	Non-communicable disease
NEAP	Net endogenous acid production

NWU	North-West University
ORS	Oxygen reactive species
$PaCO_2$	Partial pressure of carbon dioxide
PaCT	Partnership for Cohort Research and Training
PICOS	Population, intervention, comparator, outcome and study design
$PTCO_2$	Plasma Total Carbon Dioxide
PTH	Parathyroid hormone
PhD	Doctor of Philosophy
PRAL	Potential renal acid load
PVD	Peripheral vascular disease
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomised controlled trial
RD	Registered dietitian
RNAE	Renal net acid excretion
RRT	Renal replacement therapy
SA	South Africa
S_k	Serum potassium
SNS	Sympathetic nervous system
TA	Titratable acidosis
UPE	Urinary phosphate excretion
Phos	Phosphate
Prot	Protein (net in table)
vs	versus

LIST OF SYMBOLS AND UNITS

%	percentage
dl	decilitre
g	gram
mg/g:	milligram per gram
ml	millilitre
min	minute
m	metre
m^2	square metre
mEq/L	milliequivalent
mg	milligram
<	less than
>	greater than
Mm Hg	millimetre of mercury
mmol	millimol
mmol/L	millimol per litre
pH	power of hydrogen
K+	Potassium
R	Rand

TABLE OF CONTENTS

LIST OF TABLES

List of Figures

CHAPTER 1 INTRODUCTION

1.1 Background

Chronic kidney disease (CKD) occurs when kidney function fails to return to normal after acute kidney injury (AKI). It can also be caused by progressive renal decline as a result of disease (Willis *et al*., 2012). The most common causes of CKD include diabetes mellitus (DM), hypertension (HPT) and cardiovascular disease (CVD) (Fishbane *et al*., 2015). The conditions set by Kidney Disease Improving Global Outcomes (KDIGO) to describe CKD are: decreased renal function (estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2) present for longer than three months, or indicators of kidney damage such as albuminuria (albumin to creatinine ratio (ACR) >30 mg/24hours or ACR >3 mg/mmol), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, or structural abnormalities detected by imaging (Willis *et al*., 2012; Hill *et al*., 2016).

Chronic kidney disease is a major health concern globally, affecting about 10% of the world's population (Hill *et al*., 2016) and the incidence increases approximately 8% annually (Tonelli *et al*., 2016). It can be estimated that five million South Africans older than 20 years of age have CKD, and in black South Africans, the figure is even higher (Meyers, 2015). Statistics indicate that the prevalence of DM, HPT and CVD will continue to rise, particularly in developing countries. Chronic non-communicable diseases (NCDs) are the number one cause of death and mortality worldwide (Alwan *et al*., 2010), resulting in 40.5 million (70%) deaths globally in 2016 (WHO, 2018). More than 40 million people had DM in 2015 (Mokdad, 2017). The prevalence of DM is almost 11% in most countries and caused 1.6 million deaths globally in 2016 (WHO, 2018). More than 75% of all deaths caused by NCDs occur in low- and middle-income countries (WHO, 2018). Cardiovascular disease was the main contributor in 2016, causing 17.9 million deaths or 44% of all NCD deaths (WHO, 2018). As the prevalence of DM, HPT and CVD rises, so will the global burden of CKD (Fishbane *et al*., 2015).

Renal replacement therapy (RRT) (dialysis or kidney transplant) is the only treatment for the final stage of CKD, with enormous cost to individuals and national health budgets (Matsha *et al*., 2013). A large proportion of people in low- to middle-income countries does not have health insurance and access to health care is limited (George *et al*., 2017). By December 2012, 8 559 patients were receiving chronic RRT in South Africa, of which 6 952 were on dialysis and 1 607 received a functioning kidney transplant (Meyers, 2015). Because of limited resources, only 15–20% of the patients in South Africa who require RRT obtain such treatment. In 2015, it was estimated that the approximate annual cost of dialysis was R 200 000 per patient, while that of

transplantation was R 300 000 in the first year, and R 160 000 to R 180 000 in subsequent years (based on 2014 figures) (Meyers, 2015). A systematic review on outcomes in adults and children with end-stage renal disease (ESRD) requiring dialysis in sub-Saharan Africa found that most patients with ESRD who start dialysis, discontinue treatment passed away as a result of the unaffordable cost (Ashuntantang *et al*., 2017). Only 19% of adult patients received kidney transplantations (Ashuntantang *et al*., 2017).

Furthermore, because of the increased risk and added costs of CVD, including heart failure, myocardial infarction (MI) and stroke, it is essential to prevent the decline of eGFR in patients in any stage of CKD (Fishbane *et al*., 2015). The risk of cardiac death is increased by 46% in people with eGFR levels between 30–60 ml/min/1.73m^2, independent of traditional cardiovascular risk factors (Bidani & Griffin, 2011). The cardiovascular mortality risk increases by 5% with every 10 mL/min/1.73m^2 decrease in eGFR (Subbiah *et al*., 2016). The term cardio-renal syndrome (CRS) has been used to describe the overlapping clinical conditions in heart and kidney dysfunction (Tonelli *et al*., 2016; Di Lullo *et al*., 2017). Ageing, albuminuria, DM, dyslipidaemia, HPT, obesity and smoking are some of the traditional risk factors contributing to CVD in CKD patients (Subbiah *et al*., 2016; Tonelli *et al*., 2016). Besides the traditional risk factors, uraemia-specific factors also contribute to CKD and CVD (Stenvinkel *et al*., 2008; Stinghen *et al*., 2015; Subbiah *et al*., 2016; Tonelli *et al*., 2016). Anaemia, albuminuria, abnormal bone and mineral metabolism, inflammation, oxidative stress and endothelial dysfunction are examples of uraemia-specific factors that arise from accumulating toxins contributing to CKD (Alani *et al*., 2014).

Metabolic acidosis is frequently observed in patients with CKD and may be present in 30–50% of patients in stages 4 or 5 with eGFR <30ml/min/1.73m^2 (Chen & Abramowitz, 2014; De Brito-Ashurst *et al*., 2015). Kraut & Medias (2010) define metabolic acidosis as a primary reduction in serum bicarbonate (HCO_3^-) concentration, a secondary decrease in the arterial partial pressure of carbon dioxide ($PaCO_2$) of ~1 mmHg for every 1 mmol/l fall in serum HCO_3^- concentration, and a reduction in blood pH. Metabolic acidosis occurs when the mechanism regulating the acid-base in the body or the renal acidification mechanisms are compromised as a result of increased production of non-volatile acids or a loss of bicarbonate (Kraut & Medias, 2010; Chen & Abramowitz, 2014). It was found that for the 3 939 participants in stages 2 to 4 CKD who enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study conducted in the United States, every 1 mEq/L higher serum bicarbonate level was associated with a 3% lower risk of developing the investigated renal endpoint (progression of ESRD or a 50% decline in eGFR) during follow-up (Dobre *et al*., 2013). There are various mechanisms proposed by which metabolic acidosis and/or a high dietary acid load may contribute to the progression of kidney

disease (Chen & Abramowitz, 2014). These include ammonia-induced complement activation and increased production of endothelin (ET) and aldosterone (Chen & Abramowitz, 2014; De Brito-Ashurst *et al*., 2015).

Historically, medical nutrition therapy (MNT) has been a significant part of CKD management and treatment, with emphasis on reducing protein, sodium, phosphorus, and potassium intake, limiting fruit and vegetable consumption (Gutierrez *et al*., 2014). For the purpose of this mini-dissertation, the emphasis will be on potassium and phosphorus intake only as this is the focus of this research project. Patients who are advised to follow a low potassium diet (2 000 to 3 000 mg/d) are traditionally advised to avoid high potassium foods such as nuts, seeds, beans, peas, legumes and many fruit and vegetables that contain >200 mg potassium per serving, such as avocados, grapes, kiwi, mango, melon, nectarine, prunes, butternut, mushrooms, potato and sweet potato (NKF, 2017; St-Jules *et al*., 2016). Although potassium restrictions are widely prescribed, there seems to be little evidence to support the premise that a high dietary potassium intake is actually associated with high serum potassium levels (Noori *et al*., 2010; Korgaonkar *et al*., 2010; Goraya *et al*., 2013; Selamet *et al*., 2016; Chang & Anderson, 2017; Snelson *et al*., 2017).

Phosphate intake is restricted in patients with stages 3 to 5 CKD and, while evidence shows that phosphorus is strongly associated with CVD, progression of CKD and death, there is very little evidence to link dietary phosphorus intake directly to adverse clinical outcomes (Murtaugh *et al*. 2012; Selamet *et al*., 2016; Chang & Anderson, 2017; Chang *et al*., 2017). Phosphate restrictions are hard to comply with as organic phosphate is found mainly in protein-rich food such as legumes, meat, poultry, fish, eggs and dairy products (Snelson *et al*., 2017). Legumes have the lowest bioavailability of phosphorus – about 40% (Chang & Anderson, 2017). Dairy products have a bioavailability of 30–60% and meat products up to 80% (Snelson *et al*., 2017), whereas almost 100% of the phosphorus in food additives is absorbed (Bell *et al*., 1977; Chang & Anderson, 2017). Because protein is a great source of dietary phosphate, patients will have to restrict protein intake in order to restrict phosphate intake. Protein restrictions may contribute to the development of protein-energy malnutrition in CKD patients (Cannata-Andia *et al*., 2000; Kates *et al*., 1997).

Evidence shows that fruit and vegetables intake improve metabolic acidosis, decrease systolic blood pressure (BP) and decrease kidney damage in stage 4 CKD without causing hyperkalaemia (Goraya *et al*., 2013). De Brito-Ashurst *et al*. (2015) found that correcting acidosis decreases progression of renal failure, improves nutritional status and also improves the well-being and quality of life of CKD patients. Studies that focus on overall dietary patterns

to predict CVD and cardiovascular risk found favourable outcomes in participants with a higher consumption of fruit, vegetables, legumes, whole grains, poultry and fish and a lower consumption of red meat, salt, and refined sugars (Widmer *et al*., 2015; Kelly *et al*., 2017). Western eating patterns generally considered to be high in red - and processed meat, sugary snacks, fried food and refined carbohydrate have been shown to produce a high dietary acid load, which leads to reduced kidney function by causing metabolic acidosis or subclinical acid retention (Kraut & Medias, 2010; Chen & Abramowitz, 2014). Cheese, meat, eggs and grains are the common foods known to provide a high dietary acid load, while fruit and vegetables are more base producing (Chen & Abramowitz, 2014; Scialla & Anderson, 2013).

A high dietary acid load enhances eGFR regression by increasing kidney ET and aldosterone production, while dietary alkali improves eGFR (Chen & Abramowitz, 2014; Goraya & Wesson, 2014; Scialla & Anderson, 2013). A higher fruit and vegetable intake results in lower net production and retention of hydrogen ions, with better preservation of kidney function (Adeva & Souto, 2011). Increased vegetable intake may have favourable effects on phosphorus metabolism in CKD. Phosphate from foods of plant origin is much less efficiently absorbed by the intestine due to the lower bioavailability of phytate compared to phosphate from foods of animal origin, in particular, processed foods (Chang & Anderson, 2017). The HPT reduction effect of fruit and vegetables is another mechanism by which they can preserve kidney function (Dauchet *et al*., 2006; He *et al*., 2007). Increased fruit and vegetable intake also increase fibre intake, which improves the levels of uraemic toxins in patients with CVD (Snelson *et al*., 2017). As mentioned earlier, there is little evidence indicating that phosphate intake is associated with serum phosphate concentrations in CKD stages 3 to 5, and that higher phosphate intake is linked to ESRD, CVD or all-cause mortality in patients with CKD stages 3 to 5 (Selamet *et al*., 2016). Restricting phosphate also means restricted protein intake, which is associated with malnutrition and higher mortality rates in CKD patients; for this reason, consideration of the phosphate to protein ratio of food is recommended to ensure that patients will receive enough protein while controlling phosphate intake (Selamet *et al*., 2016; Snelson *et al*., 2017).

Fruit and vegetable intake might, therefore, be a cost-effective and acceptable management option for patients with CKD but the quantity and types of fruit and vegetables suitable during each stage of CKD are not well defined. Therefore, the aim of this dissertation was to investigate the current evidence available on the effect of fruit and vegetable intake on clinical outcomes of patients with CKD.

1.2 Study aim and objectives

The aim of this study was to perform a systematic review of studies that investigate the effect of various fruit and vegetable portions specified/identified clinical outcomes of patients with CKD.

The following specific objectives were identified:

1. To conduct a detailed search on randomised controlled trials (RCTs) meeting the inclusion criteria.to identify relevant studies.

2. To evaluate included studies regarding risk of bias and quality.

3. To conduct meta-analysis if possible.

1.3 Clinical outcomes that were investigated in this study

- eGFR
- Metabolic acidosis (Potential renal acid load (PRAL), plasma total carbon dioxide ($PTCO_2$))
- Systolic BP
- ESRD or commencement of dialysis
- Mortality

1.4 Structure of this dissertation

Chapter 1 is an introduction to the topic and describes the aims, objectives, clinical outcomes and structure of the dissertation, as well as the research output and contributions of the members of the research team. The ethical approval documents for this dissertation can be found in Annexure A.

Chapter 2 consists of a literature review of the topic. This includes a discussion of the definition and stages of CKD, the prevalence and impact of CKD, the link between CKD and CVD, metabolic acidosis in CKD and medical nutrition therapy (MNT) in CKD, looking specifically at the current nutritional recommendations for patients with CKD, potassium and phosphorus intake and the protein to phosphorus ratio.

Chapter 3 is an article prepared for submission to the Journal of Renal Nutrition titled: “Effect of fruit and vegetable intake on the progression of kidney failure in adults with chronic kidney

disease: A systematic review". The study eligibility criteria and data extraction form can be seen in Annexure B and C respectively. This article has been written according to the instructions of the journal to authors as seen in Annexure D. It is a systematic review of randomised controlled trials (RCTs). This systematic review has been registered on the PROSPERO register with registration number: CRD42019145160.

Chapter 4 is a follow-up narrative systematic review to further expand on the findings. This is a narrative systematic review of cohort studies to investigate the effect of dietary patterns on the progression of kidney disease and mortality in adults with CKD. The original systematic review (Chapter 3) was conducted only on RCTs, whereas observational studies were used for this review. Very few RCTs were conducted on this topic because of the severity of the disease. It was decided to add this additional chapter of observational studies to address the gaps in the RCTs. The observational studies included are of value as they provide longer follow-up data and larger sample sizes. This review is also prepared for submission to the Journal of Renal Nutrition and is titled: "Dietary patterns and progression of kidney failure and mortality in adults with chronic kidney disease: A narrative systematic review."

Chapter 5 consists of a general discussion of the findings of the study, together with recommendations for future studies and conclusion.

Chapters 1, 2 and 5 were referenced according to the NWU Harvard style, whilst chapters 3 and 4 were referenced according to the American Medical Association style and format according to the specifications to authors for publication in the Journal of Renal Nutrition (Annexure D). The references for each chapter are found at the end of the chapter. The certificate of language editing can be seen in Annexure E.

1.5 Research output

These systematic reviews will be submitted to the Journal of Renal Nutrition for publication. It is further anticipated that the results will be presented at relevant national and/or international conferences.

1.6 Contributions of the members of the research team

The contributions of the members of the research team can be seen in Table 1.1.

Table 1-1: Research team particulars

Name	Qualification	Professional registration*	Role and responsibility
Jacomie Nel	B.Sc. Dietetics	DT0022020	M.Sc. student Developed a research proposal and title for study. Set problem statement, aims and objectives. Data search, data extraction, critical appraisal of the data extracted and statistical analysis. Writing of protocol, literature study and systematic review. Compiling of dissertation and editing of articles according to journal specifications.
Dr R. Dolman	PhD Dietetics	DT0011738	Supervisor Critically appraised the data extracted and supported student in the writing of the protocol and systematic review. Provided expert advice on CKD and CVD.
Dr M. Lombard	PhD Dietetics	DT0014702	Co-Supervisor Critically appraised of the data extracted and supported student in the writing of the protocol and systematic review. Provided of expert advice on systematic reviews and meta-analysis

B.Sc.: Bachelor of Science, CKD: chronic kidney disease, CVD: cardiovascular disease, Dr: doctor, M.Sc.: Master of Science, PhD: Doctor of Philosophy *Registered at the Health Professionals Council of South Africa (HPCSA).

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CHAPTER 2 LITERATURE REVIEW

2.1 Introduction

Chronic kidney disease (CKD) occurs when kidney function fails to return to normal after acute kidney injury (AKI), or can be caused by progressive renal decline as a result of disease (Willis *et al*., 2012). Diabetes mellitus (DM), hypertension (HPT) and cardiovascular disease (CVD) are the most common causes of CKD (Fishbane *et al*., 2015). Patients suffering from CKD are at increased risk of the development of CVD and have an 8- to 10-fold increased risk of cardiovascular mortality (Fishbane *et al*., 2015) and developing end-stage renal disease (ESRD). Proteinuria, metabolic acidosis and HPT are three of the potentially modifiable risk factors in CKD. Traditional dietary treatment of CKD has focused on reducing protein, sodium, phosphorus and potassium intake, limiting fruit and vegetable intake (Willis *et al*., 2012; Gutierrez *et al*., 2014). Alkali treatment (bicarbonate and fruit and vegetable intake), however, seems beneficial in reducing metabolic acidosis in patients with CKD (Scialla & Anderson, 2013). Studies have found that fruit and vegetables reduce metabolic acidosis, decrease systolic blood pressure (BP) and decrease kidney damage in CKD, without causing hyperkalaemia (Goraya *et al*., 2013; Goraya *et al*., 2013). In this review of the literature, the effect of fruit and vegetable intake on the progression of CKD be investigated and discussed. To do so, the link between CKD and CVD is explored. Dietary patterns and the quantity of fruit and vegetable intake most beneficial in CKD and CVD treatment is discussed. The occurrence and treatment of metabolic acidosis in CKD are included, as well the effect that micronutrient intake, specifically of potassium and phosphate, has on CKD progression.

2.2 Prevalence and impact of chronic kidney disease

Chronic kidney disease is a global health concern affecting about 10–13% of people (Hill *et al*., 2016), with a rising incidence of approximately 8% annually (Tonelli *et al*., 2016). A recent systematic review and meta-analysis of CKD prevalence globally by Hill *et al*. (2016), found a prevalence of 13.4% in all five stages of CKD. The review included 100 studies of diverse quality, comprising 6,908,440 participants. Regarding sub-Saharan Africa, a meta-analysis which included 90 articles with data for 21 countries (South Africa, Nigeria and Ethiopia covered half of the data), reported an estimated CKD prevalence of 13.9% (Stanifer *et al*., 2014).

It is speculated that the incidence of CKD in South Africa is 3- to 4-fold higher than in developed countries (Naicker, 2010). The reason for this is that CKD is disproportionately associated with low-income status, with increased risk of albuminuria, progression of CKD and ESRD (Fishbane

et al., 2015) and therefore the fastest increase in CKD is expected in developing countries (Tonelli *et al*., 2016). This is due to non-infectious diseases (mainly T2DM and HPT), infectious diseases and poor health care (George *et al*., 2017). A 2018 meta-analysis of 98 studies involving 98 432 participants found an overall CKD prevalence of 15.8% on the African continent (Kaze *et al*., 2018). It is predicted that five million South Africans older than 20 years of age have CKD, and in black South Africans, the figure is even higher (Meyers, 2015). In a study by Matsha *et al*. (2013) in the Western Cape, the prevalence of CKD stages 3 to 5 was 14.8%.

Chronic Non-Communicable Diseases (NCDs) are the number one cause of death and mortality worldwide (Alwan *et al*., 2010), resulting in 40.5 million (70%) deaths globally in 2016 (WHO, 2018). The prevalence of DM is almost 11% in most countries and caused 1.6 million deaths in 2016 (WHO, 2018). More than 75% of all deaths caused by NCDs occur in low- and middle-income countries (WHO, 2018). Cardiovascular disease was the main culprit in 2016, causing 17.9 million deaths or 44% of all NCD deaths (WHO, 2018). As mentioned earlier, the main causes of CKD are DM, HPT and CVD. Statistics indicate that the prevalence of these main causes of CKD will continue to rise, particularly in developing countries (Alwan *et al*., 2010; Mokdad, 2017; WHO, 2018). This will most probably result in increasing the global burden of CKD even further. In addition, the presence of CKD in patients with CVD is associated with premature mortality. The risk of cardiac death is increased by 46% in people with estimated glomerular filtration rate (eGFR) levels between 30-60 ml/min/1.73m^2, independent of traditional cardiovascular risk factors (Bidani & Griffin, 2011).

The medical management in early stages of CKD, prior to reaching the stage where dialysis or transplantation is needed, surpasses medical costs of other chronic conditions such as stroke and cancer (Small *et al*., 2017). The final stage of CKD requires renal replacement therapy (RRT), including dialysis and kidney transplant, at enormous cost to individuals and national health budgets (Matsha *et al*., 2013). Developed countries spend 2 to 3% of their entire national health-care budget on treatment for ESRD. It is estimated that 2 million people worldwide receive RRT to prolong life (Fishbane *et al*., 2015). A small number of individuals have health insurance in low- to middle-income countries, and access to health care is limited (George *et al*., 2017).

Consequently, an estimated one million people die from untreated ESRD each year (Meyers, 2015). By December 2012, 8 559 patients were receiving chronic RRT in South Africa – 6 952 on dialysis and 1 607 with a functioning kidney transplant (Meyers, 2015). Only 15–20% of the patients in South Africa who require RRT obtain such treatment, due to limited access to

treatment. In 2015, the approximate annual cost of dialysis was estimated at R 200 000 per patient and that of transplantation, at R 300 000 in the first year and R 160 000 to R 180 000 in subsequent years (based on 2014 statistics) (Meyers, 2015). A systematic review on outcomes in adults and children with ESRD requiring dialysis in sub-Saharan Africa, found that most patients with ESRD that start dialysis, discontinue treatment because of the cost and suboptimum dialysis quality, and passed away (Ashuntantang *et al*., 2017). Only 10% of adults and 35% of children with ESRD in the study received dialysis for at least three months as they could not afford to continue treatment (Ashuntantang *et al*., 2017). Ashuntantang *et al* (2107) also reported that fewer than 20% of the adult patients received kidney transplantations. The global demand for RRT is predicted to more than double by 2030 (Liyanage *et al*., 2015). Slowing or preventing CKD progression will considerably cut health care costs as health care costs more than double in the later stages of CKD (Kramer *et al*., 2018).

2.3 Definition and staging of chronic kidney disease

As mentioned earlier, CKD occurs when kidney function fails to return to normal after AKI or can be caused by progressive renal decline as a result of disease (Willis *et al*., 2012). The Kidney Disease Improving Global Outcomes (KDIGO) use the following criteria to diagnose CKD: decreased renal function (eGFR <60 ml/min/1.73m^2) present for longer than 3 months, or indicators of kidney damage such as albuminuria (albumin to creatinine ratio (ACR) >30 mg/24 hours or >3 mg/mmol), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, or structural abnormalities detected by imaging (Willis *et al*., 2012; NICE, 2014; Hill *et al*., 2016).

Patients with CKD are classified in five stages, using the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (Willis *et al*., 2012) as seen in Table 2.1. KDOQI recommend that CKD be categorised according to cause, GFR category and albuminuria category (CGA) (as seen in Table 2.2). A higher stage represents lower kidney function. Glomerular filtration rate stage 3 has been separated into 3a and 3b to reflect the increasing CVD risk (NICE, 2014). Dialysis should be initiated when the patient presents with at least one of the following: signs of kidney failure such as acid–base or electrolyte abnormalities or pruritus; inability to control volume status or BP, progressive worsening of nutrition status or loss of cognitive function (Willis *et al*., 2012). This usually occurs when the patient is in the G5 GFR category with a GFR value of 5 to 10 ml/min/1.73m^2. Renal transplantation should be considered when the GFR is <20 ml/min/1.73m^2 and there is evidence of permanent GFR regression during the previous 6 to 12 months (Willis *et al*., 2012).

Table 2-1: Glomerular filtration rate categories of chronic kidney disease (Willis *et al.*, 2012)

GFR category	Description of stage	GFR value (ml/min/1.73m^2)
G1	Normal or high kidney function	>90
G2	Mildly decreased kidney function	60-89
G3a	Mildly to moderately decreased kidney function	45-59
G3b	Moderately to severely decreased kidney function	30-44
G4	Severely decreased kidney function	15-29
G5	Kidney failure	<15

GFR: glomerular filtration rate

Table 2-2: Albuminuria categories in chronic kidney disease (Willis *et al.*, 2012)

Category	Description of stage	AER (mg/24 hours)	ACR (mg/mmol)	ACR (mg/g)
A1	Normal to mildly increased	<30	<3	<30
A2	Moderately increased	30-300	3-30	30-300
A3	Severely increased	>300	>30	>300

ACR: albumin-to-creatinine ratio; AER: albumin excretion rate

2.4 The link between chronic kidney disease and cardiovascular disease

Chronic kidney disease increases risk for CVD and CVD increases the risk of developing CKD. The link between CKD and CVD is well recognised and was first suggested around 1830 by Richard Bright (Subbiah *et al.*, 2016). The link can manifest in several different ways, including atrial or ventricular arrhythmias, congestive heart failure (CHF), coronary artery disease (CAD), myocardial infarction (MI) and stroke (Tonelli *et al.*, 2016). The risk of cardiovascular mortality has been seen to increase by 5% with every 10 mL/min per 1.73 m^2 reduction in eGFR (Subbiah *et al.*, 2016). The term cardio-renal syndrome (CRS) has been used to describe the overlapping clinical conditions in heart and kidney dysfunction (Alani *et al.*, 2014; Tonelli *et al.*,

2016; Di Lullo *et al.*, 2017). Some of the traditional risk factors contributing to CVD in CKD patients by accelerating the atherosclerotic process, include ageing, albuminuria, DM, dyslipidaemia, HPT, obesity and smoking are (Subbiah *et al.*, 2016; Tonelli *et al.*, 2016).

The main cause of CKD in 21% of patients on RRT in the South African Registry is HPT (Adrogue & Madias, 2007; Moosa *et al.,* 2015). Hypertension is almost inevitable in patients who have developed CKD due to sodium retention and the stimulation of the renin-angiotensin system in renal disease (Alani *et al.,* 2014). A population-based cross-sectional study that was performed in 6 sites in 4 African countries, namely Burkina Faso, Ghana, Kenya and South Africa found that the prevalence of HPT ranged from 15.1–54.1%. Of concern was the fact that fewer than half of the hypertensive participants were aware of their BP status (Gomez-Olive *et al.*, 2017). The average prevalence of HPT in the three South African sites was >40%. It is predicted that 60% of adults globally will have HPT by 2025 (Adrogue & Madias, 2007). In CKD, HPT may cause cardiac damage by causing left ventricular hypertrophy (LVH) (Locatelli *et al.,* 2003). The control of HPT is the most important factor in both the primary prevention of CKD and the progression of CKD. In patients with CKD, the goal BP is <130/80 mmHg (Moosa *et al.,* 2015). The recommended goal is $\leq$140/90 mmHg for patients with CKD and normal to mildly increased albuminuria (Willis *et al.*, 2012; Taler *et al.,* 2013). Strong evidence proves the link between HPT and CVD, but reaching optimal BP targets remains a significant challenge in patients with CKD (Alani *et al.,* 2014).

Cardiovascular disease is the leading NCD globally, contributing to 17 million deaths per annum (Mendis & Alwan, 2011; WHO, 2018). CVD such as ischaemic heart disease (IHD) and stroke is projected to overtake human immunodeficiency virus (HIV) as the leading cause of mortality in sub-Saharan Africa by 2030 (Laurence *et al*., 2016). The South African Partnership for Cohort Research and Training (PaCT) pilot study, which included 489 teachers from 11 schools, found that the prevalence of CVD risk factors was high in this population group: HPT – 48.5%; hypercholesterolaemia – 20.5%; smoking – 18%; DM – 10.1%; CKD – 10.4%, while 84.7% were overweight (31.1%) or obese (53.6%) (Laurence *et al*., 2016). Almost 20% of the participants were at high risk of a heart attack or stroke in the next decade.

Although overlapping risk factors contribute to CKD and CVD, factors other than just the traditionally known risk factors contribute to the pathogenesis of CVD in CKD patients. Uraemia-specific factors that arise from accumulating toxins also contribute (Stenvinkel *et al.*, 2008; Stinghen *et al.*, 2015; Subbiah *et al.*, 2016; Tonelli *et al.*, 2016). Anaemia, albuminuria, abnormal bone and mineral metabolism, inflammation, oxidative stress and endothelial dysfunction are examples of uraemia-specific factors contributing to CKD (Alani *et al.*, 2014).

2.4.1 The five subtypes of cardio-renal syndrome

Cardio-renal syndrome (CRS) is the term used to define overlapping clinical conditions in heart and kidney dysfunction (Alani *et al*., 2014; Tonelli *et al.*, 2016; Di Lullo *et al.*, 2017). Cardio-renal syndrome can be divided into cardio-renal and reno-cardiac CRS depending on the origin of the CRS, which can then be divided again according to acute or chronic onset (Di Lullo *et al.*, 2017). The five subtypes describing the link between renal disease and CVD can be seen in Table 2.3.

Table 2-3: The five subtypes of cardio-renal syndrome (Di Lullo *et al.*, 2017; Tonelli *et al.*, 2016)

Subtype	Name of subtype	Description/ example of subtype
Type 1	Acute cardio-renal	Characterised by acute heart failure leading to AKI. Example: acute coronary syndrome leading to acute heart and kidney failure
Type 2	Chronic cardio-renal	Chronic heart failure leading to CKD
Type 3	Acute reno-cardiac syndrome	Linked to acute heart failure caused by AKI, usually due to AKI-related uraemia.
Type 4	Chronic reno-cardiac syndrome	Represents CKD leading to heart failure. Example: CKD or diabetic nephropathy causing LVH and diastolic heart failure
Type 5	Secondary CRS	Systemic diseases such as sepsis, vasculitis, DM, amyloidosis and immune-mediated diseases leading to heart and kidney failure

AKI: Acute Kidney Injury; CKD: Chronic kidney disease; CRS: cardio- renal syndrome; DM: diabetes mellitus; LVH: left ventricle hypertrophy.

2.4.2 Pathophysiology of cardio-renal syndrome

During **Type 1 CRS**, acute cardiac failure leads to decreased renal blood flow and decreased effective glomerular perfusion pressure resulting in AKI (Di Lullo *et al.*, 2017). This is caused by the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) activation leading to vasoconstriction in patients with acute heart failure. Ischaemic injury to the renal tubular epithelium causes cell death, which results in a loss of epithelial cell structure and function (Di Lullo *et al.*, 2017).

Type 2 CRS describes chronic cardiac failure leading to the onset or progression of CKD. The main pathophysiological mechanisms involved in this type of CRS include neurohormonal

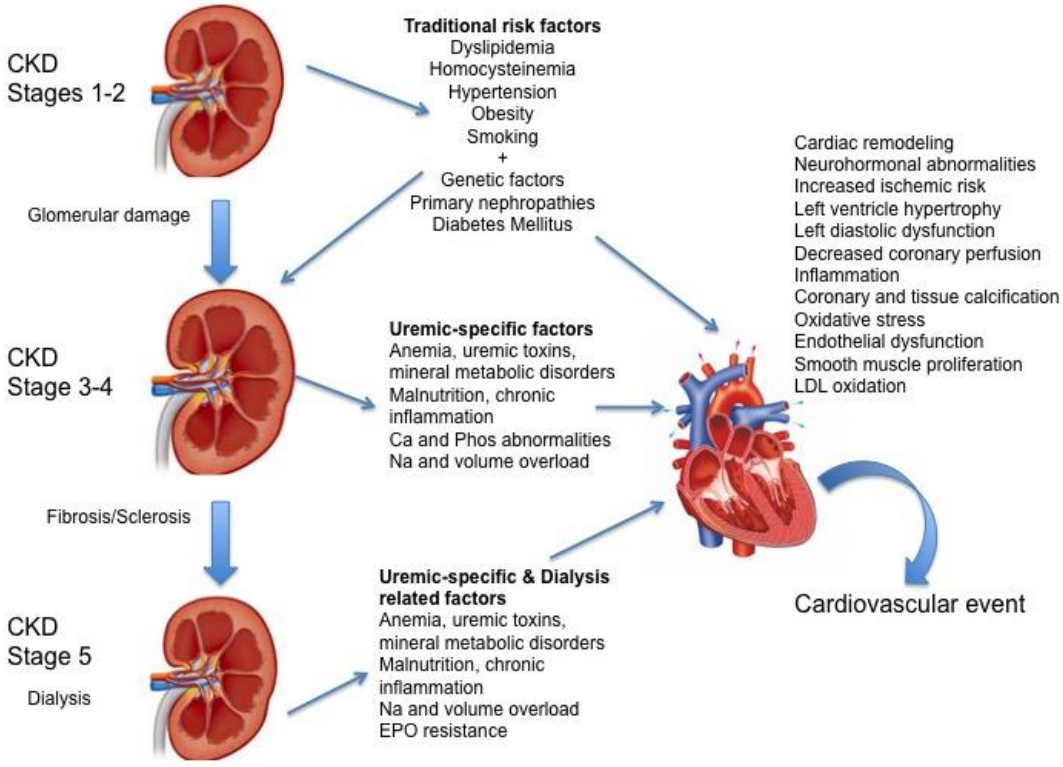
activation, renal hypoperfusion and venous congestion, inflammation, atherosclerosis and oxidative stress (Di Lullo *et al.*, 2017).

Type 3 CRS occurs when AKI contributes to or triggers the development of acute cardiac dysfunction. Possible mechanisms by which AKI directly contributes to heart failure include inflammatory surge, oxidative stress and secretion of neurohormones. Acute kidney injury can also indirectly trigger cardiac dysfunction by volume overload, metabolic acidosis and electrolyte disorders like hyperkalaemia and hypocalcaemia (Di Lullo *et al.*, 2017).

Type 4 CRS occurs when CKD (at any stage) leads to cardiac dysfunction as seen in Figure 2.1. In stages 1 and 2 of CKD the traditional risk factors for CKD and CVD act as triggers leading to damaging modifications in the heart structure and causing CKD progression (Di Lullo *et al.*, 2017). In stages 3 and 4 of CKD the uraemic-specific factors involved in the pathogenesis of CVD, such as anaemia, mineral metabolic disorders and systemic inflammation begin to manifest. The decline of eGFR leads to accumulation of toxins such as microglobulin, guanidines, phenols, indoles, aliphatic amines, furans, polyols, nucleosides, leptin, serum amyloid A protein, asymmetric dimethyl arginine, parathyroid hormone (PTH) and erythropoiesis (EPO) inhibitors, which contribute to chronic inflammation, leading to cardiac dysfunction (Di Lullo *et al.*, 2017). In stage 5 CKD, both uraemia-specific factors and dialysis-related factors contribute to cardiac dysfunction. Systemic low-grade chronic inflammation evident in high levels of C-reactive protein (CRP) plays a central role in the pathophysiology. Increased oxidative stress occurs due to decreased antioxidant capacity associated with renal function loss and increased production of oxygen reactive species (ORS) (Cachofeiro *et al.*, 2008; Tonelli *et al.*, 2016). Inflammation and oxidative stress can cause damage directly to the cardiac tissues or escalate the atherosclerotic process (Ramana *et al.*, 2016; Stinghen *et al.*, 2015). Bone and mineral disorders such as hypophosphataemia, hyperparathyroidism and Vitamin D deficiency lead to cardiovascular calcification. Chronic kidney disease independently accelerates IHD and contributes to pressure and volume overload as a result of HPT and calcification. In this stage, sudden death and CHF occur, caused by numerous damaging myocardial modifications, especially those associated with fibrosis and vascular calcifications (Di Lullo *et al.*, 2017). Volume overload with underlying anaemia of chronic disease and the presence of haemodialysis arterio-venous (AV) fistulae worsen CHF. Atherosclerotic damage in the medium and large arteries leads to cerebrovascular accidents (CVA), peripheral vascular disease (PVD), and abdominal aorta aneurysm (Bucharles *et al.*, 2010).

In **Type 5 CRS**, heart and kidney dysfunction occur simultaneously as a result of many systemic processes such as sepsis, drug toxicity, infection and connective tissue disorders. The

underlying disease determines the pathophysiology of Type 5 CRS (Di Lullo *et al.*, 2017).



Ca: calcium; CKD: chronic kidney disease; EPO: Erythropoietin, LDL: low-density lipoprotein; Na: sodium, phos: phosphate.

Figure 2-1: Pathophysiological pathway of chronic kidney disease resulting in cardiovascular dysfunction in Type 4 cardio-renal syndrome Adapted from Bucharles *et al.* (2010) and Di Lullo *et al.* (2017).

2.4.3 Nutritional therapy in the prevention and treatment of cardiovascular disease

Diet and lifestyle modifications are extremely important in the prevention and treatment of CVD (Alissa & Ferns, 2015; Gallieni & Cupisti, 2016). Lifestyle choices are responsible for an estimated 40% of early CVD deaths (Widmer *et al.,* 2015). Nutrients such as potassium, folate, vitamins, fibre and phenolic compounds found in fruit and vegetables protect against the development of CVD by various pathways. Examples include: decreasing oxidative stress by providing antioxidants, improving dyslipidaemia, decreasing BP, lessening insulin resistance, and improving haemostasis regulation (Dauchet *et al.*, 2006; He *et al.*, 2007). Numerous observational studies have consistently found positive results relating to fruit and vegetable intake and CVD outcomes; however, evidence in the form of randomised controlled trials

(RCTs) is still lacking. Efforts to find individual links between protective nutrients and disease outcomes have been disappointing and therefore, recent studies focus more on overall dietary patterns (Alissa & Ferns, 2015).

For decades, researchers focused on single nutrient theories, which were found to be inadequate in explaining many effects of diet on NCD. Thus, a new field of study on the complexity of the biological effects of foods and diet patterns were created (Heidemann *et al*., 2008; Mozaffarian *et al*., 2018). Dietary patterns analysis focuses on the overall diet; the foods, food groups and nutrients included; their combination and variety; and the frequency and quantity with which they are habitually consumed (Cespedes & Hu, 2015; Mozaffarian *et al*., 2018). Physiological intervention trials, large cohort studies, and RCTs showed more consistent evidence for diet patterns, such as the Mediterranean diet or the Dietary Approaches to Stop Hypertension (DASH) diet and similar food-based patterns, than for single nutrients (Wirth *et al*., 2012; Mozaffarian *et al*., 2018).

One example of this is the well-known and documented protective effect of fruit, vegetables, and whole grains against several chronic diseases. However, the evidence for this effect is linked to whole foods, rather than supplements of individual dietary constituents (Alissa & Ferns, 2015). The actions of individual dietary constituents do not fully explain the observed health benefits of diets rich in fruit and vegetables (Alissa & Ferns, 2015). Supplementation with individual antioxidants has been investigated in RCTs but has not consistently shown a benefit (Yusuf *et al.,*2000; Alissa & Ferns, 2015). Isolated components of the diet may either lose their bioactivity, may not behave the same way as they do in whole foods, or may require other constituents of the whole food for their full functional activity (Alissa & Ferns, 2015). Much attention has been paid to antioxidant vitamins found in fruit and vegetables, yet these foods are also rich in fibre (Smith & Tucker, 2011) and nitrate (Lidder & Webb, 2013). A diet rich in fruit and vegetables will therefore also be rich in a complex mixture of micronutrients, phytochemicals and fibre, with the exact combination depending on the type of fruit and vegetables consumed. The additive and synergistic effects of these nutrients in fruit and vegetables may thus be responsible for their potent antioxidant activities (Wolfe *et al.,* 2008; Song *et al.,* 2010). Such synergy may partially explain why no single antioxidant can replace the combination of nutrients in fruit and vegetables in achieving the observed health benefits. Individuals do not consume nutrients or food in isolation and, therefore, nutritional advice is often easier to understand in the context of foods rather than the individual nutrients they contain (Cespedes & Hu, 2015).

Studies that focused on overall dietary patterns to predict cardiovascular risk found favourable

outcomes in participants with a higher consumption of fruit, vegetables, legumes, whole grains, poultry and fish and a lower consumption of red meat, salt, and refined sugars (Widmer *et al.,* 2015; Kelly *et al*., 2017). Western eating patterns with a diet high in red and processed meat, sweets, fried food and refined carbohydrates were related to higher cardiovascular risk (Alissa & Ferns, 2015; Hu *et al.,* 2000). Dauchet *et al.* (2006) conducted a meta-analysis consisting of nine observational studies including 221 080 participants, found that fruit intake decreased the risk of coronary heart disease (CHD) by 7% and each additional portion of fruit and vegetables daily decreased the risk of CHD by another 4%. It is important to note that an increased fruit and vegetable intake is also associated with a healthier lifestyle, including exercise and non-smoking, which also affects cardiovascular risk, although this was not adjusted for in all the included studies. Another meta-analysis of 13 cohort studies with a total of 278 459 individuals found a 17% decline in CHD risk in individuals consuming more than five portions of fruit and vegetables daily (He *et al.*, 2007). Individuals consuming 3 to 5 servings of fruit and vegetables daily had a 7% reduction in CHD risk compared with patients consuming fewer than three portions daily (He *et al.*, 2007).

A meta-analysis of 16 prospective cohort studies that included 833 234 participants found that higher consumption of fruit and vegetables is associated with a lower risk of all-cause mortality, especially CVD mortality (Wang *et al*., 2014). Each additional daily serving of fruit and vegetables combined was found to reduce the risk of CVD mortality by 4%. Similarly, one serving of fruit reduced it by 5% and one serving of vegetables alone reduced the mortality risk by 4%. The study also found that lower all-cause mortality was detected when intake included about two servings of fruit a day and about three servings of vegetables daily (Wang *et al.,* 2014). The threshold was found at about five servings of fruit and vegetables daily, whereafter the mortality risk did not reduce further with a higher intake (Wang *et al.,* 2014).

Both the DASH and Mediterranean diets have proven to be effective in preventing and treating CVD. Both these diets are well balanced and rich in fruit and vegetables (Gallieni & Cupisti, 2016; Widmer *et al.,* 2015). Fruit and vegetable intake can help to reduce the total energy intake of an individual and replace unhealthy food in the diet, subsequently lowering the body mass index (BMI) and risk of obesity (Epstein *et al.,* 2001; Lin & Morrison, 2002). Fruit and vegetables contain magnesium and potassium, which help to lower BP (Wang *et al.,* 2014; Zhang *et al.,* 2012). There are differences in the classification of fruit and vegetables across studies; the quantity and bioavailability of nutrients can vary widely, the portion sizes of fruit and vegetables may vary and different methods are used in studies to gather the diet history. Despite all the factors that could affect the results, there is evidence of a strong association between consumption of fruit and vegetables, and risk of CVD mortality.

As described in Figure 2.1, CVD and CKD share overlapping risk factors and exacerbate each other. Cardiovascular disease directly influences CKD; therefore dietary patterns which modify several risk factors in CVD should be beneficial not only in preventing CKD but also in delaying regression of kidney function in patients with CKD.

2.5 Metabolic acidosis in chronic kidney disease

2.5.1 Definition of metabolic acidosis

Metabolic acidosis is frequently observed in patients with CKD and may be present in 30 to 50% of patients in stages 4 or 5 with eGFR <30 ml/min/1.73m^2 (Chen & Abramowitz, 2014; de Brito-Ashurst *et al.*, 2015).

Kraut & Medias (2010) define metabolic acidosis as:

1) A primary reduction in serum bicarbonate (HCO_3^-) concentration dropping below 22 mEq/L; 2) a secondary decrease in the arterial partial pressure of carbon dioxide (PCO_2) of ~1 mmHg for every 1 mmol/l fall in serum HCO_3^- concentration; 3) and a reduction in blood pH. The reference values for these markers under normal conditions can be seen in Table 2.4.

Metabolic acidosis occurs when the mechanism regulating the acid–base in the body or the renal acidification mechanisms are compromised as a result of increased production of nonvolatile acids or loss of bicarbonate (Chen & Abramowitz, 2014; Kraut & Medias, 2016). Acute metabolic acidosis is common in critically ill patients as a result of increasing production of organic acids like keto acids or lactic acid. Chronic metabolic acidosis is caused by bicarbonate wasting and/or impaired renal acidification (Kraut & Medias, 2016). A decline in eGFR leads to an increase in the incidence and severity of metabolic acidosis (Willis *et al.*, 2012).

Table 2-4: Reference value under normal conditions (Rodrigues Neto Angèloco *et al*., 2017)

pH: 7.40 ± 0.02
PCO_2: 38 ± 2 mmHg
HCO_3: 24 ± 2 mmol/L

2.5.2 Effects of metabolic acidosis on the body and mechanisms of acidosis-induced acceleration of chronic kidney disease

Optimal bicarbonate levels are in the range of 24-26 mEq/L (Dobre *et al.*, 2013). Serum bicarbonate concentrations of <22 mmol/L are linked to an increased risk of CKD progression (Di Iorio *et al.,* 2016; Kovesdy *et al*., 2009; Willis *et al.*, 2012) and a 43% higher mortality risk (Chen & Abramowitz, 2014; Kovesdy *et al.*, 2009). Metabolic acidosis contributes to various complications in the body; acute metabolic acidosis in particular, affects the cardiovascular system (Kraut & Medias, 2010; de Brito-Ashurst *et al.*, 2015). Chronic metabolic acidosis affects the musculoskeletal system, causing uraemic bone disease, skeletal muscle wasting, increased protein catabolism, inflammation, impaired glucose homeostasis, accelerated kidney degradation and increased mortality (Chen & Abramowitz, 2014; de Brito-Ashurst *et al.*, 2015; Kraut & Medias, 2016; Rodrigues Neto Angéloco *et al*., 2017). Even mild metabolic acidosis could decrease eGFR and lead to regression of kidney function (Kraut & Medias, 2010; de Brito-Ashurst *et al*., 2015). For the 3,939 participants in stages 2 to 4 CKD who enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study, every 1 mEq/L higher serum bicarbonate level was found to be associated with a 3% lower risk of developing renal outcomes, such as ESRD or a significant decline in eGFR during follow-up (Dobre *et al.*, 2013).

Various mechanisms are proposed by which metabolic acidosis and/or a high dietary acid load (discussed in section 2.5.3) may contribute to progression of kidney disease (Chen & Abramowitz, 2014). These include ammonia-induced complement activation and increased production of endothelin (ET) and aldosterone (Figure 2.2). Total ammonium excretion decreases with progressive CKD, but the ammonia generation per nephron actually increases as a normal compensatory mechanism to excrete increased acid load per nephron in the setting of progressive renal mass loss (Chen & Abramowitz, 2014; de Brito-Ashurst *et al.*, 2015). This excessive ammonia production per nephron results in a non-enzymatic activation of the alternative complement pathway in the renal interstitium, resulting in a chronic inflammatory state (de Brito-Ashurst *et al.*, 2015). Acidosis has also been shown to increase ET-mediated tubule-interstitial injury. Endothelin is an endothelial cell-derived peptide which regulates multiple renal functional parameters, including acid–base handling. Specifically, ET-1 mediates increased renal acid excretion in response to a systemic acid challenge. Excess aldosterone could also mediate the decline in GFR caused by acidosis, through its haemodynamic effects and its pro-fibrotic actions. Hyperaldosteronism in the setting of reduced nephron mass contributes to HPT, proteinuria and glomerulosclerosis in the remnant kidney model (Chen & Abramowitz, 2014).

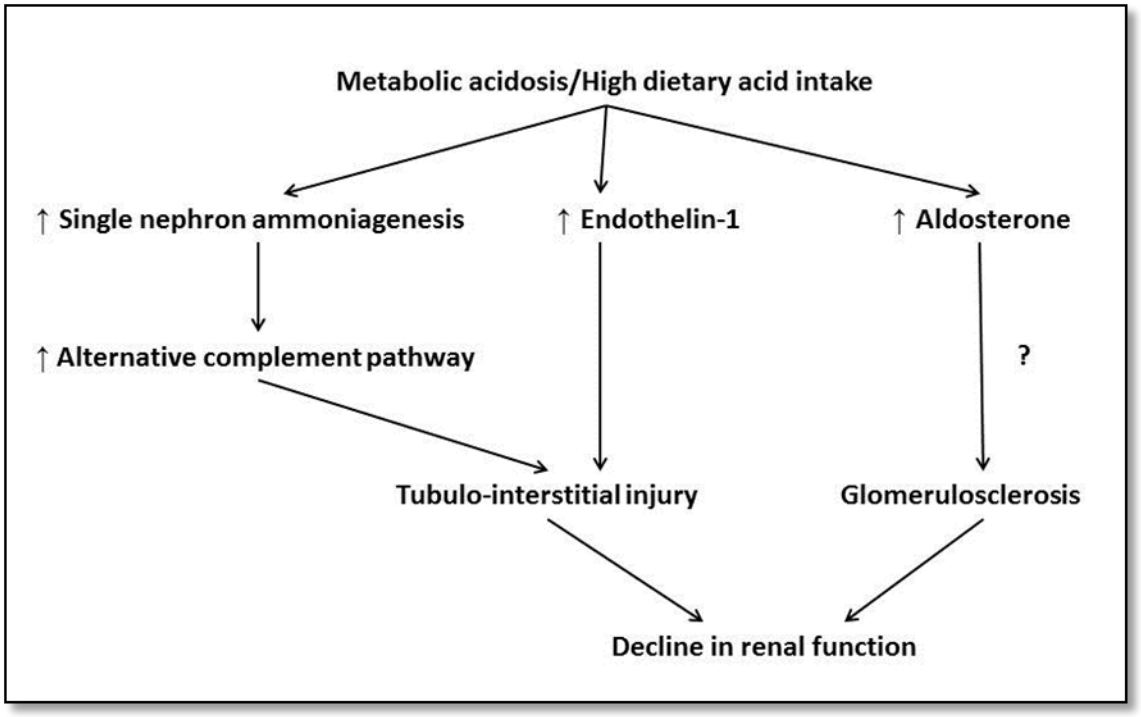


Figure 2-2: Possible mechanism underlying acidosis-induced acceleration of chronic kidney disease (Chen & Abramowitz, 2014)

2.5.3 Dietary acid load

Current Western eating patterns have been shown to produce a high dietary acid load, which leads to reduced kidney function by causing metabolic acidosis or subclinical acid retention (Kraut & Medias, 2010; Chen & Abramowitz, 2014). Cheese, meat, eggs and grains are the common foods known to result in a high dietary acid load, while fruit and vegetables are more base producing (Chen & Abramowitz, 2014; Scialla & Anderson, 2013). Fruit and vegetables contain potassium salts of metabolising anions, like citrate and malate, which consume hydrogen ions and therefore have an alkalising effect (Adeva & Souto, 2011). Plant proteins contain more glutamate than animal proteins, which is an anionic amino acid that neutralises hydrogen ions (Adeva & Souto, 2011). As can be seen in Figure 2.2, a high dietary acid load enhances eGFR regression by increasing kidney ET and aldosterone production, while dietary alkali improves eGFR (Chen & Abramowitz, 2014; Goraya & Wesson, 2014; Scialla & Anderson, 2013).

High animal protein diets usually produce high levels of net endogenous acid production (NEAP), whereas base-producing proteins in fruit and vegetables result in low, or negative, NEAP (Goraya & Wesson, 2014). Net endogenous acid production is the difference between

endogenous acid production and the input of alkali absorbed from the diet (Kanda *et al.,* 2014). This represents the total amount of non-volatile acid that is excreted to maintain the acid–base balance in the body (Frassetto *et al.*, 2007). The metabolism of organic sulphur in dietary protein produces non-volatile acid (Scialla & Anderson, 2013). A number of different formulas can be used to calculate NEAP, two of which are included in this review. In formula 1, NEAP can be estimated from the protein content in the diet (an acid precursor) and from the potassium intake (an index of base precursors from organic anions) (Frassetto *et al.*, 2007). Formula 2 relies on Potential Renal Acid Load (PRAL) that considers other food besides protein that might also interfere with the control of acidosis (Rodrigues Neto Angéloco *et al*., 2017). Potential Renal Acid Load is based on the average intestinal absorption rate of the specific nutrients as mentioned in Formula 2 (Rodrigues Neto Angéloco *et al*., 2017). Food with a PRAL value less than 0 increases alkalinity of the body fluids and food with a PRAL value more than 0 increases acid production in the body (Rodrigues Neto Angéloco *et al*., 2017).

Formula 1 (Frassetto *et al.*, 2007).

Estimated NEAP (mEq/day) = [54.5 x protein (g/d) / potassium (mEq/d)] – 10.2

NEAP: net endogenous acid production.

Formula 2 (Rodrigues Neto Angéloco *et al*., 2017).

Estimated NEAP (mEq/d) = PRAL + OA

Where PRAL is calculated as follows:

PRAL (mEq/d) = 0.49 x protein (g/d)
+ 0.037 x phosphorus (mg/d)
+ 0.021 x potassium (mg/d)
+ 0.026 x magnesium (mg/d)
+ 0.013 x calcium (mg/d)

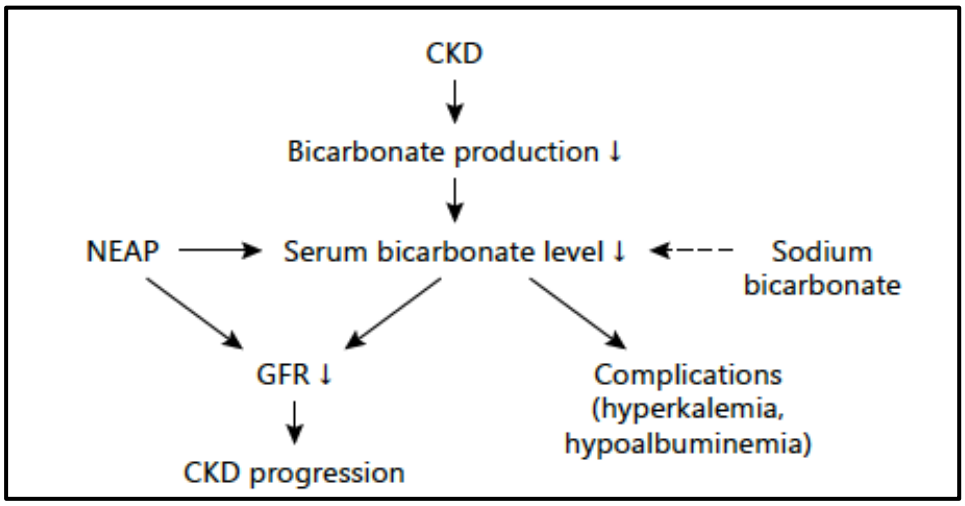
NEAP: net endogenous acid production; OA: Organic acids; PRAL: Potential Renal Acid Load.

A higher intake of dietary protein increases renal ET production which will, in turn, lead to distal nephron acidification. Net endogenous acid production will thus affect CKD progression by distal nephron acidification and ET activation (Kanda *et al.*, 2014). The following factors affect

NEAP:

1. Type and quality of protein in the diet.
2. Type and quality of fruit and vegetables consumed.
3. Type and quality of organic acid anions excreted.
4. Acid–base status of the patient.
5. Proximal tubular function (Kraut & Madias, 2016).

Figure 2.3 demonstrates that a higher NEAP leads to decreased GFR and thus progression of renal failure directly and also indirectly by causing low serum bicarbonate (Kanda *et al.*, 2014). This association is the strongest in people with more advanced CKD, middle-aged and older individuals or populations in whom the capacity to excrete an acid load is relatively impaired (Chen & Abramowitz, 2014). The DASH trial showed that increased fruit and vegetable intake can help to accomplish low NEAP even while consuming dietary protein (Scialla & Anderson, 2013). The dietary protein effect on NEAP (whether acid- or base-producing) is more important to determine eGFR loss than the amount of dietary protein (Goraya & Wesson, 2014).



CKD: chronic kidney disease; GFR: glomerulas filtration rate; NEAP: net endogenous acid production.

Figure 2-3:Factors leading to chronic kidney disease progression (Kanda *et al*., 2014)

2.5.4 Treatment of metabolic acidosis in chronic kidney disease

The KDOQI guidelines propose that patients with CKD and serum bicarbonate concentrations <22 mmol/l be treated with oral bicarbonate supplementation to maintain serum bicarbonate within the normal range unless contraindicated (Willis *et al.*, 2012). It seems that alkali supplementation (sodium bicarbonate or a diet rich in fruit and vegetables) might be an

affordable and accessible treatment option for CKD patients. There are concerns regarding possible sodium loading when using sodium bicarbonate but De Brito-Ashurst *et al.* (2015) reported that sodium bicarbonate did not aggravate HPT. In a study by Goraya *et al.* (2013), patients with stage 4 CKD with metabolic acidosis were randomly assigned to one year of oral bicarbonate treatment (n = 35) or fruit and vegetable intake to reduce dietary acid by half (n = 36). The patients in the fruit and vegetable group showed a significant increase in $PTCO_2$ after one year compared with baseline, indicating improved metabolic acidosis. The urine indices of kidney injury were lower than baseline in the fruit and vegetable group and the plasma [K+] did not increase. Systolic BP was also lower than the baseline ($P < 0.01$) in the fruit and vegetable group. These results show that fruit and vegetables improved metabolic acidosis, decreased systolic BP and decreased kidney damage in stage 4 CKD in this study population. An important finding was that increased fruit and vegetable intake did not cause hyperkalaemia (Goraya *et al.*, 2013). De Brito-Ashurst *et al.* (2015) also found that correcting acidosis decreases progression of renal failure, improves nutritional status and also improves the wellbeing and quality of life of CKD patients. A decrease in dietary acid level by the intake of fruit and vegetables decreases urinary ET-1 and aldosterone levels in stage 2 CKD patients (Figure 2.2) (Goraya *et al.*, 2012). The decrease in acid level by alkali therapy may decrease kidney ET-1 and aldosterone levels in CKD patients by decreasing retained acid levels (Kanda *et al.*, 2014).

2.6 Medical nutrition therapy in chronic kidney disease

Diet is one of the major modifiable risk factors that can be utilised to prevent or slow the development of CKD (Snelson *et al.*, 2017). Historically, the emphasis has been on reducing protein, sodium, phosphorus and potassium intake in patients with CKD (Willis *et al.*, 2012; Gutierrez *et al.*, 2014). In an observational study by Dunkler *et al.* (2013), 6213 patients with DM were observed for 5.5 years to determine the link between diet and incidence of CKD. The study found that healthy diets high in fruit and vegetables and moderate alcohol consumption reduced the incidence and progression of CKD (Dunkler *et al.*, 2013). For the purpose of this section, the discussion will be on potassium and phosphorus intake only as this is the focus of this research project.

2.6.1 The current nutritional recommendations for chronic kidney disease

The current nutritional recommendations by KDIGO (Willis *et al.*, 2012) and the Academy of Nutrition and Dietetics (A.N.D., 2010) is presented in Table 2.5.

Table 2-5: Nutritional recommendations for patients with chronic kidney disease (A.N.D, 2010; Willis *et al.*, 2012)

Nutrient	Recommendation for patients with CKD
Protein	≤0.8 g/kg in adults with diabetes or GFR stages 4-5 (eGFR <30 ml/min/1.73m^2) Avoiding high protein intake (>1.3 g/kg/d) in adults with CKD at risk of progression
Sodium	<2 g sodium daily translating to 5 g of sodium chloride in adults with CKD, unless contraindicated
Potassium	In patients with CKD stages 3-5 presenting with hyperkalaemia the RD should prescribe a potassium intake of <2.4 g/d
Phosphorus	For adults with CKD stages 3-5, an RD should recommend a low-phosphorus diet providing 800 mg to 1 000 mg per day or 10 mg to 12 mg phosphorus per gram of protein.

CKD: chronic kidney disease; d: day; eGFR: estimated glomerular filtration rate; RD: registered dietitian.

2.6.2 Potassium intake in patients with chronic kidney disease

Potassium is the key cation in the intracellular space, while sodium is the main extracellular cation (Adrogue & Madias, 2007; Musso, 2004). Total body potassium levels in healthy adults are about 3700 mmol (Musso 2004). Potassium retention can lead to hyperkalaemia (serum potassium [S_k] >5.5 mmol/L) in patients with CKD, especially when the eGFR rate falls to >20 ml/min/1.73m^2 (Korgaonkar *et al.*, 2010; Musso, 2004). Adaptive mechanisms to prevent hyperkalaemia include redistribution of potassium in the intracellular space and increased renal and intestinal potassium excretion (Musso, 2004). Hyperkalaemia stimulates the secretion of aldosterone which is responsible for the renal fractional excretion of potassium (Korgaonkar *et al.*, 2010; Musso, 2004). Potassium excretion per functioning nephron increases as the eGFR decreases (Korgaonkar *et al.,* 2010). Both hyperkalaemia and hypokalaemia (S_k ≤3.5 mmol/L) are associated with a higher risk of mortality in patients with CKD by causing heart arrhythmia (He *et al.,* 2015).

Dietary restrictions of potassium are, therefore implemented for patients with advanced CKD to avoid hyperkalaemia (Korgaonkar *et al*., 2010; Musso, 2004). Patients who are advised to follow a low potassium diet (2 000 to 3 000 mg/d), have to avoid high potassium food such as nuts, seeds, beans, peas, legumes and many commonly available fruit and vegetables that contain >200 mg potassium per serving, as seen in Table 2.5 (St-Jules *et al*., 2016). However, a diet rich in fruit and vegetables and thus higher in potassium, may delay the progression of CKD in

early stages of CKD by lowering BP (Adrogue & Madias, 2007). Although the focus is usually on hyperkalaemia in the CKD setting, Korgaonkar *et al.* (2010) found that CKD patients with low or even low-normal S_k levels (<3.9 mmol/L) have a greater mortality risk than those with mild to moderate hyperkalaemia (S_k 5.5–5.9 mmol/L). Hypokalaemia may cause ventricular arrhythmias and sudden cardiac death (Schulman & Narins, 1990). Diuretics are associated with lower potassium levels and, because they are commonly used for volume and BP control in CKD patients, serum potassium needs to be closely monitored in this population group (Korgaonkar *et al.,* 2010). Although widely prescribed, there seems to be little evidence to support the premise that high dietary potassium intake is actually associated with high S_k levels. A study by Noori *et al.* (2010), which included 224 patients on haemodialysis (HD), reported that dietary potassium was responsible for only about 2% of the variance in pre-dialysis S_k levels (Noori *et al.*, 2010).

It is difficult to establish a link between higher potassium levels and mortality as most patients with hyperkalaemia who reached ESRD are initiated on dialysis, which helps to remove excess potassium (Korgaonkar *et al.,* 2010). It seems that the benefits of plant-based diets naturally high in potassium and fibre and low in acidogenic proteins and minerals could outbalance the possible risk of developing hyperkalaemia in early CKD (Snelson *et al.,* 2017) and even later stages of CKD (Goraya & Wesson, 2014). The classification of food according to the potassium content can be seen in Table 2.6. It is important to note that the contribution of potassium additives to dietary potassium is unknown and unaccounted for in conventional nutrient composition assessments in food. A study by Sherman & Metha (2009), for example, found that although marinated meat strips can contain 930 mg potassium/100g, which is far above 200 mg/portion, meat is not on the high potassium list.

Table 2-6: **Potassium content of commonly consumed food** (Herselman & Esau, 2005; NKF, 2017)

Food high in potassium		
Fruit >200 mg/portion	**Vegetables >200 mg/portion**	**Other food >100 mg/portion**
Avocado	Mixed vegetables, canned	Chocolate with nuts, raisons
Dates	Bamboo Shoots	Yogurt
Dried fruit	Potato	Wine, ciders, beer
Fig	Mushrooms, cooked	Dark chocolate

Grapes	Baked beans	Fruit cake
Kiwi	Gem squash	peanut butter
Mango	Butternut	Bran/ bran products
Melon, yellow	Marog	Potato chips
Nectarine	Spinach, small	Muffins
Papaya	Gherkins	Nuts
Prunes	Tomato and onion relish	Milk, all types
Raisins	Sweet potato	
Food moderate in potassium		
Fruit 120-200 mg/portion	Vegetables 120-200 mg/portion	Other food
Apricot	Beetroot	
Banana	Asparagus	
Grapefruit	Brinjal	
Guava	Brussels sprouts	
Mango	Carrot	
Melon, white	Cauliflower	
Naartjie	Green beans	
Pawpaw	Patty pan	
Watermelon	Pumpkin	
	Spinach	
	Sweetcorn	
	Tomato	
	French salad	
Food low in potassium		
Fruit <120 mg/portion	Vegetables <120 mg/portion	Other food
Apple	Artichoke	Rice
Cherry	Broccoli	Noodles

Granadilla	Cabbage	Pasta
Kumquat	Celery	White bread
Litchi	Cucumber	Cake
?	Lettuce	Cookies without nuts or chocolate
Pear	Leek	Tea
Pineapple	Onion	Coffee
Plum	Peas	Sugar
Strawberry	Pepper	Honey
	Radish	Butter/ margarine

Adopted from the South African renal exchange lists

2.6.3 Phosphorus intake in patients with chronic kidney disease

The average person consumes about 1000 to 1500 mg phosphorus daily, of which about 65% is absorbed in the gastrointestinal tract (GIT) to perform functions in the body such as cellular signal transduction, mineral metabolism and energy exchange (Chang & Anderson, 2017; Tonelli *et al.*, 2005). The unabsorbed phosphorus is excreted in stools (Chang & Anderson, 2017). Most of the phosphorus is located in the intracellular space (70%); about 29% is located in bone and less than 1% in the blood (Gonzalez-Parra *et al.*, 2012). Approximately 800 to 1000 mg of phosphorus is excreted in the urine daily and 150 mg is excreted by the GIT (Gonzalez-Parra *et al.*, 2012). Besides these two mechanisms of maintaining phosphorus homeostasis, phosphorus also shifts into and out of bone (Chang & Anderson, 2017). Patients with renal failure gradually lose the ability to excrete phosphorus. When the eGFR decreases to <60 ml/min/1.73m^2, the patient is at risk for hyperphosphataemia and its associated conditions such as hyperparathyroidism, renal bone disease, progression of renal failure and soft tissue calcification leading to increased CVD risk (Chang & Anderson, 2017; Eddington *et al.,* 2010; Ix *et al.,* 2014; O'Seaghdha *et al.,* 2011). The initial compensation mechanism to uphold phosphorus excretion is decreased tubular reabsorption, regulated by PTH and Fibroblast Growth Factor 23 (FGF23) (Gonzalez-Parra *et al.*, 2012). An increase in these two hormones may contribute to LVH and bone disease (Ix *et al.,* 2014). As the nephron mass and eGFR decrease, there will be an increased amount of phosphorus excreted per individual nephron (Chang & Anderson, 2017).

Tonelli *et al.* (2005) did a post hoc analysis of data from the Cholesterol and Recurrent Events (CARE) study on the data of 4 127 participants with a prior MI with or without CKD. The study found an independent association between baseline fasting serum phosphate levels and the risk of all-cause death, development of new heart failure, and coronary events. The study was unable to identify potential mechanisms for the association between serum phosphate levels and adverse outcomes. In a study by Eddington *et al.* (2010), 1 230 non-dialysis CKD patients from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS) were included in order to investigate the association between serum phosphorus and mortality in patients with CKD. The study found a higher risk of all-cause and cardiovascular mortality associated with higher serum phosphorus levels in patients with stages 3 to 4 CKD. There was a 26% increase in all-cause mortality and an increase of 50% in CVD mortality for each 0.323 mmol/L (1 mg/dl) increase of baseline phosphate, even if it was within the normal range. No association was found between mortality and serum phosphorus in patients with stage 5 CKD (Eddington *et al.,* 2010). In both studies there was a significant association between the following risk factors and higher serum phosphate levels: female gender, DM, higher levels of serum albumin, lower levels of haemoglobin, and smoking; Tonelli *et al.* (2005) also found black race, B-adrenergic blockers and high levels of alcohol consumption to be risk factors.

Phosphorus-based food additives found in processed food are notable sources of inorganic phosphorus and contribute to high levels of serum phosphorus in patients with CKD (Benini *et al.,* 2011). Additives can add up to 1000 mg phosphorus to the diet daily, depending on individual food choices (Sullivan *et al.*, 2007). Benini *et al.* (2011) found that food which contains phosphate additives has a phosphorus level up to 70% greater than food samples without additives. In a study by León *et al.,* (2013), the top five best-selling products in different food categories were matched with food without phosphorus additives and the following differences in phosphorus levels were found: prepared frozen foods (72%), packaged meat (65%), bread and baked goods (57%), soup (54%) and yoghurt (51%). Almost 100% of the phosphorus in food additives is absorbed whereas only about 60% is absorbed from food that naturally contains phosphorus (Chang & Anderson, 2017). Organic phosphate is mainly found in protein-rich food such as legumes, meat, poultry, fish, eggs and dairy products (Snelson *et al.,* 2017). Legumes have the lowest bioavailability of phosphorus at about 40% (Chang & Anderson, 2017). Dairy products have a bioavailability of 30 to 60% and meat products up to 80% (Snelson *et al.,* 2017). Treatment of hyperphosphataemia includes dietary phosphate restriction; phosphate binders, and calcium and vitamin D supplementation. Because protein is an excellent source of dietary phosphate, patients will have to restrict protein intake in order to restrict phosphate intake (Cannata-Andia *et al.,* 2000; Kates *et al.,* 1997).

In the Modification of Diet in Renal Disease (MDRD) study by Selamat *et al.* (2016), 795 patients with stages 3 to 5 CKD were included to investigate the relationship of dietary phosphate intake with risk of ESRD and mortality in CKD. This study found a modest inverse correlation between phosphate excretion and serum phosphate concentrations that was absent when adjusted for GFR. There was no link found between 24-hour urinary phosphate excretion (UPE) and risk of ESRD, CVD or all-cause mortality in the study. Urinary phosphate excretion is the gold standard for evaluating intestinal phosphate absorption (Selamet *et al.,* 2016). The study concluded that phosphate intake is not strongly associated with serum phosphate concentrations in CKD stages 3 to 5, and that there was no evidence that higher phosphate intake is linked to ESRD, CVD or all-cause mortality in patients with CKD stages 3 to 5 (Selamet *et al.,* 2016). A study by Chang & Anderson (2017) found that, although serum phosphorus is strongly associated with CVD, progression of CKD and death, there is very little evidence to link dietary phosphorus intake directly to adverse clinical outcomes. Murtaugh *et al*. (2012) found similar results and concluded that high dietary phosphorus intake is not associated with an increase in mortality in moderate CKD. In a randomised, crossover study by Chang *et al.* (2017), 32 participants received phosphorus-containing or non-phosphorus-containing commercially available diet beverages and breakfast bars during the different arms of the study. There was no significant link between the groups receiving a high phosphorus diet and albuminuria in the study (Chang *et al.,* 2017).

Other factors besides diet are therefore responsible for serum phosphate concentrations and it is unclear whether the restriction of dietary phosphate would translate into improved clinical outcomes in CKD (Selamet *et al.,* 2016; Snelson *et al.,* 2017). Possible factors to consider, include altered renal tubule phosphate control, changing bone and muscle phosphate buffering, the effects of sex hormones or altered changes of phosphate between the intracellular and extracellular compartments (Selamet *et al.,* 2016). Prospective studies are needed to determine whether phosphorus intake is a modifiable risk factor for kidney disease (Chang & Anderson, 2017; Newsome *et al.,* 2013; Snelson *et al.,* 2017).

2.6.4 Protein and phosphorus intake in patients with chronic kidney disease

Protein is an excellent source of phosphate in the diet and phosphate-restricting diets will inevitably lead to restricted protein intake (Cannata-Andia *et al.,* 2000; Kates *et al.,* 1997). Low protein intake is, in turn, associated with malnutrition and higher mortality in CKD patients, and therefore caution should be exercised when recommending a low phosphate diet (Selamet *et al.,* 2016; Snelson *et al.,* 2017). Moe *et al.* (2010) found that, in patients with CKD, the source of protein had a significant effect on phosphorus homeostasis. After one week on a vegetarian

diet, the patients had lower serum phosphorus and FGF23 levels compared with the meat-based diet despite comparable protein and phosphorus intake (Moe *et al.,* 2010). The study also found that the phosphorus content of the vegetarian diet was lower than predicted by standard databases. They conclude that if these results can be confirmed by long-term studies, it will be recommended that patients with CKD follow a plant-based diet (Moe *et al.,* 2010). Patients with CKD can then consume higher amounts of protein without the risk of hyperphosphataemia (Moe *et al.,* 2010). The difference in phosphorus bioavailability between plant and meat protein sources may partially explain the benefits of consuming more protein from plant sources (Snelson *et al.,* 2017). Cereals, nuts, hard cheese, legumes, egg yolk, meat, poultry and fish have the highest phosphorus content of food per 100 g edible part (D'Alessandro *et al.,* 2015). Reporting the phosphorus content per mg per gram of protein will help to identify food with a favourable phosphorus to protein ratio (food with <12 mg phosphorus per gram of protein) (D'Alessandro *et al.,* 2015). This ratio is recommended to ensure that patients will receive enough protein while controlling phosphate intake (Snelson *et al.,* 2017). The GI absorption and phosphorus to protein ratio of different types of dietary phosphorus can be seen in Table 2.7.

Table 2-7: Gastrointestinal absorption and phosphorus to protein ratio of different types of dietary phosphorus (Cupisti *et al.,* 2013)

Type of dietary phosphorus	Source	Example	GI absorption	Phos/Prot ratio	Benefits
Organic plants	Plant prot	Nuts, beans, grains	20-40%	5-15 mg/g	Prot rich
Organic animals	Animal prot	Chicken, fish, meat	40-60%	10-20 mg/g	High value prot & aa
Inorganic	Additives	Soft drinks	≈ 100%	>50 mg/g	None

Aa: amino acids; GI: gastrointestinal; phos: phosphate; prot: protein.

2.7 Conclusion

Chronic kidney disease is an increasing world-wide threat and low-and-middle income countries such as South Africa are facing an even higher risk for developing CKD. Chronic kidney disease increases the risk of CVD five-fold and, although the control of HPT is the most important factor in the primary prevention and progression of CKD, reaching optimal BP targets remains a significant challenge in CKD. Diet and lifestyle are key modifiable risk factors that can be utilised to prevent or slow the development of CKD. Fruit and vegetables are well proven to modify risk

factors in CVD that will also modify risk factors in CKD through various mechanisms. Fruit and vegetables are shown to reduce metabolic acidosis in patients with CKD. A higher fruit and vegetable intake results in lower net production and retention of hydrogen ions, with better preservation of kidney function. Increased vegetable intake may have favourable effects on phosphorus metabolism in CKD. The intestinal absorption of phosphate from plant-origin foods is much lower, owing to the lower bioavailability of phytate compared with phosphate from animal-origin foods, in particular, processed foods. The HPT reduction effect of fruit and vegetables is another mechanism by which they can preserve kidney function. Increased fruit and vegetable intake also increases fibre intake, which improves the levels of uraemic toxins in patients with CVD. A relatively weak link exists between dietary potassium and serum potassium and the benefits of plant-based diets, naturally high in potassium and fibre and low in acidogenic proteins and minerals, could outbalance the possible risk of developing hyperkalaemia in CKD. There is also little evidence to indicate that the phosphate intake is associated with serum phosphate concentrations in CKD stages 3 to 5, and that higher phosphate intake is linked to ESRD, CVD or all-cause mortality in patients with CKD stages 3 to 5. Restricting phosphate also means restricted protein intake which is associated with malnutrition and higher mortality in CKD patients; the phosphate to protein ratio of food is therefore recommended to ensure that patients will receive enough protein while controlling phosphate intake. Current recommendations for CKD patients focus on restricting protein, sodium, potassium and phosphate intake, thereby limiting protective foods such as nuts, seeds, beans, peas, legumes and commonly consumed fruit and vegetables. These restrictions are hard to comply with and might even be detrimental to the health of patients; it is time to update these recommendations. Further high-quality studies are required to establish the role of fruit and vegetables in the diet of a patient with CKD.

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CHAPTER 3

EFFECT OF FRUIT AND VEGETABLE INTAKE ON THE PROGRESSION OF KIDNEY FAILURE IN ADULTS WITH CHRONIC KIDNEY DISEASE: A SYSTEMATIC REVIEW

This chapter is an article that has been prepared for the Journal of Renal Nutrition. The article has been prepared according to the instructions for authors and can be found in Annexure A

Title page

Effect of fruit and vegetable intake on the progression of kidney failure in adults with chronic kidney disease: A systematic review

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3.1 Abstract

Background: This systematic review aimed to investigate the effect of fruit and vegetable intake on clinical outcomes of patients with chronic kidney disease (CKD), especially the estimated Glomerular Filtration Rate (eGFR).

Methods: A search was performed on EBSCO Host, Google Scholar, MedLine, Pubmed, Science Direct, Scopus, The Web of Science and The Cochrane Central Register of Controlled Trials systematically using keywords and MeSh terms. Randomised controlled trials (RCTs) investigating the effect of fruit and vegetable intake on blood pressure, metabolic acidosis and eGFR in adult patients with CKD (eGFR <60 ml/min/1.73m^2) published before April 2019 were included. Control groups received usual care.

Results: Two studies comprising a total of 143 participants were included. In the first study, the eGFR of the fruit and vegetable group was the same after one year as that of the group receiving sodium bicarbonate. Overall, the eGFR was significantly higher in the fruit and vegetable groups when compared with usual care. The included studies found a significant reduction in body weight, systolic blood pressure and Potential Renal Acid Load (PRAL) in the fruit and vegetable group when compared with baseline and the control group. There was a significant improvement in plasma total carbon dioxide (TCO_2) in the fruit and vegetable group when compared with baseline. Fruit and vegetable intake had no effect on plasma potassium when compared with baseline and/or the control group in both the included studies.

Conclusion: Fruit and vegetables are an effective way of delaying progression of kidney failure in CKD patients with metabolic acidosis, without producing hyperkalaemia.

Keywords: Chronic kidney disease, fruit intake, vegetable intake, metabolic acidosis, GFR

3.2 Introduction

Chronic kidney disease (CKD) has become a global key health concern, affecting about 10–13% of the world's population,[1] with an annual rise in incidence of 8%.[2] It is estimated that five million South Africans older than 20 years of age have CKD.[3] Diabetes mellitus (DM), hypertension (HPT) and cardiovascular disease (CVD) are the most common causes of CKD.[4] Chronic kidney disease is defined as the progressive loss of kidney function characterised by a decreased renal function (estimated Glomerular Filtration Rate (eGFR) <60 ml/min/1.73m^2) present for longer than 3 months, or indicators of kidney damage.[5] Patients with CKD are classified in five stages using the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.[5] Stage 3 is classified a eGFR value is 30 to 59 ml/min/1.73m^2; stage 4: eGFR 15 to 29 ml/min/1.73m^2 and stage 5: eGFR <15 ml/min/1.73m^2. Dialysis or kidney transplant are the only treatments for the final stage of CKD. These treatments place a significant financial burden on individuals and national health budgets.[6] A large proportion of people in low- to middle-income countries do not have health insurance and access to health care is limited.[7] Because of limited resources, in South Africa only 15–20% of the patients who require renal replacement therapy (RRT) obtain such treatment.[8]

There is a well established link between CVD and CKD. Subbiah *et al*.[9] found that the risk of cardiovascular mortality increased by 5% with every 10 mL/min/1.73 m^2 reduction in eGFR. The term cardio-renal syndrome (CRS) has been used to describe the overlapping clinical conditions in heart and kidney dysfunction.[2,10,11] Ageing, albuminuria, DM, dyslipidaemia, HPT, obesity and smoking are some of the traditional risk factors contributing to CVD in CKD.[2,9] There are also overlapping non-traditional risk factors such as anaemia, albuminuria, abnormal bone and mineral metabolism, acidosis, inflammation, oxidative stress and endothelial dysfunction, which are all uraemia-specific factors.[10] This increased risk and the added costs of CVD make it essential to prevent the decline of eGFR in patients in any stage of CKD.[4]

Medical nutritional therapy has been a significant part of CKD treatment. The emphasis has been on reducing protein, sodium, phosphorus, and potassium intake, therefore, limiting fruit and vegetable consumption.[5,12] The rationale behind restricting potassium intake is the prevention of hyperkalaemia (serum potassium [Sk] >5.5 mmol/L), which, by causing heart arrhythmia, is associated with a higher risk of mortality in patients with CKD.[13] Although such restriction is widely prescribed, there seems to be little evidence to support the premise that high dietary potassium intake is actually associated with high Sk levels.[14-17] Phosphate intake is restricted in patients with CKD to prevent hyperphosphataemia, which causes hyperparathyroidism, renal bone disease, progression of renal failure and soft tissue

calcification leading to increased CVD risk.[18-21] Although evidence shows that phosphorus is strongly associated with CVD, progression of CKD and death, there is very little evidence to link dietary phosphorus intake directly to adverse clinical outcomes.[18,22-24]

Evidence shows that fruit and vegetables improve metabolic acidosis, decrease systolic blood pressure (BP) and decrease kidney damage in stage 4 CKD without causing hyperkalaemia.[25-27] A higher fruit and vegetable intake results in lower net production and retention of hydrogen ions, with better preservation of kidney function.[28] Increased vegetable intake may have favourable effects on phosphorus metabolism in CKD. Phosphate from plant-origin foods is much less readily absorbed by the intestine owing to the lower bioavailability of phytate (20-40%) compared with phosphate from animal-origin foods (40-60%), and additives found in processed foods (≈100%).[18]

Increased fruit and vegetable intake increases fibre intake, which decreases the levels of uraemic toxins in patients while increasing protein intake to reduce the risk of malnutrition in CKD patients.[17,23] Current recommendations for CKD patients focus on restricting protein, sodium, potassium and phosphate intake, thereby limiting protective foods such as nuts, seeds, beans, peas, legumes and commonly consumed fruit and vegetables. These restrictions are hard to comply with and might even be detrimental to the health of patients. Further high-quality studies are required to establish the role of fruit and vegetables in the diet of a patient with CKD. Fruit and vegetable intake might be a cost-effective and acceptable treatment option for patients with CKD but the quantity and type of fruit and vegetables suitable for each stage of CKD is not well defined.

This study therefore aimed to perform a systematic review of randomised controlled trials (RCTs) investigating the effect of dietary fruit and vegetable intake on clinical outcomes of patients with CKD, especially on eGFR as a measure of progression of kidney failure.

3.3 Materials and methods

Our primary aim was to assess the effect of fruit and vegetable intake on clinical outcomes of adult patients with CKD, especially the progression of kidney failure. The primary outcomes were eGFR (cystatin C-estimated GFR (cysGFR) and creatinine-estimated GFR (crGFR) in response to fruit and vegetable intake or usual care. The secondary outcomes included markers indicating acidosis (potential renal acid load (PRAL), plasma total carbon dioxide (TCO_2)), body weight, BP and plasma potassium. This systematic review was conducted according to a pre-established review protocol registered on the PROSPERO register with registration number: CRD42019145160.

The net changes between end and baseline values were reported as mean ± standard deviation (SD). A P-value <0.05 indicated a statistically significant difference between the net changes from baseline to end, as well as the end values of the fruit and vegetable (experimental) group compared with those receiving standard care (control group).

3.3.1 Eligibility criteria

Randomised controlled trials with an adult population group (aged ≥18 years) with CKD defined as eGFR <60 ml/min/1.73m^2, and not receiving dialysis were included. Fruit and vegetable intake was the primary intervention compared with standard or usual care or lower frequency and amount of fruit and vegetable consumption. This allowed standardised classification of fruit and vegetable intake.

Papers in languages other than English, duplicated articles, review papers, congress abstracts, editorials and case reports were excluded from this review. Studies were also excluded if mixed healthy diet or dietary patterns were reported and if the effect of fruit and vegetables intake was not reported separately.

3.3.2 Search methods for identification of reviews

Two reviewers (JN and ML) searched EBSCO Host, Google Scholar, MedLine, Pubmed, Science Direct Scopus Web of Science and The Cochrane Central Register of Controlled Trials systematically for studies published before April 2019, and the reference lists of primary studies, review articles and clinical practice guidelines independently, to find relevant studies. Studies considered to be potentially relevant by one or more reviewers were retrieved for title screening.inspection.

The search strategies were created by a research librarian using MeSH terms and keywords in databases without MeSH terms. The search string used was based on Population/ Intervention/ Comparison and Outcome (PICO) and were: (chronic kidney failure[MeSH Terms]) OR chronic (kidney insufficiencies[MeSH Terms]) OR (chronic kidney insufficiency[MeSH Terms]) AND (renal failure[MeSH Terms]) AND (chronic renal failure[MeSH Terms]) AND (kidney disease[MeSH Terms]) AND (kidney failure[MeSH Terms]) OR (kidney failure, acute[MeSH Terms]) OR (kidney failures[MeSH Terms]) OR (kidney failures, acute[MeSH Terms]) OR (kidney failure, chronic[MeSH Terms]) OR (acute kidney failure[MeSH Terms]) OR (acute kidney failures[MeSH Terms]) AND (end-stage renal disease[MeSH Terms]) OR (renal disease, end-stage[MeSH Terms]) OR (disease, end-stage kidney[MeSH Terms]) OR (disease, end-stage renal[MeSH Terms]) OR (end-stage kidney disease[MeSH Terms]) OR (end-stage liver

disease[MeSH Terms]) OR (end-stage renal disease[MeSH Terms]) OR (end-stage renal failure[MeSH Terms]) OR (end-stage kidney disease[MeSH Terms]) OR (renal disease, end-stage[MeSH Terms]) OR (renal failure, end-stage[MeSH Terms]) AND (filtration rate, glomerular[MeSH Terms]) OR (filtration rates, glomerular[MeSH Terms]) OR (glomerular filtration rate[MeSH Terms]) OR (glomerular filtration rates[MeSH Terms]) AND (adults[MeSH Terms]) OR (adult children[MeSH Terms]) OR (adult daughter[MeSH Terms]) OR (adult daughters[MeSH Terms]) AND (patients[MeSH Terms]) AND (fruits[MeSH Terms]) AND (vegetables[MeSH Terms]) AND (dietary allowance, recommended[MeSH Terms]) OR (dietary allowances, recommended[MeSH Terms]) OR (dietary habit[MeSH Terms]) OR (dietary habits[MeSH Terms]) OR (dietary management[MeSH Terms]) AND (acetate, potassium[MeSH Terms]) AND 9hyperkalaemia[MeSH Terms]) AND (hypertension[MeSH Terms]) AND (acidosis, metabolic[MeSH Terms]) AND (acid base balance[MeSH Terms]) OR (acid base equilibrium[MeSH Terms]) OR (balance, acid base[MeSH Terms]) AND (serum bicarbonate[MeSH Terms]).

3.3.3 Selection of studies

After searches of all the specified databases were conducted, duplicate results were removed. Thereafter, exclusion based on title screening was done. The abstracts of the remaining studies were obtained and screened. Lastly, full-text articles were obtained and assessed for eligibility.

3.3.4 Data collection and analysis

A study eligibility form was used to determine inclusion or exclusion of studies and a data extraction form was used for piloting data extraction of the studies. Data of the eligible studies were extracted and summarised by two independent review authors (JN and ML) and disputes were resolved by a third reviewer (RD). Where studies with two or more review arms were included, only data from intervention and control groups that met the eligibility criteria were extracted.

The following data were extracted from eligible studies: bibliographic data, including date of publication, country of origin, trial design, care setting, aim of study, population group, age of participants, number of participants in each arm, key baseline participant data including eGFR, BP, details of treatment regimen received by each group, duration of treatment, details of any co-interventions, primary and secondary outcomes (with definitions), outcome data for primary and secondary outcomes (by group), duration of follow-up, number of withdrawals by group with reasons, confounders adjusted for and source of funding for trial.

3.3.5 Assessment of risk of bias and evidence quality of studies

The assessment of risk of bias was conducted independently by two review authors (JN and ML). The Cochrane Collaboration tool for assessing risk of bias was used to assess the risk of bias for the included studies.[29] Seven judgment descriptions were included for each study. If the answer was 'Yes' there was a low risk of bias; 'No' indicated a high risk of bias and 'Unclear' indicated a lack of information or uncertainty over the potential for bias.[29] An overall low risk of bias was allocated to a study where all domains were satisfied. Where one or more of the domains were inadequate, a high risk of bias was allocated.[29]

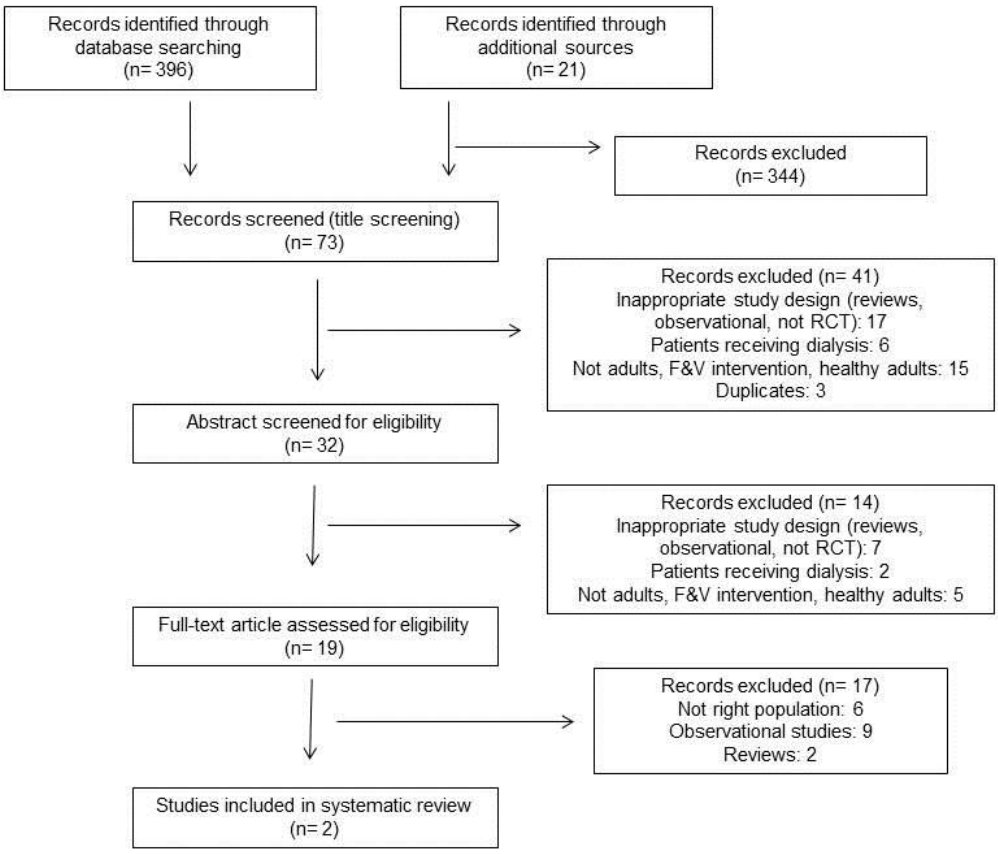
Quality assessment of the studies was done according to the critical appraisal checklist for RCTs as prescribed by the Joanna Briggs Institute (JBI).[30] The criteria for each guideline were classified as yes, no, unclear or not applicable. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool was then used to rate the quality of evidence as high, moderate, low or very low.[31]

The Preferred Reporting Items for Systematic Review and Meta-Analysis of individual participant data (PRISMA-IPD) statement was used as a guideline to compile the article.[32]

3.4 Results

3.4.1 Study selection

The database search delivered a total of 396 studies and 21 studies were added from a manual search. A total of 73 studies was identified by title screening of the initial search results. Thirty-two studies were selected for abstract review, after which 19 studies remained for full-text review. The reasons for the exclusion of the 71 studies included the following: 40 studies had an inappropriate study design (reviews, editorials, observational studies, abstracts), three studies were in duplicate and 28 studies had an inappropriate population group. Two RCTs met the final criteria and were included in the systematic review. No further studies were added from the manual search. An overview of the literature search can be seen in Figure 3.1; the PRISMA-IPD flow diagram was used.[32]



Tool used: PRISMA IPD flow diagram.[32]
F&V: Fruit and vegetables; n: amount; RCT: randomised controlled trial

Figure 3-1: Flow diagram of studies that were considered for inclusion

3.4.2 Study characteristics

The study characteristics of the two included RCTs and details of the data collected from the studies is reported in Table 3.1 and Table .3.2 respectively.

The included RCTs compared base-producing fruit and vegetables with usual care, regarding the primary outcome of follow-up eGFR and secondary outcomes of improved metabolic acidosis and reduced urinary indices of kidney injury. Both studies described the fruit and vegetable intervention as base-producing fresh fruit and vegetables calculated to reduce dietary acid by 50%. The primary fruit provided included apples, apricots, oranges, peaches, pears, raisins and strawberries. Vegetables given to the intervention group consisted of carrots, cauliflower, eggplant, lettuce, potatoes, spinach, tomatoes and zucchini. The amount and the types of fruit and vegetables were prescribed by a registered dietitian but participants did not receive specific dietary instructions. They were told to incorporate the fruit and vegetables in

their diet as they chose. The first study[25] included participants with stage 4 CKD, macroalbuminuria (urine albumin to creatinine ratio (ACR) >200 mg/g creatinine) and metabolic acidosis (plasma TCO_2 <22 mmol/l) due to hypertensive nephropathy. The control group for this study received oral sodium bicarbonate ($NaHCO_3$) at 1.0 mEq/kg, according to the KDOQI guidelines for patients with metabolic acidosis and plasma TCO_2 <22 mmol/l.[5] The second study[33] included participants with stage 3 CKD, macroalbuminuric with metabolic acidosis (plasma TCO_2 22-24 mmol/l) due to hypertensive nephropathy. The control group received usual care but it was not specified what usual care entailed. The duration of the two studies was one and three years respectively.

Table 3-1: Characteristics of the included randomised controlled trials

Author, year. country	Study title	Characteristics of participants	No. of participants	Age of participants (years)	Duration of intervention (years)	Intervention and control	eGFR (ml/min/1.73m^2)	Outcomes measured
Goraya *et al*., 2013.[25] **United States**	A comparison between treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with F&V or $NaHCO_3$	≥18 y; Non-malignant HPT; Stage 4 CKD; Metabolic acidosis (plasma TCO_2 <22 mM)	I: 36 C: 35	I: 53.9±6.9. C: 54.2±5.3	1	Base-producing fresh F&V designed to reduce dietary acid by 50% vs bicarbonate group*	15-20	BW, Systolic BP, PRAL, PK, eGFR (crGFR & cysGFR), TCO_2.
Goraya *et al*., 2014.[34] **United States**	Treatment of metabolic acidosis in patients with stage 3 CKD with fruit and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate	Stage 3 CKD; Macroalbuminuric; Metabolic acidosis (plasma TCO_2 22-24 mmol/l); Hypertensive nephropathy	I: 36; C: 36.	I: 53.5±5.2; C:53.9±4.8	3	Base-producing fresh F&V designed to reduce dietary acid by 50% vs usual care.	30-59	BW, Systolic BP, PRAL, PK, eGFR (crGFR & cysGFR), TCO_2.

BP: blood pressure; BW: body weight; C; control; CKD: chronic kidney disease; cysGFR: cystatin C-estimated glomerular filtration rate; crGFR: creatinine-estimated glomerular filtration rate eGFR: estimated glomerular filtration rate; F&V: fruit and vegetables; HPT; hypertension; I: intervention; PK; plasma potassium; PRAL: Potential Renal Acid Load; TCO_2: plasma total carbon dioxide; vs: versus; y: year. * receiving oral $NaHCO_3$ at 1.0 mEq/kg

Table 3-2: Results of the included randomised controlled trials

Study	Dietary exposure	Results					Conclusion
		Outcome	**F&V baseline**	**F&V end**	**Control baseline**	**Control end**	
Goraya *et al*., 2013.[25]	Fruit given primarily included apples, apricot, oranges, peaches, pears, raisins and strawberries. Vegetables given consisted of carrots, cauliflower, eggplant, lettuce, potatoes, spinach, tomatoes and zucchini. The amount and type of F&V was prescribed by a RD designed to reduce dietary acid by 50%	BW (kg)	82.7 ± 6.1	78.0 ± 5.3*+	84.3 ± 5.4	84.4 ± 5.0	F&V improve metabolic acidosis and reduce kidney injury in stage 4 CKD without producing hyperkalaemia.
		Systolic BP (mm Hg)	136.3 ± 4.8	131.7 ± 3.3*+	136.1 ± 4.7	136.0 ± 4.4	
		PRAL (mmol/dl)	62.1 ± 6.8	39.6 ± 10.4*+	59.0 ± 6.5	59.3 ± 6.3	
		PK (meq/l)	4.1 ± 0.2	4.1 ± 0.1	4.1 ± 0.2	4.1 ± 0.1	
		crGFR (ml/min)	22.8 ± 4.9	21.9 ± 5.1*	23.0 ± 3.5	21.4 ± 3.3*	
		cysGFR (ml/min)	21.6 ± 4.6	20.7 ± 4.7*	21.7 ± 3.4	20.3 ± 3.2*	
		Plasma TCO_2 (mM)	19.3 ± 1.9	19.9 ± 1.7*+	19.5 ± 1.5	21.2 ± 1.3*	
Goraya *et al*., 2014.[33]	Fruit given primarily included apples, apricot, oranges, peaches, pears, raisins and strawberries. Vegetables given consisted of carrots, cauliflower, eggplant, lettuce, potatoes, spinach, tomatoes and zucchini. The amount and type of F&V was prescribed by a RD designed to reduce dietary acid by 50%	BW (kg)	84.2 ± 6.1	80.2 ± 5.1*	83.1 ± 6.0	81.2 ± 6.0*	F&V improve metabolic acidosis and reduce kidney injury in stage 3 CKD without producing hyperkalaemia. F&V is an effective alkali treatment.
		Systolic BP (mm Hg)	163.3 ± 11.7	128.3 ± 4.5*+	158.6 ± 10.6	135 ± 6.2*	
		PRAL (mmol/dl)	61.9 ± 7.6	38.1 ± 5.9*+	60.5 ± 7.7	60.3 ± 8.2	
		PK (meq/l)	4.28 ± 0.14	4.29 ± 0.12	4.29 ± 0.14	4.26 ± 0.13	
		crGFR (ml/min)	42.3 ± 7.1	36.9 ± 6.7*+	42.6 ± 7.6	28.8 ± 7.3*	
		cysGFR (ml/min)	39.4 ± 6.4	34.3 ± 6.4*+	39.5 ± 6.8	26.6 ± 7.0*	
		Plasma TCO_2 (mM)	23.0 ± 0.6	23.9 ± 0.6*+	23.0 ± 0.5	22.4 ± 0.6	

BP: blood pressure; BW: body weight; CKD: chronic kidney disease; cysGFR: cystatin C-estimated glomerular filtration rate; crGFR: creatinine-estimated glomerular filtration rate; F&V: fruit and vegetables; PK; plasma potassium; PRAL: Potential Renal Acid Load; RD: registered dietitian; TCO_2: plasma total carbon dioxide; *P<0.05 versus baseline. +P<0.05 versus Control

3.4.3 Outcomes

There was no difference eGFR, calculated using plasma cystatin C (cysGFR) or using plasma creatinine (crGFR), between the test and control groups in baseline in either study.[25,33] Goraya *et al*.[25] found that the one-year cysGFR and crGFR were not different between the group receiving fruit and vegetable and the group receiving bicarbonate. In the study by Goraya *et al*.,[33] cysGFR was comparable at baseline in the group receiving usual care and the group receiving fruit and vegetables (42.6 ± 7.6 vs 42.3 ± 7.1, P=0.99), but after three years cysGFR was significantly lower in the group receiving usual care compared with the group receiving fruit and vegetables (28.8 ± 7.3 vs 36.9 ± 6.7, P <0.05. The three-year crGFR was also higher for the group receiving fruit and vegetables compared with the group receiving usual care (P <0.01).

In both studies, the fruit and vegetable group showed a significant reduction in body weight, systolic BP and PRAL when compared with baseline data (P <0.01).[25,33] The systolic BP and PRAL were also significantly lower (P <0.01) in both studies in the fruit and vegetable group compared with the control group after follow-up.

The plasma TCO_2 improved significantly (P <0.05) in the fruit and vegetable group in both studies while the plasma potassium levels remained the same with follow-up.

3.4.4 Risk of bias and quality assessment in included studies

A critical appraisal of the RCTs for the risk of bias was conducted according to the guidelines prescribed in the Cochrane collaboration tool for assessing the risk of bias, as seen in Table 3.3.[29] The quality assessment was done according to the critical appraisal checklist for RCTs by JBI in Table 3.4.[30]

Both studies have a high risk of bias and a low-quality score.[25,33] The method of randomisation was not described in either of the studies and it is therefore unclear if true randomisation took place. It was not possible to blind the participants and fieldworkers delivering the treatment in the two RCTs as the fruit and vegetable group received the fruit and vegetables from the fieldworkers. It is unclear whether the outcome assessors were blind to the assigned groups.

Table 3-3: Risk of bias of included studies according to the guidelines prescribed in the Cochrane collaboration tool for assessing risk of bias[29]

	Goraya *et al*., 2013[25]	**Goraya *et al*., 2014**[33]
Adequate sequence generation?	?	?
Allocation concealment?	?	?
Blinding? (Patient-reported outcomes)	-	-
Blinding? (Mortality)	NA	NA
Incomplete outcome data addressed?	+	+
Free of selective reporting?	+	+
Free of other bias?	+	+

NA: Not applicable. Key: + Low risk; ? Unclear risk; - High risk.

Table 3-4: Quality assessment of the studies according to the critical appraisal checklist for randomised controlled trials by the Joanna Briggs Institute[30]

		Goraya *et al*., 2013[25]	**Goraya *et al*., 2014**[33]
1	Was true randomisation used for assignment of participants to treatment groups?	?	?
2	Was allocation to treatment groups concealed?	?	?
3	Were treatment groups similar at the baseline?	Y	Y
4	Were participants blind to treatment assignment?	N	N
5	Were those delivering treatment blind to treatment assignment?	N	N
6	Were outcomes assessors blind to treatment assignment?	?	?
7	Were treatment groups treated identically other than the intervention of interest?	Y	Y
8	Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?	Y	Y
9	Were participants analysed in the groups to which they were randomised?	Y	Y
10	Were outcomes measured in the same way for treatment groups?	Y	Y
11	Were outcomes measured in a reliable way?	Y	Y
12	Was appropriate statistical analysis used?	Y	Y
13	Was the trial design appropriate, and were any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial?	Y	Y
	Overall quality score	61.5%	61.5%

Y: Yes; N: no; ?:unclear; NA: not applicable; RCT: Randomised controlled trial.

3.5 Discussion

The evidence suggests that fruit and vegetable intake can lower metabolic acidosis, decrease systolic BP and decrease kidney damage in CKD without causing hyperkalaemia.[25-27] The aim of this systematic review was to investigate the effect of fruit and vegetable intake on clinical outcomes of patients with CKD, especially eGFR as a measure of progression of kidney failure.

Quality of the evidence

Two articles were included after reviewing all the potentially relevant articles.[25,33] A critical appraisal of the risk of bias was made for the included RCTs according to the guidelines as prescribed in the Cochrane collaboration tool for assessing the risk of bias.[29] The quality assessment was done according to the critical appraisal checklist for RCTs by JBI.[30] Risk of bias present includes selection bias and performance bias.[29] The studies included have a high risk of bias and a low-quality score. This is mainly because the method of randomisation was not described in the studies and therefore it is unclear if true randomisation took place. It was not possible to blind the participants and fieldworkers delivering the treatment in the two RCTs as the fruit and vegetable group received the fruit and vegetables from the fieldworkers The participants in the fruit and vegetable group received apples, apricots, oranges, peaches, pears, raisins and strawberries, carrots, cauliflower, eggplant, lettuce, potatoes, spinach, tomatoes and zucchini. The amount and the types of fruit and vegetables were prescribed by a registered dietitian but participants did not receive specific dietary instructions. They were told to incorporate the fruit and vegetables in their diet as they chose. It is unclear whether the outcome assessors and statisticians were blind to the assigned groups.

Outcomes

The eGFR of the group receiving fruit and vegetables in the study by Goraya *et al.*[25] was the same after one year as that of the group receiving bicarbonate. This indicates that base-producing fresh fruit and vegetables calculated to reduce dietary acid by 50%, are just as effective in delaying the progression of kidney failure as sodium bicarbonate, as prescribed by the KDOQI guidelines for patients with metabolic acidosis.[5] The eGFR was significantly higher in the group receiving fruit and vegetables when compared with the group receiving usual care in the study by Goraya *et al*.[33] This indicates that fruit and vegetable intake helps to preserve kidney function and delays progression of kidney damage. Similar results were reported from in a cohort study by Wai *et al.,*[27] who found that healthy dietary patterns rich in fruit and vegetables were associated with a delay in CKD progression and improved survival in patients with stages 3 or 4 CKD.

The included studies found a significant reduction in body weight and systolic BP in the group receiving fruit and vegetables when compared with baseline data and the control group.[25,33] Fruit and vegetable intake can help to reduce the total energy intake of an individual and replace unhealthy food in the diet, subsequently lowering the body mass index (BMI) and risk of obesity.[34,35] This is supported by the 3-day food diaries of the participants in the group receiving

fruit and vegetables, showing lower energy intake compared with baseline.[25] Fruit and vegetables contain magnesium, potassium, antioxidants, fibre and nitrate, which help to lower BP.[36-38] The reduction in body weight is another contributing factor leading to reduction of BP.[39] It is important, however, to note that only body weight was reported in the studies and not BMI. The reduction in body weight can thus not be interpreted as a positive effect as patients with CKD are known to suffer from protein-energy wasting syndrome.[40]

Metabolic acidosis occurs when the mechanism regulating the acid–base balance in the body or the renal acidification mechanisms are compromised as a result of increased production of non-volatile acids or loss of bicarbonate. The serum bicarbonate concentration drops to less than 22 mEq/L.[41,42] A secondary decrease in the arterial partial pressure of carbon dioxide (PCO_2) then follows, leading to a reduction in blood pH.[43] The included studies found a significant reduction in PRAL in the intervention group when compared with baseline as well as in comparison with end values in the control group.[25,33] The PRAL of food is based on the average intestinal absorption rate of protein, phosphorus, potassium, magnesium and calcium.[26,44] Food with a PRAL value of less than 0 increases alkalinity of the body fluids and food with a PRAL value of more than 0 increases acid production in the body, leading to metabolic acidosis.[44] The PRAL affects the net endogenous acid production (NEAP) which, in turn, will affect CKD progression by distal nephron acidification and endothelin activation.[45] Both studies found a significant improvement in plasma TCO_2 in the fruit and vegetable group when compared with baseline. Most fruit and vegetables contain potassium salts of metabolising anions like citrate and malate which consume hydrogen ions and therefore have an alkalising effect.[28] Plant proteins are higher than animal proteins in glutamate, which is an anionic amino acid that neutralises hydrogen ions, leading to a reduction of metabolic acidosis.[28]

Fruit and vegetable intake had no effect on plasma potassium when compared with baseline and/or the control group in both the RCTs.[25,33] No patient in any group in the included studies had plasma potassium levels >4.6 mEq/L during follow up. The exclusion criteria of the studies might have excluded participants at high risk of hyperkalaemia, such as patients with diabetes. However, the results were supported by Scialla *et al.,*[46] who found that a higher percentage of plant protein intake was not associated with higher serum potassium in patients with CKD. Patients who are advised to follow a low-potassium diet (2 000 to 3 000 mg/d) have to avoid high-potassium food such as nuts, seeds, beans, peas, legumes and many commonly available fruit and vegetables that contain >200 mg potassium per serving.[47] A diet rich in fruit and vegetables and thus a higher potassium intake may delay the progress of CKD in early stages by lowering BP.[48] It seems that the benefits of plant-based diets naturally high in potassium and fibre and low in acidogenic proteins and minerals could outbalance the possible risk of

developing hyperkalaemia in early CKD.[17] It is rather the use of potassium additives such as monosodium phosphate, dicalcium phosphate and phosphoric acid that patients should avoid.[24,49]

A meta-analysis by Kelly *et al*.[50] concluded that dietary patterns rich in fruit and vegetables, legumes, whole grains and fibre, together with lower consumption of red meat, sodium and refined sugars were consistently associated with lower mortality in people with CKD. This meta-analysis aimed to evaluate the association between dietary patterns and mortality or ESRD among adults with CKD. Seven studies were included with a total of 15 285 participants. Evidence is pointing away from single-nutrient renal diets, where the emphasis is on restriction of potassium, phosphate and protein, towards more plant-based diets.[12,27,46,51,52] Single-nutrient approaches are difficult to comply with and have provided few positive results.[50] In fact, they may even be detrimental to health as they limit the use of common and easily available fruit and vegetables, as well as limiting protein in an already malnourished patient population.[53,54]

As mentioned earlier, there is a well-established link between CKD and CVD, with HPT being the main cause of CKD.[48,55] The management of HPT is the most important factor in both the primary prevention as well as progression of CKD. The included studies showed that higher fruit and vegetable intake significantly reduced systolic BP.[25,33] Nutrients such as potassium, folate, vitamins, fibre and phenolic compounds found in fruit and vegetables protect against CVD by various pathways.[13,56] Examples include decreasing oxidative stress by providing antioxidants, improving dyslipidaemia, decreasing BP, lowering insulin resistance, and improving haemostasis regulation.[56,57] Dietary patterns such as the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diet, which modifies several risk factors in CVD, would be beneficial not only in preventing CKD but also in delaying regression of kidney function in patients with CKD. It is important to note that these dietary patterns are not only high in fruit and vegetables but also contain other important nutrients from nuts, seeds and legumes. Scialla *et al.*[46] found that a higher percentage plant protein intake was associated with higher bicarbonate in patients with CKD and thus lower metabolic acidosis. Gutierrez *et al.*[12] found diets rich in fruit and vegetables were associated with a lower risk of mortality. The findings by Smyth *et al.*[52] support an association between healthy dietary patterns and reduced risk of major renal outcomes such as mortality and initiation of dialysis.

The strengths of this systematic review are that 1) the search was done systematically according to the PRISMA statement;[32] 2) the search string was created by a research librarian to ensure a very targeted search on multiple databases; 3) studies for inclusion was chosen and subsequent data extracted was done by two independent review authors s; and 4) validated

assessment tools were used to evaluate the risk of bias and quality of the included studies. High-quality clinical trials are very limited and the included studies have a high risk of bias. Shortcomings of the two RCTs include the fact that clear categories for fruit and vegetable intake were not reported in terms of quantity and variety. Both studies described the fruit and vegetable intervention as base-producing fresh fruit and vegetables calculated to reduce dietary acid by 50%. The primary fruit provided included apples, apricots, oranges, peaches, pears, raisins and strawberries. Vegetables given to the intervention group consisted of carrots, cauliflower, eggplant, lettuce, potatoes, spinach, tomatoes and zucchini. The amount and the types of fruit and vegetables were prescribed by a registered dietitian but participants did not receive specific dietary instructions. They were told to incorporate the fruit and vegetables in their diet as they chose. The results should be interpreted with caution as the two included studies have a high risk of bias and low quality score. The two included studies have possible risk of selection bias and performance bias. After this systematic review it is very clear that limited RCTs are available on the topic.

In conclusion, this systematic review showed that a diet including selective fruit and vegetables could reduce metabolic acidosis and BP while preserving kidney function in CKD without causing hyperkalaemia over one to three years of follow-up. Future studies conducted on the topic should use clear categories to identify the type and quantity of fruit and vegetables given to participants.

3.6 Acknowledgements

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3.7 Author contributions

Jacomie Nel: Developed the research proposal and title for study. Set problem statement, aims and objectives. Data search, data extraction, critical appraisal of the data extracted and statistical analysis. Writing of the protocol, literature study and systematic review. Editing of article according to journal specifications.

Dr Martani Lombard: Student co-supervisor; contributed to data extraction, risk of bias and quality control, critically appraised the data extracted and supported the writing of the protocol and systematic review. Provided expert advice on systematic reviews and meta-analysis

Dr Robin Dolman: Student supervisor; critically appraised the data extracted and supported student in the writing of the protocol and systematic review. Provided expert advice on CKD and CVD.

3.8 Conflict of interest

None of the authors has any conflict to declare.

3.9 Differences between protocol and review

It was planned in the protocol to do a meta-analysis of the data but because of differences in study design and sample population, it was not possible to pool data.

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CHAPTER 4

DIETARY PATTERNS AND PROGRESSION OF KIDNEY FAILURE AND MORTALITY IN ADULTS WITH CHRONIC KIDNEY DISEASE: A NARRATIVE SYSTEMATIC REVIEW

This chapter is an article that has been prepared for the Journal of Renal Nutrition. The article has been prepared according to the instructions for authors and can be found in Annexure D.

Title page

Dietary patterns and progression of kidney failure and mortality in adults with chronic kidney disease: A narrative systematic review

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4.1 Abstract

Background: The current dietary recommendations for patients with chronic kidney disease (CKD) are very restrictive and difficult to comply with. Recent evidence shows that overall healthy dietary patterns rich in fruit and vegetables (3-5 portions daily) may improve clinical outcomes of these patients.

Methods: This narrative systematic review of cohort studies aimed to investigate the effect of dietary patterns on clinical outcomes of patients with CKD, especially the progression of kidney failure. A search was systematically performed on EBSCO Host, Google Scholar, MedLine, Pubmed, Science Direct, Scopus and The Web of Science for studies published before July 2019. Cohort studies on adults older than 18 years with CKD, defined as estimated glomerular filtration rate (eGFR <60 ml/min/1.73m^2), not receiving dialysis, were included.

Results: Five observational studies with a total of 8 649 participants were included in this narrative systematic review. Four of the included studies found that a higher plant-based dietary pattern and intake of fruit and vegetables reduced all-cause mortality in patients with CKD when compared with the lowest quintile of intake.

Conclusion: Dietary patterns rich in fruit and vegetables are associated with lower mortality in patients with CKD. This data should be interpreted with caution as the exact cause of mortality is unknown and the quality of the studies is poor.

Keywords: Chronic kidney disease, dietary patterns, fruit intake, vegetable intake, metabolic acidosis, GFR

4.2 Introduction

Chronic kidney disease (CKD) affects more than 10% of all people.[1] In South Africans five million people older than 20 years have CKD.[2] Diet is one of the main modifiable risk factors that can be utilised to prevent or slow the development of CKD.[3] Historically, dietary intervention has been a major part of CKD treatment and the current recommendations include the restriction of protein, sodium, potassium and phosphate intake.[4,5] This limits the intake of protective foods such as nuts, seeds, beans, peas, and legumes, as well as commonly consumed fruit and vegetables such as avocado, butternut, grapes, mango, nectarines, papaya, gem squash, spinach and sweet potato, to name a few.[6,7] These restrictions are hard to comply with and might even be detrimental to the patients' health as patients with CKD are at risk of cardiovascular disease (CVD), protein-energy wasting syndrome and metabolic acidosis.[3,8-10]

Studies found that fruit and vegetable intake improves metabolic acidosis, decreases systolic blood pressure (SBP) and decreases kidney damage in patients with CKD without causing hyperkalaemia.[11-13] A number of mechanisms explain why fruit and vegetable intake is beneficial to patients with CKD. Firstly, higher fruit and vegetable intake results in lower net production and retention of hydrogen ions, with better preservation of kidney function.[14] Phosphorus metabolism can be improved by vegetable intake in patients with CKD. Phosphate from foods of plant-origin is far less readily absorbed by the intestine because of the lower bioavailability of phytate compared with phosphate from animal-origin foods and, in particular, from processed foods.[15] Fruit and vegetables contain magnesium and potassium, which help to lower blood pressure (BP).[16,17] Increased fruit and vegetable intake also increases fibre intake, which improves the levels of uraemic toxins in patients while increasing protein intake to lower the risk of malnutrition.[3,18]

Despite all the information on the topic, only two randomised controlled trials (RCTs) were found when conducting a systematic review on the effect of fruit and vegetable intake on the progression of chronic kidney disease.[11,12] It was found that most of the studies conducted on this topic focused on overall dietary patterns analysis, looking at the overall diet of individuals; the foods, food groups, and nutrients included; their combination and variety; and the frequency and quantity of habitual consumption.[19,20] Although fruit and vegetable intake may be a cost-effective and acceptable treatment option for patients with CKD, the quantity and type of fruit and vegetables suitable during each stage of CKD is not well defined.

Studies that focused on overall dietary patterns with a high of consumption of fruit, vegetables, legumes, whole grains, poultry and fish and lower consumption of red meat, salt, and refined sugars found a positive association with clinical outcomes such as CKD progression, metabolic

acidosis and mortality.[21-23] Western eating patterns high in red and processed meat, sweets, fried food, and refined carbohydrate have been shown to produce a high dietary acid load which leads to reduced kidney function by causing metabolic acidosis or subclinical acid retention.[9,24] The Mediterranean diet seems to be beneficial in delaying progression of CKD.[22,23] The Mediterranean diet is well balanced and rich in fruit and vegetables[21,25] which reduce metabolic acidosis by decreasing the net endogenous acid production (NEAP).[23] The Mediterranean diet also improves endothelial function, inflammation, lipid profile and BP.[23]

Individuals do not consume nutrients or food in isolation, therefore, nutritional advice is often easier to understand in the context of foods rather than the individual nutrients they contain.[19] This study aimed to perform a narrative systematic review of observational studies investigating the effect of dietary patterns on clinical outcomes of patients with CKD especially the progression of kidney failure.

4.3 Materials and methods

Our primary aim was to assess the effect of healthy dietary patterns high in fruit and vegetables on clinical outcomes of patients with CKD, especially the progression of kidney failure. The primary outcomes were estimated glomerular filtration rate (eGFR) in response to dietary patterns high in fruit and vegetables. The secondary outcomes included the risk of mortality and end-stage renal disease (ESRD). This narrative systematic review was conducted following a previous systematic review done on RCTs. This narrative systematic review was conducted according to a pre-established review protocol.

The eGFR of the exposure category and reference category were reported as mean ± standard deviation (SD). A P-value <0.05 indicates a statistically significant difference between the exposure group compared with the reference group. The hazard ratio (HR) was reported with a 95% confidence interval (CI).

4.3.1 Criteria for considering reviews for inclusion

Observational cohort studies were included with an adult study population (aged ≥18 years),with CKD defined as eGFR <60 ml/min/1.73m^2, and not receiving dialysis. Dietary patterns higher in fruit and vegetables were the primary intervention compared with dietary patterns with a lower frequency and amount of fruit and vegetable consumption. Dietary patterns were determined by using self-reporting tools such as 24-hour dietary recalls, food diaries and food frequency or dietary habits questionnaires and then categorised by using diet quality score and dietary pattern analysis. There is no standardised classification of dietary patterns. Follow-up had to

occur for at least one year. Papers in languages other than English, duplicated articles, review papers, congress abstracts, editorials and case reports were excluded from this review. Non-randomised studies (NRS) were used in this narrative systematic review to provide evidence of the effect on CKD of dietary patterns rich in fruit and vegetables.

4.3.2 Search methods for identification of studies

Two reviewers (JN and ML) searched EBSCO Host, Google Scholar, MedLine, Pubmed, Science Direct, Scopus and Web of Science systematically for cohort studies published before July 2019, and the searched reference lists of primary studies, review articles and clinical practice guidelines independently to find relevant studies. Studies found potentially relevant by one or more reviewers were retrieved for title screening.

The search strategies were created by a research librarian, using MeSH terms and keywords in databases without MeSH terms. The search string used was based on Population/ Intervention/ Comparison and Outcome (PICO) and were as follows: (chronic kidney failure or chronic kidney insufficiencies) AND renal failure AND chronic renal failure AND (kidney disease or renal disease or renal failure or kidney failure) AND (end-stage renal disease or end-stage renal failure or chronic kidney disease or kidney failure) AND glomerular filtration rate AND adults AND patient AND (fruits and vegetables) AND (dietary habits or eating habits or dietary patterns) AND (potassium and hyperkalaemia) AND (hypertension or high blood pressure and metabolic acidosis and acid–base balance and serum bicarbonate).

4.3.3 Data collection and analysis

A study eligibility form was used to determine inclusion or exclusion of studies and a data extraction form was used for extraction of the relevant information. The titles and abstracts of the articles identified were independently evaluated by two reviewers (JN and ML) to decide if they met the inclusion criteria for the review. Data of the eligible studies were extracted and summarised by the two independent reviewers (JN and ML) and disputes were resolved by a third reviewer (RD). Where studies with two or more review arms were included, only data from intervention and control groups that met the eligibility criteria were extracted.

The following data were extracted from eligible studies: bibliographic data, including date of publication, country of origin, trial design, care setting, aim of study, population group, age of participants, number of participants in each arm, key baseline participant data, including eGFR, BP, details of treatment regimen received by each group, duration of treatment, details of any co-interventions, primary and secondary outcomes (with definition), outcome data for primary

and secondary outcomes (by group), duration of follow-up, number of withdrawals by group with reasons, cofounders adjusted for and source of funding for trial.

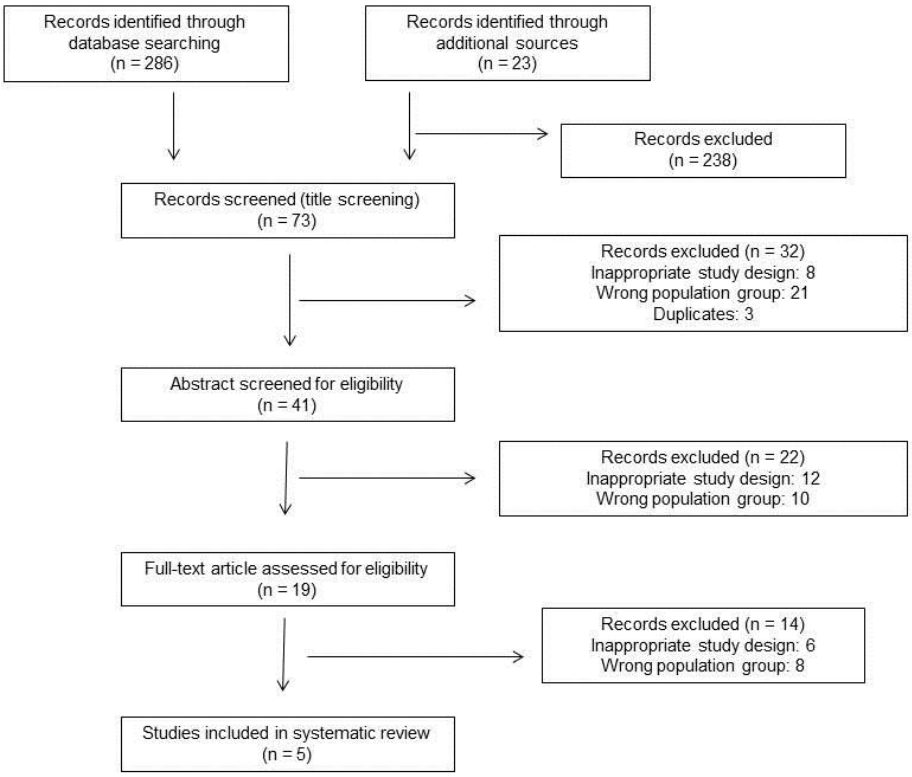
4.3.4 Assessment of risk of bias and quality assessment of studies

Assessment of risk of bias was conducted independently by two review authors (JN and ML). The Newcastle-Ottawa scale for assessing the risk of bias of cohort studies was used to assess the risk of bias for the included studies.[27] Quality assessment of the studies was conducted according to the critical appraisal checklist for cohort studies as prescribed by Joanna Briggs Institute (JBI).[28] The criteria for each guideline were classified as yes, no, unclear or not applicable. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool was then used to rate the quality of evidence as high, moderate, low or very low.[29]

4.4 Results

4.4.1 Study selection

The database search delivered a total of 286 studies and 23 studies were added from a manual search. A total of 73 studies was identified by title screening of the initial search results. Forty-one studies were identified for abstract review and 19 studies for full-text review. The 68 studies were excluded for the following reasons: 26 studies had an inappropriate study design (RCTs), or were reviews, editorials, or abstracts; three studies were duplicates and 39 studies had an inappropriate population group (healthy adults; younger than 18 years, receiving dialysis). Five observational studies met the final criteria and were included in this narrative systematic review.[5,30-33] No further studies were added from the manual search. An overview of the literature search can be seen in Figure 4.1; the Preferred Reporting Items for Systematic Review and Meta-Analysis of individual participant data (PRISMA-IPD) flow diagram was used.[34]



Tool used: PRISMA IPD flow diagram[34]

Figure 4-1: Flow diagram of studies considered for inclusion

4.4.2 The rationale for inclusion of observational studies

Very few RCTs have been done to determine the effect of fruit and vegetables on clinical outcomes of patients with CKD due to practical and logistical constraints. Therefore, observational and cohort studies were used for this narrative systematic review. The observational studies included are of value as they provide longer follow-up data and larger sample sizes that RCTs. Five observational studies were identified after full-text revision as these studies met all the inclusion criteria. The data of the included observational studies could not be pooled due to differences in study design and outcomes measured; the results of the observational studies will, therefore, be reported in the form of a narrative description.

4.4.3 Baseline characteristics

Five prospective, cohort observational studies were included in this narrative systematic review.[5,30-33] A total of 8 649 participants with CKD was included, all with eGFR <60 ml/min/1.73m^2. Three of the five observational studies were conducted in the United States; one was conducted in Australia and one in Sweden. All of the studies were published between 2013

and 2016. The duration of follow-up was between four and nine years. The dietary patterns described in the included studies differ and include: diets rich in plant protein,[32] plant-based diets,[5] healthy diets high in fruit and vegetables[33] and the Mediterranean diet.[30] Characteristics of the included observational studies and details of the data collected can be seen in Table 4.1 and Table 4.2 respectively.

4.4.4 Risk of bias and quality assessment in included studies

A critical appraisal for the risk of bias was conducted according to the guidelines prescribed by The Newcastle-Ottawa scale for assessing risk of bias of cohort studies, as seen in Table 4.3.[27] The overall risk of bias of the studies was low except for Huang *et al*.[30] for which the risk was moderate. Although all of the participants in the studies had CKD at baseline, Huang *et al*.[30] was not representative of the exposed cohort as only Swedish men between the ages of 50 and 70 years were included. The risk of bias for the ascertainment of exposure to eating patterns was unclear in all the included studies, as the eating patterns were determined by using self-reporting tools such as 24-hour dietary recalls, food diaries, and food frequency or dietary habits questionnaires. All of the studies accounted for a number of confounding factors but three of the studies failed to account for energy intake.[30,31,33]

The quality assessment was done according to the critical appraisal checklist for cohort studies (Table 4.4), as prescribed by the JBI.[28] The quality of the studies was moderate, but the same patterns could be identified as with the risk of bias. It is unclear if the exposure was measured in a valid and reliable way, as it was self-reported. By using the GRADE tool, the overall quality of the studies is assessed as low as observational studies are considered low-quality evidence.[29]

Table 4-1: Characteristics and data collection of the included observational studies

Author, year. country	Name of cohort study	Study population	No of participants	Age (years)	Duration (years)	Dietary predictors	Outcomes	Adjusting factors
Gutierrez *et al*., 2014.[5] United States	REGARDS	CKD eGFR <60 ml/min/1.73 m^2 or ACR ≥30 mg/g	3 927	≥ 45	6.4	Plant-based (F&V)	All-cause mortality and ESRD	Age, sex, ethnicity, energy intake, smoking, lifestyle, PA, Heart disease, HPT, education, family income, ACR, eGFR.
Chen *et al.*, 2016.[32] United States	NHANES lll	CKD eGFR <60 ml/min/1.73 m^2	1065	44.8 ± 15.8	8.4	Plant protein vs animal protein	All-cause mortality	Demographics, smoking, alcohol use, comorbidity, BMI, calorie and total protein intake and physical inactivity
Wai *et al*., 2016.[33] Australia	CKD.QLD Nutrition Study	CKD stage 3-4 eGFR 15-59 ml/min/1.73 m^2	145	71 ± 12	<4	F&V and limited alcohol intake	All-cause mortality, commencement of dialysis and doubling of serum creatinine	Age, sex, eGFR, BMI, malnutrition, CVD, DM, cancer, liver disease,
Huang *et al*., 2013.[30] Sweden	ULSAM	eGFR <60 ml/min Men	506	-	9.9	Mediterranean Diet	Cardiometabolic risk factors All-cause mortality	BMI, PA, smoking status, education, HPT, DM
Ricardo *et al*., 2015.[31] United States	CRIC	eGFR 20-70	3006	58 ± 11	4	Healthy diet	CKD progression (50% decrease in eGFR or ESRD), all-cause mortality	BMI, age, sex, ethnicity, education, DM, HPT, CVD, eGFR, log 24 urine protein.

ACR: Albumin to creatinine ratio; BMI: Body Mass Index; CKD: chronic kidney disease; CKD.QLD: Chronic Kidney Disease in Queensland CRIC: Chronic Renal Insufficiency Cohort; CVD: cardiovascular disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; F&V: fruit and vegetables; no: number; NHANES: National Health and Nutrition Examination Survey; PA: physical activity; REGARDS: Reasons for Geographic and Racial Differences in Stroke; ULSAM: Uppsala Longitudinal Study of Adult Men.

Table 4-2: Exposure and outcomes of the included cohort trials

Reference	Dietary predictor	Exposure	Exposure category	Reference category	Results		
					Outcome	**Reference category**	**Exposure category**
Gutierrez *et al.*, 2014[5]	Plant based	Lowest intake compared to highest intake of F&V	Quartile 4 (highest intake of % plant protein)	Quartile 1 (lowest intake of % plant protein)	eGFR (ml/min/1.73m^2)	68.1 (0.8)	70.1 (0.8)
					ACR (mg/g)	42.4 [12.9-103.2]	43.3 [15.8-101.8]
					Mortality (HR, 95% CI)	1.00 (ref)	0.77 (0.61, 0.97)
					ESRD (HR, 95% CI)	1.00	1.18 (0.71, 1.98)
Chen *et al.*, 2016[32]	Plant protein %	Highest plant % intake compared with lowest intake. Plant products including grains, F&V, legumes, nuts and seeds.	Quartile 4 Plant protein >40.9%	Quartile 1 Plant protein <22.4%	ACR ≥30 mg/g (%)	8.1	9.0
					All-cause mortality (HR, 95% CI)	1.00	0.67 (0.46, 0.96)
Wai *et al.*, 2016[33]	F&V	High DHQ score vs low DHQ score for increasing F&V.	High DHQ score	Low DHQ score	eGFR (ml/min/1.73m^2)	30 ± 14	35 ± 11*
					Composite clinical outcome[a] (HR, 95% CI)	1.00	0.38 (0.18-0.82)*
					All-cause mortality (HR, 95% CI)	1.00	0.35 (0.15-0.83)*
Huang *et al* ., 2013.[30]	MD	Low adherence vs high adherence to the MD	High adherence (MDS 6-8)	Low adherence (MDS 1-2)	All-cause mortality (HR, 95% CI)	1.00	0.77 (0.44-1.36)*
Ricardo *et al.*, 2015[31]	Healthy diet	Low vs high healthy diet score allocated by above the median consumption of F&V, fish and whole grains; and below the median 24-hour urine sodium excretion and consumption of sugar	Score 5	Score 0	eGFR	43.39 ± 13.34	44.05 ± 13.15*
					CKD progression (HR, 95% CI)	1.00	NS
					Atherosclerotic CV events (HR, 95% CI)	1.00	NS
					All-cause mortality (HR, 95% CI)	1.00	NS

ACR: Albumin to creatinine ratio; CI: confidence interval; DHQ: Dietary History Questionnaire; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; F&V: fruit and vegetables; HR: hazard ratio; MD: Mediterranean Diet; MDS: Mediterranean Diet Score; NS: no significance; ref: reference. For each pattern, Q1 represents least consistency with pattern and Q4 represents most consistency with pattern. [a]Refers to death, commencement of dialysis or doubling of serum creatinine. The most adjusted data are used from the included studies. *P value <0.0

Table 4-3: Risk of bias for the included cohort studies, using the Newcastle-Ottawa Scale[27]

	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure to eating patterns	Demonstration that outcome was not present at baseline	Study accounts for energy intake in analyses	Ascertainment of outcome	Follow up sufficient for outcomes to occur	Adequacy of follow-up
Gutierrez *et al.*, 2014[5]	+	+	?	+	+	+	+	+
Chen *et al.*, 2016[32]	+	+	?	+	+	+	+	+
Wai *et al.*, 2016[33]	+	+	?	+	-	+	+	+
Huang *et al.*, 2013[30]	-	+	?	+	-	+	+	+
Ricardo *et al.*, 2015[31]	+	+	?	+	-	+	+	+

Key: + Low risk; ? Unclear risk; - High risk.

Table 4-4: Quality assessment of the included cohort studies according to the guidelines as prescribed by Joanna Briggs Institute[28]

		Gutierrez *et al*., 2014[5]	Chen *et al*., 2016[32]	Wai *et al*., 2016[33]	Huang *et al*., 2013[30]	Ricardo *et al*., 2015[31]
1	Were the two groups similar and recruited from the same population?	Y	Y	Y	Y	Y
2	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Y	Y	Y	Y	Y
3	Was the exposure measured in a valid and reliable way?	?	?	?	?	?
4	Were confounding factors identified?	Y	Y	Y	Y	Y
5	Were strategies to deal with confounding factors stated?	Y	Y	Y	Y	Y
6	Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	Y	Y	Y	Y	Y
7	Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y	Y
8	Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Y	Y	Y	Y	Y
9	Was follow-up complete, and if not, were the reasons for loss to follow up described and explored?	Y	Y	Y	Y	Y
10	Were strategies to address incomplete follow-up utilised?	Y	Y	?	N/A	Y
11	Was appropriate statistical analysis used?	Y	Y	Y	Y	Y

Y: Yes; N: no; ?:unclear; NA: not applicable.

4.4.5 Outcomes

4.4.5.1 Estimated glomerular filtration rate

Three of the included studies[5,31,33] investigated eGFR in the exposure group compared with the reference group. All three of these studies found a higher eGFR value in the exposed category with healthier dietary patterns which included more fruit and vegetables. Ricardo *et al*.[31] and Wai *et al*.[33] found the eGRF to be significantly higher in the exposed category. The exposure versus reference category was 44.05 ± 13.15 vs 43.36 ± 13.34 in Ricardo *et al*.[31] and 35 ± 11 versus 30 ± 14 in Wai *et al*.[33]

4.4.5.2 Progression of chronic kidney disease by decrease in estimated glomerular filtration rate, reaching end-stage renal disease or initiation of dialysis

Three of the included studies[5,31,33] investigated CKD progression, composite clinical outcomes and development of ESRD in patients with CKD. In the study by Gutierrez *et al.*,[5] 141 ESRD events were reported but no association was found between a plant-based dietary pattern and incident ESRD. Wai *et al*.[33] found a significant association between low and high Dietary History Questionnaire (DHQ) scores for increasing fruit and vegetables intakes and composite clinical outcomes, referring to death, the commencement of dialysis or doubling of serum creatinine. The HR (95% CI) was 0.38 (0.18-0.82). Ricardo *et al*.[31] compared low versus high healthy diet score allocated by above the median consumption of fruit and vegetables, fish and whole grains and below the median 24-hour urine sodium excretion and consumption of sugar. The study did not find a significant association between a healthy diet and CKD progression.

4.4.5.3 All-cause mortality

All the included studies investigated mortality as an outcome in CKD.[5,30-33] A total of 1 451 deaths occurred during the follow-up period, data from Chen *et al.,*[32] were excluded as the number of deaths were not given distinctly for the CKD subpopulation. All but one study[31] found that a higher plant-based dietary pattern and intake of fruit and vegetables reduced all-cause mortality in patients with CKD when compared with the lowest quintile intake. The HR and 95% CI for the respective studies can be seen in Table 4.2.

4.5 Discussion

The aim of this study was to perform a narrative systematic review of observational studies investigating the effect of dietary patterns on clinical outcomes of patients with CKD, especially the progression of kidney failure. The literature suggests that healthy dietary patterns rich in fruit and vegetables, legumes, whole grains, poultry and fish and lower in red meat, salt, and refined

sugars are beneficial for prevention of CKD and delaying of ESRD in patients with CKD.[9,22,23,35] Dietary patterns high in fruit and vegetables decrease NEAP, and improve metabolic acidosis, endothelial function, inflammation, lipid profile and blood pressure, resulting in improved kidney function and lower mortality risk, without causing hyperkalaemia.[11,13,16,23]

Quality of the evidence

Five articles with a total of 8 649 participants with CKD were included after reviewing all the potentially relevant articles.[5,30-33] The Newcastle-Ottawa scale was used to assess the risk of bias for the included cohort studies..[27] Quality assessment of the studies was done according to the critical checklist for cohort studies by JBI.[28] All the included studies had a low risk of bias except for Huang *et al*.,[30] which had a moderate risk of bias as it was not representative of the exposed cohort. All the included studies had an unclear risk of bias for the ascertainment of exposure to eating patterns as the eating patterns were determined by using self-reporting tools such as 24-hour dietary recalls, food diaries, food frequency or dietary habits questionnaires. The studies accounted for a number of confounding factors but three of the studies failed to account for energy intake.[30,31,33]

The studies had a low overall quality score as non-randomised studies are considered as low-quality evidence.[29]

Outcomes

Estimated glomerular filtration rate

Three of the five included studies reported on eGFR in the reference versus exposure categories. The three studies[5,31,33] that investigated eGFR in the exposure group compared with the reference group found a higher eGFR value in the exposed category with healthier dietary patterns. All three of these studies have a low risk of bias and poor quality score. Two of the studies[31,33] found the eGFR to be significantly higher in the exposed category. The exposure of these three studies differs greatly in the sense that Gutierrez *et al.*[5] used quartiles to compare the lowest with the highest intake of fruit and vegetables whereas the other two studies[31,33] used DHQ's. It is reported in the literature that a diet high in vegetable sources of protein may lead to lower endogenous production of acid. This is associated with higher serum bicarbonate levels and the preservation of GFR.[4,36,37]

It is essential to preserve the kidney function of a patient with CKD to delay the development of ESRD and cardiovascular complications. The only treatment for ESRD is renal replacement therapy (RRT) such as dialysis and renal transplantation.[38] Because of limited resources, only

15–20% of patients in South Africa who require RRT obtain such treatment.[2] It is predicted that the global demand for RRT will more than double by 2030.[39] Slowing or preventing CKD progression will considerably cut health care costs as these costs more than double in the later stages of CKD.[40]

Progression of chronic kidney disease to decline in estimated glomerular filtration rate, reaching end-stage renal disease or initiation of dialysis

Rapid progression of kidney failure is defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m^2/year.[4] One of the studies found a significant association between low and high DHQ score for increasing fruit and vegetables and composite clinical outcomes, which referred to death, the commencement of dialysis or doubling of serum creatinine.[33] Two of the studies[5,31] found no significant association between a healthy diet and CKD progression to ESRD. The same results were found in a 2017 systematic review by Kelly *et al*.[22] that included a total of seven studies involving 15,285 participants; That systematic review found no statistically significant association between healthy dietary patterns and ESRD (RR and 95% CI of 1.04 (0.68,1.40). It is important to note, however, that the quality of all three these studies is low and the dietary patterns are not standardised but were obtained by using self-reported information from participants.

All-cause mortality

Four of the five included studies found a positive association between higher plant-based dietary patterns with fruit and vegetables and reduced all-cause mortality in patients with CKD.[5,30,32,33] These data correlate with results from the systematic review by Kelly *et al*.,[22] which found that healthy dietary patterns were consistently associated with lower mortality in patients with CKD (RR and 95% CI of 0.73 (0.63,0.83)). Mortality should nonetheless be interpreted with caution as the exact cause of mortality is not known and could include other causes besides CKD-related complications. The studies that found an association between dietary patterns and reduced all-cause mortality had a low to moderate risk of bias. The quality score is low for all four of these studies as they are observational studies. Ricardo *et al.*[31] is the only study that found no significance between higher plant-based dietary patterns with fruit and vegetables and reduced all-cause mortality in patients with CKD. Ricardo *et al.*[31] used a low versus high dietary score that included other dietary factors besides fruit and vegetable intake. These factors included above the median intake of fish and whole grains, and below the median 24-hour urine sodium excretion and consumption of sugar.

Traditionally, research has focused on single nutrient outcomes; and it is only recently that there has been a shift to investigating dietary patterns and all the included studies, therefore, were published between 2013 and 2016. Current dietary guidelines for nutritional therapy of CKD are very restrictive and hard to comply with. The current nutritional therapy for CKD patients includes the restriction of protein, sodium, potassium and phosphate intake.[4,11] Fruits and vegetables are rich in potassium and well known for their cardiovascular protection properties.[21] Two large meta-analyses consisting of more than 220 000 participants each found that fruit and vegetable intake of three to five servings daily decreases the risk of coronary heart disease (CHD) by 7% when compared with a lower intake of fewer than three servings per day.[41,42] Cardiovascular disease and CKD share overlapping risk factors[25,43] and the risk of cardiovascular mortality can increase by 5% with every 10 mL/min per 1.73 m^2 reduction in eGFR.[44] Cardiovascular health should be a priority in patients with CKD.

Even though potassium restrictions are widely prescribed, there seems to be little evidence to support the premise that high dietary potassium intake is indeed associated with high serum potassium levels.[3,11,15,18,45,46] A study by Noori *et al.,*[45] which included 224 patients on haemodialysis (HD), reported that dietary potassium was responsible only for about 2% of the variance in pre-dialysis serum potassium levels. It seems that the benefits of plant-based diets, naturally high in potassium and fibre and low in acidogenic proteins and minerals, could outbalance the possible risk of developing hyperkalaemia in early[3] and even later stages of CKD.[47] Serum potassium was not one of the outcomes reported in the included studies, but we recommend that it be included in future studies.

This narrative systematic review has the following strengths: The search was done systematically, according to the PRISMA statement.[34] The search string was created by a research librarian to ensure a very targeted search on multiple databases; Studies were chosen for inclusion and data extracted for the possible eligible studies by two independent researchers and validated assessment tools were used to evaluate the risk of bias and quality of the included studies. Although the PRISMA statement was used to ensure the specific requirements of reporting systematic reviews, this study has limitations.[34] This review is conducted on NRS, which automatically lowers the quality of evidence. All the included studies featured different dietary patterns with no standardisation of the dietary patterns included. The aim was to compare dietary patterns rich in fruit and vegetables with dietary patterns with a lower frequency and amount of fruit and vegetable consumption. Although we managed to achieve this, the upper and lower quartiles used for the comparison differed greatly between the studies included and some studies used diet scores that included other dietary components besides fruit and vegetables. Dietary patterns in the included studies were generated by using food frequency questionnaires, food diaries and healthy eating scores; all of these methods rely on self-

reported data from the participants. Although all participants had eGFR <60 ml/min/1.73m^2, the participants included were in different stages of CKD, making it difficult to know which dietary pattern would be best during which stage of CKD. Lastly, all the included studies were conducted in the United States, Australia and Sweden and are thus not globally representative of all countries, especially developing countries such as South Africa.

In conclusion, this narrative systematic review showed that dietary patterns rich in fruit and vegetables may reduce mortality in patients with CKD. Less restrictive diets are good news for populations that already does not have an adequate fruit and vegetable intake. Patients with CKD can be encouraged to available fruit and vegetables instead of restricting fruit and vegetables high in potassium. While good quality clinical trials are needed to investigate the effects of fruit and vegetable intake in different stages of CKD, it may be very difficult to conduct RCTs on this topic. Cohort study designs may work better, but future studies should specify the type and quantity of fruit and vegetables or specific dietary patterns better by using clear categories.

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4.7 Author contributions

Jacomie Nel: Development of research proposal and title for study. The setting of the problem statement, aims and objectives. Data search, data extraction, critical appraisal of the data extracted and statistical analysis. Writing of the protocol, literature study and narrative systematic review. Compiling of dissertation and editing of the article according to journal specifications.

Dr Tani Lombard: Student co-supervisor; assisted with data search, data extraction, critical appraisal of the data extracted and support in the writing of the methods in the protocol and narrative systematic review. Provision of expert advice on systematic reviews and meta-analysis.

Dr Robin Dolman: Student supervisor; critical appraisal of the data extracted and support of the student in the writing of the protocol and narrative systematic review. Provision of expert advice on CKD and CVD.

4.8 Conflict of interest

None of the authors has any conflict to declare.

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CHAPTER 5 GENERAL DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

This chapter serves as a summary of the results found in the previous chapters. The details discussed in this chapter are only broad discussions, recommendations and conclusions, as the more comprehensive data, have already been presented in previous chapters.

The aim of chapter 5 is to present a conclusion on the effect of fruit and vegetable intake on CKD outcome, by summarising the main results found. These conclusions will be of assistance to patients with CKD, health care providers specialising in CKD and researchers interested in the topic.

5.2 Study aim

To perform a systematic review of studies that investigate the effect of various fruit and vegetable portions on clinical outcomes of patients with CKD.

5.3 Specific objectives of the study

5.3.1 To conduct a detailed search on studies meeting the inclusion criteria

A detailed search was performed on EBSCO Host, Google Scholar, MedLine, Pubmed, Science Direct, Scopus, The Web of Science and The Cochrane Central Register of Controlled Trials and the reference lists of primary studies, review articles and clinical practice guidelines to find relevant studies, systematically using the keywords and MeSh terms as determined by the librarian. Two different search strategies were used to find RCTs that investigate the effect of fruit and vegetable intake on CKD and cohort studies that look at dietary patterns and CKD progression.

5.3.2 To evaluate relevant studies regarding risk of bias and quality

Assessment of risk of bias was conducted independently by two review authors (JN and ML) by using two different tools for RCTs and observational studies. The Cochrane Collaboration tool for assessing risk of bias was used to assess the risk of bias for the included RCT studies (Higgins & Green, 2009) whereas the Newcastle-Ottawa scale for assessing risk of bias of cohort studies was used to assess the risk of bias for the observational studies (Wells *et al*., 2011).

Both the critical appraisal checklist for RCTs and the critical appraisal checklist for cohort studies, as prescribed by the Joanna Briggs Institute (JBI), were used (Tufanaru *et al*., 2017; Moola *et al*., 2017). The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool was then used to rate the overall quality of evidence as high, moderate, low or very low (Guyatt *et al*., 2011).

5.3.3 To conduct a meta-analysis where possible

It was not possible to conduct a meta-analysis with the data extracted from the included studies owing to considerable heterogeneity between studies in terms of study design and sample population.

5.4 Summary of main findings

In the systematic review that included RCTs on fruit and vegetable intake, the primary outcome was eGFR in response to fruit and vegetable intake or usual care. The secondary outcomes included markers indicating acidosis (potential renal acid load (PRAL), plasma total carbon dioxide (TCO_2), body weight, BP and plasma potassium. Two studies met the final inclusion criteria. In both studies, the fruit and vegetable group showed a significant reduction in body weight, systolic BP and PRAL when compared with baseline data ($P < 0.01$) (Goraya *et al*., 2013; Goraya *et al*., 2014). The systolic BP and PRAL were also significantly lower ($P < 0.01$) in the fruit and vegetable group compared with the control groups after follow-up in both studies (Goraya *et al*., 2013; Goraya *et al*., 2014). The plasma TCO_2 improved significantly ($P < 0.05$) in the fruit and vegetable group of both studies while the plasma potassium remained the same with follow-up (Goraya *et al*., 2013; Goraya *et al*., 2014). These two studies have a high risk of bias (selection bias and performance bias) and a low-quality score (Higgins & Green, 2009). It was unclear if real randomisation took place as the method of randomisation was not described in the studies. Furthermore, it was not possible to blind the participants and fieldworkers delivering the treatment in the two RCTs as the fruit and vegetable group received the fruit and vegetables from the fieldworkers, but it is unclear whether the outcome assessors and statisticians were blind to the assigned groups. The methods described in theses to studies were very similar.

A follow-up article was written to include data published in cohort studies on the effect of dietary patterns on CKD outcomes.

In the systematic review on cohort studies, the primary outcome was progression of CKD in response to dietary patterns rich in fruit and vegetables. The secondary outcome was all-cause mortality. Five cohort studies met the final inclusion criteria. Three of the five studies looked at

progression of CKD. One of the studies found a significant association between low and high Dietary History Questionnaire (DHQ) score for increasing fruit and vegetables and composite clinical outcomes, which refer to death, the commencement of dialysis or doubling of serum creatinine (Wai *et al*. (2016). Two of the studies (Gutierrez *et al*., 2014; Ricardo *et al*., 2015) found no significant association between a healthy diet and CKD progression. All the included studies investigated mortality as an outcome in CKD (Huang *et al*., 2013; Gutierrez *et al*., 2014; Ricardo *et al*., 2015; Chen *et al*., 2016; Wai *et al*., 2016) and all but one (Ricardo *et al*., 2015) found that a higher plant-based dietary pattern and intake of fruit and vegetables reduced all-cause mortality in patients with CKD when compared with the lowest quintile intake. These five included studies had a low to moderate risk of bias and poor quality score as it is non-randomized studies. The risk of bias for the ascertainment of exposure to eating patterns was unclear in all the included studies, as the eating patterns were determined by using self-reporting tools such as 24-hour dietary recalls, food diaries, food frequency or dietary habits questionnaires. All of the studies accounted for a number of confounding factors but three of the studies failed to account for energy intake (Huang *et al*., 2013; Ricardo *et al*., 2015; Wai *et al*., 2016). The study by Huang *et al*. (2013) included only Swedish men between the ages of 50 and 70 years and was thus not representative of the exposed cohort.

5.5 Strengths of the study

A detailed search was conducted by two independent. Additional sources were searched manually to ensure that no studies were missed. All relevant articles were inspected independently by two researchers. Data extraction was done by two independent reviewers and then compared. The PRISMA statement was used to ensure that the specific requirements of reporting systematic reviews were met (Stewart *et al*., 2015). Validated assessment tools were used to evaluate the risk of bias and quality of the included studies. The original search was for RCTs, which are the strongest form of evidence. Even though the original protocol was aimed at RCTs, we conducted an alternative search on cohort studies to make sure that we included all relevant evidence.

5.6 Limitations of the study

Even though the PRISMA statement was used to ensure the specific requirements of reporting systematic reviews, the study does have a few limitations (Stewart *et al*., 2015). The systematic review of cohort studies is NRS, which automatically lowers the quality of evidence. All the included studies had different dietary patterns with no standardisation of the included dietary patterns. Our aim was to compare dietary patterns rich in fruit and vegetables with dietary patterns with lower frequency and amount of fruit and vegetable consumption. Although we

managed to achieve this, the upper and lower quartiles used for the comparison differed considerably between the included studies. Dietary patterns were generated by using food frequency questionnaires, food diaries and healthy eating scores; all of these methods rely on self-reported data from the participants. Even though all participants had eGFR <60 ml/min/1.73m^2, the participants included were in different stages of CKD, making it difficult to know which dietary pattern would be best during which stage of CKD. The studies were conducted in the United States, Australia and Sweden and are thus not globally representative of all countries, especially developing countries such as South Africa.

5.7 Recommendations arising from the study

5.7.1 For patients with CKD

Dietary patterns like the Mediterranean diet, which is higher in fruit and vegetables, are beneficial for patients with CKD to prevent progression of kidney failure, improve metabolic acidosis and blood pressure. More plant-based diets like vegetarian or vegan diets are also preferred above diets high in meat, especially red meat and processed meat as it has higher production of NEAP. Patients from populations that already does not have an adequate fruit and vegetable intake can be encouraged to eat available fruit and vegetables instead of restricting fruit and vegetables high in potassium.

5.7.2 For health care professionals

It is important to look at the overall nutritional intake and lifestyle of a patient with CKD. Additional red flags such as hypertension, diabetes, metabolic acidosis, and progression to ESRD and CVD must be monitored. It is imperative to remember that CKD and CVD share overlapping risk factors and these two conditions exacerbate each other. Prevention of CVD comorbidities is crucial and therefore, a renal diet should also be heart-friendly.

Caution should be taken when prescribing dietary restrictions such as limiting potassium-rich foods including nuts, seeds, beans, peas, legumes and many fruits and vegetables. There is limited evidence that indicates consumption of these foods is associated with high serum potassium levels. Potassium-rich foods are essential for the health of patients. Restrictions on phosphate intake should also be advised with care as there is very little evidence to link dietary phosphorus intake directly to adverse clinical outcomes in patients with CKD. Phosphate restrictions are hard to comply with and limit protein-rich food such as legumes, meat, poultry, fish, eggs and dairy products in the diet. Cutting back on the intakes of these foods increases the patient's risk for protein-energy malnutrition. Worthy to note is that legumes have the lowest

bioavailability of phosphorus – approximately 40% whereas almost 100% of the phosphorus in food additives is absorbed.

5.7.3 For further research

The systematic review performed indicated that more research is needed. There is a great need for proper clinical trials as only two studies were found that met these criteria. It will be impossible to do double-blinded studies as participants have to receive extra fruit and vegetables or not, but it is recommended that the data analysts are blinded.

Standardisation of fruit and vegetable intake or dietary patterns is necessary to enable easier comparison of studies.

Future studies need to clearly define the intake of fruit and vegetables – types of fruit and vegetables, amounts of each, portion sizes, preparation methods and other lifestyle factors need to be included. Controlled feeding trials in patients with different stages of CKD are recommended over longer time periods of at least 6–12 months.

5.8 Conclusion

The results of the systematic review and narrative systematic review in Chapter 4 and 5 respectively indicated that consumption of fruit and vegetables may be an effective strategy in improving metabolic acidosis and reducing kidney injury in stages 3 to 5 CKD, without producing hyperkalaemia. However, randomised controlled trials on the effect of fruit and vegetable intake on CKD are very scarce. Observational studies were used to fill the gap in the literature but even that approach fell short as the aims, study design and outcomes measured in these studies differed considerably. It was found that studies focused more on eating patterns than on individual food items and that fruit and vegetable intake is not well defined, let alone standardised, in all of the studies. Therefore, further well-designed clinical trials are needed with a clearly defined fruit and vegetable intake regarding portions and type; or dietary pattern.

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ANNEXURES

Annexure A Ethical approval documents

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Tel: 086 016 9698
Web: http://www.nwu.ac.za/

North-West University Health Research Ethics Committee (NWU-HREC)

Tel: 018 299-1206
Email: Ethics-HRECApply@nwu.ac.za (for human studies)

12 September 2019

ETHICS APPROVAL LETTER OF STUDY

Based on approval by the North-West University Health Research Ethics Committee (NWU-HREC) on 12/09/2019, the NWU-HREC hereby approves your study as indicated below. This implies that the NWU-HREC grants its permission that, provided the general conditions specified below are met and pending any other authorisation that may be necessary, the study may be initiated, using the ethics number below.

Study title: Effect of fruit and vegetable intake on progression of kidney failure in adults with chronic kidney disease: A systematic review
Principal Investigator/Study Supervisor/Researcher: Dr RC Dolman
Student: J Nel - 22135936

Ethics number:

N	W	U	-	0	0	5	0	6	-	1	9	-	A	1
Institution				Study Number						Year			Status	

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Application Type: Systematic review
Commencement date: 12/09/2019
Expiry date: 30/09/2020

Risk: **Minimal**

Approval of the study is provided for a year, after which continuation of the study is dependent on receipt and review of an annual monitoring report and the concomitant issuing of a letter of continuation. A monitoring report is due at the end of September annually until completion.

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, the following general terms and conditions will apply:

- *The principal investigator/study supervisor/researcher must report in the prescribed format to the NWU-HREC:*
  - *Annually on the monitoring of the study, whereby a letter of continuation will be provided annually, and upon completion of the study; and*
  - *without any delay in case of any adverse event or incident (or any matter that interrupts sound ethical principles) during the course of the study.*
- *The approval applies strictly to the proposal as stipulated in the application form. Should any amendments to the proposal be deemed necessary during the course of the study, the principal investigator/study supervisor/researcher must apply for approval of these amendments at the NWU-HREC, prior to implementation. Should there be any deviations from the study proposal without the necessary approval of such amendments, the ethics approval is immediately and automatically forfeited.*
- *Annually a number of studies may be randomly selected for active monitoring.*
- *The date of approval indicates the first date that the study may be started.*
- *In the interest of ethical responsibility, the NWU-HREC reserves the right to:*

- *request access to any information or data at any time during the course or after completion of the study;*
- *to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process;*
- *withdraw or postpone approval if:*
  - *any unethical principles or practices of the study are revealed or suspected;*
  - *it becomes apparent that any relevant information was withheld from the NWU-HREC or that information has been false or misrepresented;*
  - *submission of the annual monitoring report, the required amendments, or reporting of adverse events or incidents was not done in a timely manner and accurately; and/or*
  - *new institutional rules, national legislation or international conventions deem it necessary.*
- *NWU-HREC can be contacted for further information via Ethics-HRECApply@nwu.ac.za or 018 299 1206*

The NWU-HREC would like to remain at your service and wishes you well with your study. Please do not hesitate to contact the NWU-HREC for any further enquiries or requests for assistance.

Yours sincerely,

Prof Wayne Towers
Chairperson NWU-HREC

Prof Minrie Greeff
Head of the Faculty of Health Sciences Ethics Office

Current details:(23239522) G:\My Drive\9. Research and Postgraduate Education\9.1.5.4 Templates\9.1.5.4.2_NWU-HREC_EAL.docm
20 August 2019

File Reference: 9.1.5.4.2

Annexure B Study eligibility criteria

Table B-1 presents the study eligibility criteria

Table B-1: Study eligibility criteria

CRITERIA	YES	NO	COMMENTS
1.Type of study			
1.1 Randomized			
1.2 Controlled			
1.3 Blinded (not possible?)			
1.3.1 Double			
1.3.2 Single			
1.3.3 Open label			
2. Participants			
2.1 Age: Adults (>18 years)			
2.2 Chronic kidney disease (eGFR <60 ml/min1.73m^2)			
2.3 Not receiving dialysis			
3. Interventions			
3.1 Fruit intake			
3.2 Vegetable intake			
4. Comparisons			
4.1 Placebo			
4.2 Group receiving less than 3 portions of fruit and vegetables daily			
4.3 Traditional treatment of CKD			
5. Outcomes			
5.1 Primary outcomes:			
· Progression of renal failure (eGFR)			
5.2 Secondary outcomes:			
· Development of CVD			
· Metabolic acidosis			
· Blood pressure			
· Albuminuria			
· Creatinine clearance			
· NEAP			
· PRAL			
ACCEPTED			
REJECTED			

CKD: chronic kidney disease, eGFR: estimated Glomerular filtration rate, NEAP: net endogenous acid production, PRAL: potential renal acid load, RCT: Randomised, controlled trials

Annexure C Data extraction form

Table C-1 presents the data extraction form to be used when extracting the data from the studies

Table C-1: Data extraction form

Study ID	**Author Surname**	**Publication details**	**Year**	**Reviewer**
Study types	Study population	Age range	Country	Care setting
Randomised				
Clinical trial				
Intervention	Control	Duration	Number of participants	
Portions of fruit:	Portions of fruit:		intervention	
Portions of vegetables:	Portions of vegetables:		control	
Other lifestyle factors:	Other lifestyle factors:		both	
	Initial	Leg 1	Leg 2	Leg 3
eGFR				
Metabolic acidosis (serum bicarbonate)				
Systolic BP				
Albuminuria				
Creatinine clearance				
Proteinuria				
Inflammation markers				
Dietary acid load (NEAP)				
Quality of life (where it is reported)				
Number of withdrawals				
Reasons for withdrawal				
Source of funding				
Study meets all final eligibility criteria?		Yes	Reviewers Initials:	Date & Sign
		No		

BP: blood pressure, eGFR: estimated glomerular filtration rate, ID: identity, NEAP: net endogenous acid production, PRAL: potential renal acid load, RCT: randomised, controlled trials

Annexure D Author guidelines for the Journal of Renal Nutrition

JOURNAL OF RENAL NUTRITION

Official Journal of the Council on Renal Nutrition of the National Kidney Foundation and the International Society of Renal Nutrition and Metabolism

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

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The Journal of Renal Nutrition is devoted exclusively to **renal nutrition** science and **renal dietetics.** Its content is appropriate for nutritionists, physicians and researchers working in **nephrology.** Each issue contains a state-of-the-art review, original research, articles on the clinical management and education of patients, a current literature review, and nutritional analysis of food products that have clinical relevance.

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To Whom It May Concern

This certifies that the following Master's dissertation has been edited for English language correctness and fluency. I trust that the corrections made have been applied after due consideration by the author of the document:

Effect of fruit and vegetable intake on the progression of kidney failure in adults with chronic kidney disease:

A systematic review

By

J Nel

Mini-dissertation submitted in partial fulfilment of the requirements for the degree *Magister Scientiae* in dietetics at the North-West University

Mary Hoffman

(SATI Registration: 1001632)