Does the use of a wheat dextrin fibre supplement improve bowel performance in renal dialysis patients? – a pilot study

A thesis presented in partial fulfillment of the requirements for a degree of

Master of Science

In

Nutrition and Dietetics

Massey University, Albany

New Zealand

Chester Edwards

2015

Abstract

Background: Constipation is common within renal dialysis patients. Current practice for the management of constipation in renal dialysis patients in Northland DHB involves prescribing laxatives and attempting to alter dietary fibre intake through dietary measures. These methods are however often ineffective and laxatives can have unwanted side effects. The use of a fibre supplement for the treatment of constipation within this patient group would be ideal; however, the currently subsidised fibre supplement in New Zealand needs to be consumed with fluid and is therefore not suitable for renal dialysis patients with severe fluid restrictions. A wheat dextrin fibre supplement is available in New Zealand and this product can be mixed into food, therefore requiring no water. This makes a wheat dextrin fibre supplement ideal for renal dialysis patients as a way to increase their fibre intake in an attempt to improve bowel performance.

Aim: To examine the effectiveness of a wheat dextrin fibre supplement on bowel performance in free living end stage renal failure patients who are currently receiving either peritoneal or haemodialysis within the Northland DHB.

Methods: Haemodialysis (HD) or peritoneal dialysis (PD) patients who were currently taking laxatives were recruited for this cross-over, single blind intervention study (n =7). After a two week observation stage (OBS), subjects consumed up to 22 g of wheat dextrin fibre supplement (WD) per day or the equivalent of a maltodextrin placebo (PB) for four weeks. Patients then switched treatments after a two week washout period. In all three study stages, subjects completed a prospective patient held record measuring stool frequency, stool form, laxative use, and the quantity of supplement consumed in the WD and OBS stages. During the final three days of each stage, subjects completed a 28 question quality of life (QOL) questionnaire designed to assess QOL with reference to constipation over the two weeks immediately prior.

Results: No significant differences were found between the OBS, WD or PB stage for laxative use (p =0.299), stool frequency (p =0.653), stool form (p =0.549), percentage of ideal stools formed (p =0.253), or QOL measures (p =0.181). When determining if WD had an effect in some individuals, it was found that one subject showed a clear increase from 4 stools/week in the OBS stage to 14 stool/week in the WD stage and five stools/week in the PB stage. Another subject managed to decrease their laxative use by 31% in the WD stage compared to the OBS

and PB stage. The percentage of stools that were ideal increased by 20% or more from the OBS to WD and/or PB stage in 67% of subjects.

Conclusion: This pilot study found the use of wheat dextrin to improve bowel performance in some individuals. Due to low subject numbers in the analysis (n =6), it was not surprising that no significant results were found between any stages of the study for any objectives, however individual subjects showed WD improving stool frequency, stool form and reducing laxative use compared to placebo. Overall, this pilot study has highlighted the difficulties in carrying out such a trial in renal dialysis patients, and these should be taken into account when designing future trial in this population.

Acknowledgements

Firstly I would like to acknowledge all the dialysis patients in Northland DHB who took part in the study. Your input and willingness to take part has helped towards creating a better future for all dialysis patients. Without your voluntary participation none of this would have been possible.

Thank you to the staff at Northland District Health Board who were welcoming and enthusiastic about the study. A special thank you to Olwyn Talbot-Titley who identified the need for the current study. Your support throughout, guidance, trust and approachable manner made for a smooth and enjoyable experience. Your enthusiasm and knowledge in identifying gaps in the research and following through with the relevant projects makes a true difference to the renal patients of Northland.

I would also like to thank my academic supervisors Rozanne Kruger and Kay Rutherfurd-Markwick for their wisdom and specific advice throughout the project. Your knowledge and expertise is very impressive and guided me throughout. Thank you for all your feedback, even when you had a million other things going on.

Thank you to my friends and family for your support and interest during the project.

Table of Contents

List of Tables

List of Figures

List of Appendices

Abbreviation List

WD	Wheat dextrin
PB	Placebo
OBS	Observation
QOL	Quality of life
CKD	Chronic Kidney Disease
ESRF	End stage renal failure
RRT	Renal replacement therapy
KDOQI	The Kidney Disease Outcomes Quality Initiative
MDRD	Modification of diet in renal disease
GFR	Glomerular filtration rate
NHANES	National Health and Nutrition Examination Survey
HD	Haemodialysis
PD	Peritoneal dialysis
CAPD	Continuous ambulatory peritoneal dialysis
PHGG	Partially hydrolysed guar gum
BSFS	Bristol stool form scale
IBS	Irritable bowel syndrome
GI	Gastrointestinal
GOS	Galacto-oligosaccharide
FOS	Fructo-oligosaccharide

Chapter One

1.0 Introduction

The main function of the kidneys is to filter waste products and eliminate excess fluid from the body. When the kidneys fail, their rate of filtration is reduced, meaning they can no longer remove wastes and excess fluid from the blood efficiently (National Kidney Foundation, 2015b). This failure of the kidney is termed kidney disease or renal failure. When this failure is extended over a period of more than three months and has implications for health, it is defined as chronic kidney disease (CKD). Over time, CKD progresses as renal function declines. Once the filtering function of the kidneys reaches a very low rate, patients reach end stage renal failure (ESRF) and require renal replacement therapy (RRT). Renal replacement therapy can be achieved with a kidney transplant, haemodialysis (HD) or peritoneal dialysis (PD). Both HD and PD are needed for the remainder of an individual's life unless a kidney transplant takes place. Although PD and HD have different mechanisms of action, both treatments allow excess potassium, phosphate, urea, creatinine and fluid to be removed from the blood. Both treatments are time intensive, with HD taking 4-5 hours three times per week and PD requiring daily exchanges of fluid from the peritoneal cavity. In New Zealand in 2013 there were 4156 patients who received RRT. Of these, 38% were from functioning transplants, with the rest receiving dialysis. Of those receiving dialysis, 34% were on PD and 66% were on HD (ANZDATA Registry Report, 2014). In New Zealand in 2013, 49% of all new ESRF patients had diabetic nephropathy causing ESRF, 22% had glomerulonephritis, 9% hypertension and 5% polycystic kidney disease (ANZDATA Registry Report, 2014).

A number of health problems are associated with renal dialysis. These include cardiovascular disease, anaemia, protein energy malnutrition, physical and psychological pain as well as a decrease in quality of life (Astor *et al.*, 2002, Davison and Jhangri, 2005, Foley *et al.*, 1998, Kalantar-Zadeh *et al.*, 2003). Chronic constipation is another common problem faced by renal dialysis patients.

Chronic constipation can be defined simply as a functional bowel disorder that presents as persistently difficult, infrequent, or seemingly incomplete defecation, which do not meet irritable bowel syndrome (IBS) criteria (Longstreth *et al.*, 2006). The causes of constipation can often be multifactorial (Wexner *et al.*, 2007), including lifestyle factors such as a low fibre diet, low fluid consumption (Anti *et al.*, 1998, Markland *et al.*, 2013) and a lack of exercise (Brown *et al.*, 2000, De Schryver *et al.*, 2005, Dukas *et al.*, 2003). Other than lifestyle related factors, neuronal disorders such as dementia, Parkinsons disease, multiple sclerosis and Hirschsprung disease can affect nerve impulses to the gut, inhibiting peristalsis. Depression as well as endocrine and metabolic disorders such as diabetes, hyperparathyroidism and hypothyroidism can also cause constipation (Candy *et al.*, 2015, Khan and Simon, 2010, Leung *et al.*, 2011). Regular uses of opioid based drugs can be more susceptible to constipation (Iacono, 2008). Within the general population, the incidence of constipation can vary depending on the defining criteria used, but has been reported to be between 5 and 35% in Europe (Peppas *et al.*, 2008) and 19.9% in one New Zealand study (Talley *et al.*, 2004). Constipation has been found to generate nausea, faecal impaction bowel perforation, bleeding, haemorrhoids, headaches, halitosis, restlessness and confusion as well as decreased mental and physical components of quality of life (QOL) scores (Belsey *et al.*, 2010, Candy *et al.*, 2015, Rao *et al.*, 2015). The impact of constipation on QOL was found to be significant and comparable to other conditions such as allergies, musculoskeletal conditions and inflammatory bowel disease (Belsey *et al.*, 2010). Due to the suffering, pain and side effects of constipation, its treatment should be a priority for patient health and wellbeing.

Increased rates of constipation have been linked with poor dietary fibre intake (Dukas *et al.*, 2003, Markland *et al.*, 2013, Murakami *et al.*, 2006). Eating a diet high in fibre may reduce the prevalence of constipation as fibre increases the bulk of a stool, putting pressure on the luminal wall and hence promoting peristalsis (Frizelle and Barclay, 2007). In addition, the treatment of constipation in the general population has been successful with the use of added dietary fibre such as fibre rich rye bread (Hongisto *et al.*, 2006), oat bran (Sturtzel *et al.*, 2010) and prunes (Attaluri *et al.*, 2011, Cheskin *et al.*, 2009, Sairanen *et al.*, 2007). The use of the fibre supplements psyllium,

inulin (Dahl *et al.*, 2005, Den Hond *et al.*, 2000, López *et al.*, 2007, Marteau *et al.*, 2011) and partially hydrolysed guar gum (Polymeros *et al.*, 2014, Takahashi *et al.*, 1994) have also been found to successfully treat the symptoms of constipation in the general population.

1.1 Justification of Study

Within the renal dialysis population, constipation is very common. Results from research studies consistently show constipation rates being higher in renal dialysis patients compared with the general population, as well as higher rates in HD patients than PD patients. Frequency of constipation has been reported to be between 14.2% and 28.9% in PD patients and between 63.1% and 71.1% in HD patients (Yasuda *et al.*, 2002, Zhang *et al.*, 2013). Objective support for this data was found using radiopaque dye to measure colonic transit time; significantly longer colonic transit times were found in HD patients (43.0 ± 22.2 hours) compared to PD patients (32.7 ± 13.7 hours) and healthy controls (24.3 ± 11.9hours) (Wu *et al.*, 2004). The reasons for the high rates of constipation within these patients are multifactorial. Due to renal dialysis patients being unable to eliminate potassium and phosphate through their kidneys, they must follow strict dietary guidelines excluding foods high in potassium and phosphate. High potassium and phosphate foods are often high in fibre such as a variety of fruits and vegetables, beans, lentils, legumes and whole grains. Studies have shown fibre intake in renal dialysis patients to be around 10 g/day, which is far lower than the recommended daily intake of 25 -30 g/day (Luttrell *et al.*, 2014, National Health and Medical Research Council, 2006, Sutton *et al.*, 2001). This lack of fibre in the diet is a risk factor for constipation. Renal dialysis patients are also fluid restricted, often to 1000 mL/day which, in combination with a lack of dietary fibre, is another factor promoting the risk of constipation. Dialysis patients have also been found to exercise less than healthy controls (Johansen *et al.*, 2000) with HD patients being more inactive than PD patients, due to the HD patients being inactive on dialysis days (Cobo *et al.*, 2014). Renal dialysis patients commonly take a number of medications which

also increases the risk of constipation. It has been reported that on average dialysis patients take 12 medications, often including phosphate binders and analgesic's which have the common side effect of increasing the risk of constipation (Iacono, 2008, Kazama, 2009). In addition, constipation is more common with older age. Over 35% of those who undergo dialysis in New Zealand are over the age of 65 (ANZDATA Registry Report, 2014). Renal dialysis patients are therefore at increased risk of constipation as they age.

As with the general population, constipation within the renal dialysis population has been shown to decrease patient QOL (Strid *et al.*, 2002, Zhang *et al.*, 2013). Constipation also reduces the ability of those on renal dialysis to excrete potassium through stools, which puts patients at risk of hyperkalaemia (Ahmed and Weisberg, 2001). Peritonitis can cause severe illness and discontinuation of PD and has been shown to occur more frequently when patients are constipated (Mitrović *et al.*, 2015). As well as peritonitis, there have been rare reports of colon perforation in constipated PD patients as a result of straining during defecation (Nakamura *et al.*, 2004).

To conclude, constipation within the renal dialysis population is very common and can be due to lifestyle factors such as: difficulty in reaching recommended intakes for fibre, having a fluid restricted diet, and having low levels of exercise. The fact that this patient group is typically of older age and taking many medications adds to the risk of constipation. As constipation within this population causes a decrease in quality of life, an increased risk of hyperkalaemia and increased risks of peritonitis, the treatment of constipation for these patients should be of priority.

1.2 Statement of research problem

Currently the first line treatment of constipation in renal dialysis patients involves the use of dietary measures. However, due to dietary restrictions, poor appetite, lack of money and other co-morbidities, using dietary measures as treatment has been difficult (Annells and Koch, 2003, Sutton *et al.*, 2007b, Sutton *et al.*, 2014). Laxatives are also used to treat constipation, however they have side effects, unknown long

term effects and the efficacy of their use is not yet established (Jones *et al.*, 2002, Quigley *et al.*, 2005, Ruston *et al.*, 2013). An alternative treatment is therefore needed. As it is difficult to increase fibre in the diet using whole foods, using a fibre supplement to add dietary fibre to the diets of renal dialysis patients could be a viable alternative. Currently, there is a psyllium husk fibre supplement available in New Zealand which is fully subsidised via a prescription. Although this supplement has evidence in reducing constipation in the general population, it is not suitable for renal dialysis patients as the recommended dose per day must be taken with 750 ml of water. There are however soluble fibres that can be taken without water, such as inulin, partially hydrolysed guar gum and wheat dextrin. Of these products, wheat dextrin is the only one readily available in New Zealand. It is a prebiotic which could potentially have a laxative effect in the renal dialysis population. However, it is not subsidised via a prescription and no research has been done using wheat dextrin to determine if it can successfully reduce constipation. It would be clinically valuable to determine if wheat dextrin could reduce symptoms of constipation in renal dialysis patients. If so, the evidence could be presented to PHARMAC to support the funding of the product specifically for renal dialysis patients.

1.3 Purpose of the research study

1.3.1 Aim

To conduct a single blind, placebo controlled, pilot study in the Northland District Health Board to examine the effectiveness of a wheat dextrin fibre supplement on bowel performance in free living patients who are currently receiving either peritoneal or haemodialysis.

1.3.2 Objectives

To determine whether the introduction of a wheat dextrin fibre supplement to the diet of free living patients on either HD or PD in Northland DHB will:

1. Improve bowel performance.

2. Reduce laxative use.
3. Improve quality of life.

1.4 Structure of the thesis

The literature will be reviewed in Chapter two. This chapter will include the different methods available for the measurement of constipation, its causes and treatments will be reviewed in both the general population as well as in renal dialysis patients with a focus on fibre supplements. Chapter three will describe the methods used in the study. Chapter four will present the results of the effects of the wheat dextrin fibre supplement on bowel performance and QOL. The findings will then be discussed in Chapter five. Finally, Chapter six will summarise the main findings as well as mentioning the strengths and limitations of the current pilot study and present recommendations for future studies.

Chapter Two

2.0 Literature review

2.1 Introduction

2.1.1 Chronic kidney disease

The function of the kidneys is to filter waste products and excess fluid from the body. The kidneys also release hormones controlling red blood cell production and blood pressure as well as producing an active form of vitamin D. When the kidneys fail, their rate of filtration is reduced meaning they can no longer remove wastes and excess fluid from the blood efficiently (National Kidney Foundation, 2015b). This failure of the kidneys is termed kidney disease or renal failure. When this failure is extended over a period of more than 3 months and his implications for health, it is defined as chronic kidney disease (CKD) (Inker *et al.*, 2014). The Kidney Disease Outcomes Quality Initiative (KDOQI) is an independent, established group governed by an international board of directors with the stated mission to "improve the care and outcomes of kidney disease patients worldwide through promoting, co-ordination, collaboration and integration of initiatives to develop and implement clinical practical guidelines." The KDOQI defines CKD specifically as "kidney damage or a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause" (Levey *et al.*, 2005). The GFR is generally accepted as the best overall index of kidney function. This is because the GFR is reduced after widespread structural damage to the kidneys and most other measures of kidney function decline in parallel with the GFR (National Kidney Foundation, 2013). The GFR can be estimated using equations such as the Modification of Diet in Renal Disease (MDRD) which takes into account serum creatinine level, age, gender and race. A decreased GFR is associated with a range of complications including hypertension, anaemia, malnutrition, bone disease and a decreased quality of life (National Kidney Foundation, 2013). Albuminuria is another marker for kidney damage and is independently related to mortality, cardiovascular events and progression to end stage renal failure ESRF (Inker *et al.*, 2014, Levey *et al.*, 2005). Albuminuria is defined as an albumin to creatinine ratio >30 mg/g in 2 of 3 spot urine specimens. Currently GFR is most widely accepted as the criterion for kidney

disease (Table 2.1). However, the use of albuminuria in addition to GFR can provide a more precise classification and is promoted as a classification and prognosis tool by KDOQI (Hallan *et al.*, 2009, Inker *et al.*, 2014).

Table 2.1 Recommendations for classification stages of GFR by KDOQI (Inker et al., 2014)

Stage	Description	GFR (mL/min/1.73m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60-89
3a	Mild to moderate decrease in GFR	45-59
3b	Moderate to severely decreased GFR	30-44
4	Severe decrease in GFR	15-29
5	Kidney Failure	<15 or dialysis

Diabetes, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity and hereditary diseases are initiation factors for the development of CKD (Levey *et al.*, 2005). From initial kidney damage, CKD may progress through the stages of CKD toward kidney failure at stage 5 (Table 2.1). Complications of CKD can occur at any stage and include drug toxicity, metabolic and endocrine complications, increased risk for CVD as well as infections, frailty, and cognitive impairment (Eknoyan *et al.*, 2004, Levey *et al.*, 2005). Thus it is important to identify CKD in the early stages to minimise adverse outcomes. Most causes of CKD are irreversible and have a lifelong progression. Treatment is mostly aimed at slowing progression to ESRF (National Kidney Foundation, 2013). Slowing the progression of CKD is a priority in CKD treatment. From stages 1 - 4 (Table 2.1) treatment involves controlling blood pressure, glycaemic control keeping HbA1c <53 mmol/L, restricting sodium intake to <2000 mg/day and adopting a healthy lifestyle such as regular exercise, smoking cessation and achieving a BMI between 20-25 kg/m^2 (National Kidney Foundation, 2013) Once patients reach stage 5, treatment involves intensive therapies as described in Section 2.1.3.

2.1.2 Prevalence of chronic kidney disease

Data from the National Health and Nutrition Examination Survey (NHANES) 2007-2012 estimated 13.6% of the United States adult population as having CKD (United States Renal Data System, 2014). Worldwide, it is estimated that 10% of people have some level of CKD (National Kidney Foundation, 2015a). Similarly, data from Australia from 2011-2012 showed that 10% of Australian adults had some form of CKD. Around 4% of adults were in stage 1 of CKD, 2.5% were in stage 2 and less than 1% were in stages 4-5 (Australian Bureau of Statistics, 2013).

As patients progress to stage 5 of CKD, renal replacement therapy (RRT) is an option. Dialysis is one form of RTT often initiated once the GFR falls to below 10 ml/min/1.73m^2 (National Kidney Foundation, 2013). Dialysis can either be HD or PD. Other than dialysis, kidney transplantation can occur through a live or cadaver kidney donor. If no form of RRT is pursued, patients are managed conservatively for end of life care. In Australia in 2013, 21,470 people underwent RRT, with 45% having transplants and the remaining 55% having dialysis. Of those on dialysis, 20% were PD patients, and 80% being HD patients (ANZDATA Registry Report, 2014). In New Zealand in 2013 there were 4156 patients receiving RRT. Of this number, 38% were from functioning transplants and 62% were dialysis patients. Of those receiving dialysis, 34% were on PD and 66% were on HD (ANZDATA Registry Report, 2014). In New Zealand 49% of all new patients in 2013 had diabetic nephropathy causing ESRF, 22% had glomerulonephritis, 9% had hypertension and 5% had polycystic kidney disease (ANZDATA Registry Report, 2014). End stage renal failure is more common in the Maori population than the NZ population with 1326 per million Maori undergoing RRT as opposed to 877 per million in New Zealand as a whole (ANZDATA Registry Report, 2014). In Northland, 32% of the population identify as being Maori compared to 15% in New Zealand as a whole (Statistics New Zealand, 2013), therefore Maori consideration in Northland in important.

2.1.3 Definition & health consequences of haemodialysis & peritoneal dialysis

Once a patient enters stage 5 of CKD, waste products are starting to build up in the blood to the point where RRT is needed. Excess potassium, phosphate, urea, creatinine and fluid can be taken from the body via HD or PD. These treatments are designed so wastes are moved out of the blood into external fluids which can then be discarded.

Haemodialysis requires blood to be taken out of the body and circulated through a dialyser or artificial kidney. For the blood to enter the dialyser, a vascular access (fistula, graft or vascular catheter) is needed (Findlay and Isles, 2015a). The blood runs through the dialyser flowing in the opposite direction to a dialysate solution. The blood and dialysate are separated by a thin membrane. Within the dialyser, solutes such as creatinine, urea, salts and water move out of the blood passing through the membrane and into the dialysate which is then discarded. A patient will typically undergo three dialysis sessions per week on alternative days with sessions lasting 4-5 hours. Dialysis can take place in the hospital or at home. In New Zealand in 2013, 67% of those on dialysis were on HD, and of those 73% were dialysed at a dialysis centre while the rest underwent dialysis at home (ANZDATA Registry Report, 2014).

Peritoneal dialysis uses the peritoneal cavity in the abdomen to remove excess creatinine, urea, salts and water from the blood. The peritoneum is lined with a semi permeable membrane which is rich with capillaries. A high glucose dialysate enters and exits the peritoneal space via a catheter inserted through the abdominal wall. Once in the cavity the dialysate attracts wastes from capillaries surrounding the peritoneum via diffusion. After the dialysate has been in the cavity for 4 to 6 hours, it is then gravity drained and replaced with fresh dialysate. This is repeated 4-6 times daily. During this time PD patients can perform everyday tasks. Two types of PD are available; this includes continuous ambulatory peritoneal dialysis (CAPD) which uses gravity to drain and fill the cavity with dialysate and does not require a machine, or ambulatory peritoneal dialysis (APD) using a machine which automatically exchanges used dialysate with fresh dialysate many times over night with a long dwell time during the day (Findlay and Isles, 2015b).

It is important to remove excess nutrients via the kidneys as they can cause side effects. Phosphate, a common compound found in foods, contributes to secondary hyperparathyroidism and vascular calcification (Lynch *et al.*, 2011). Strong links have also been found between raised serum phosphate values and mortality, especially from cardiovascular causes (Lynch *et al.*, 2011, Slinin *et al.*, 2005). An accumulation of potassium can have more immediate consequences. The healthy kidney disposes of 90-95% of the daily potassium load (Putcha and Allon, 2007). Elevated levels of extracellular potassium cause a change in the intracellular to extracellular potassium ratio which can alter muscle contraction causing fatal cardiac arrhythmias (Ahmed and Weisberg, 2001, Putcha and Allon, 2007). Amongst HD patients, it is estimated that 3-4% of deaths are caused by hyperkalaemia (Ahmed and Weisberg, 2001). As well as cardiac effects, high serum potassium can also cause general muscle weakness. Therefore an alternative means of potassium excretion in dialysis patients is important. If fluid overload occurs, there is an increased risk of all cause and cardiovascular related death (Kalantar-Zadeh *et al.*, 2009). The mechanisms by which fluid retention influences survival in dialysis patients is thought to be the same as those patients with heart failure (Kalantar-Zadeh *et al.*, 2009); that fluid retention can cause lower limb oedema, ascites, general oedema, hypertension, pulmonary vascular congestion and worsening heart failure (Kalantar-Zadeh *et al.*, 2009).

The amount of phosphate, potassium, sodium and water in the body is largely due to an individual's diet. As part of the kidneys normal function is to excrete these nutrients when they are in excess, those with ESRF will not be able to do so. Although either PD or HD can help excrete these nutrients, they can only get rid of a portion. In addition, HD occurs only every 2nd day for 4-6 hours, unlike a functioning kidney which works continuously. Dietary restrictions for patients undergoing either HD or PD are therefore considered to be more intensive and strict than any other medical condition (Kalantar-Zadeh *et al.*, 2015) (Table 2.2). It is therefore recommended to dialysis patients that foods high in phosphate are avoided. Generally high phosphate foods are protein rich foods such as milk, dairy and eggs. Processed foods such as cola drinks and other packaged foods are high in phosphate which is often used as either a flavour enhancer, preservative and stabiliser (Uribarri, 2007). Wholegrains, such as brown rice

and wholegrain bread, are also higher in phosphate that the white varieties (Uribarri, 2007). Some varieties of nuts, peas, beans and lentils are also high in phosphate. These high phosphate foods are recommended to be consumed only in small amounts by dialysis patients. As these foods are high in nutrients such as protein, fibre, vitamins and minerals, patients' nutritional status may be compromised (Lynch *et al.*, 2011, Shinaberger *et al.*, 2008).

Table 2.2 Recommendations for dietary restriction for renal dialysis patients compared to healthy adults (Ash et al., 2006)

Requirements

	Normal adult	**Haemodialysis**	**Peritoneal dialysis**
Calories	20-25 kcal/kg IBW	30-35 kcal/kg IBW	35 kcal/kg IBW
Protein	0.8-1.0 g/kg/day	1.2-1.4 g/kg IBW	>1.2 g/kg IBW
Potassium	3800 mg men 2800 mg women	39 mg/kg/day	Individual treatment recommended based on biochemistry
Phosphate	<4000 mg/day	800-1000 mg/day	800-1000 mg/day
Sodium	<2300 mg/day	1840-2530 mg/day	1840-2530 mg/day
Fluid	2600 ml/day men 2100 ml/day women	500 ml + PDUO	800 ml + PDUO

IBW = Ideal body weight (BMI of 22-25)
PDUO = Previous days urine output

It is recommended that patients with ESRF limit dietary potassium to prevent excess in the blood. Renal dialysis patients can adapt to dispose of some of the extra potassium via the gastrointestinal tract and through cellular uptake. However, these patients must still limit intake of potassium rich foods to stop extracellular potassium from reaching dangerous levels (Putcha and Allon, 2007). Although dialysis can remove some potassium, HD occurs every second day which gives potassium levels a chance to reach dangerous levels if not controlled through diet. Foods high in potassium include a large variety of fruit and vegetables as well as beans, lentils and bran (National Kidney Foundation). It is recommended that ESRF patients limit these foods which make it difficult for them to reach the suggested dietary guidelines of eating 5 or more

fruit and vegetables per day from a variety of sources. In addition, limiting whole grains, bran, lentils and beans along with fruit and vegetables makes it is difficult for ESRF patients to achieve the dietary guidelines for fibre (Kalantar-Zadeh *et al.*, 2002, Khoueiry *et al.*, 2011). Both fluid and salt intake are restricted for dialysis patients as the failing kidney function can no longer work to excrete excess water and salt from the blood.

Both HD and PD have advantages and disadvantages: HD requires long periods attached to a machine which makes mobility and travel difficult. Patients on PD however, have the advantage of mobility as they are not bound to a machine during the day. Due to the presence of a catheter in PD, patients must be vigilant of signs of infection as they are at increased risk of peritonitis. However, since PD is continuous, it doesn't lead to large increases in waste products in the blood as can happen in HD. Due to the high glucose dialysate which is partly absorbed, PD has the disadvantage of being associated with weight gain in some patients (Jolly *et al.*, 2001). However, PD has more lenient dietary restrictions than HD which suits some patients. Potassium restriction is not as strict for patients on PD as the constant dialysing can continually remove excess potassium, with approximately 423 mg of phosphate removed per day in PD compared to HD which removes 300 mg/day (Uribarri, 2007).

Both HD and PD increase the risk of developing other co-morbidities. Cardiovascular disease is the leading cause of death among PD and HD patients. Mortality in patients undergoing dialysis is 10 to 20 times higher than in the general population, even after stratification by age, gender, race and diabetes (Foley *et al.*, 1998). As kidney function declines as measured by a reduced GFR, the incidence and severity of coronary artery disease increases (Herzog *et al.*, 2011). Anaemia is a condition when there is a deficiency in red blood cells or haemoglobin and is a common symptom in those with ESRF. As the kidney function declines, so does the production of erythropoietin, the hormone used in the production of red blood cells. Studies in the USA (Astor *et al.*, 2002) showed that as GFR declines below 60 min/min/1.73m^2, there is a strong correlation with decreases in haemoglobin. Decreases in haemoglobin causes tiredness, shortness of breath, weakness and poor ability to exercise. Protein energy malnutrition (PEM) is another co-morbidity in ESRF patients. It is estimated that PEM is

prevalent within the range of 18% to 75% in HD patients (Kalantar-Zadeh *et al.*, 2003). Severely and moderately malnourished HD patients have been shown to have a higher mortality risk (33% and 5% higher, respectively (Combe *et al.*, 2004)), compared with those who are not malnourished. Suffering from a combination of physical and psychological pain is also common in this patient group. In a study of 205 HD patients, 53% reported chronic pain and 41.4 % reported moderate to severe pain (Davison and Jhangri, 2005). This pain was associated with depression, irritability, anxiousness and inability to cope with stress and likely a reduction in quality of life (Davison and Jhangri, 2005, Merkus *et al.*, 1999). It has been suggested that some stresses for dialysis patients are due to dietary constraints, time restrictions, loss of employment, change in sexual function and fear of death (Kimmel, 2002). Moreover, it has been found that 25% of patients with ESRF suffer from depression (Hedayati *et al.*, 2008). Due to kidney disease and its associated co-morbidities, it is not surprising that the average life expectancy for individuals with ESRF is 3.1 years for those 75 to 79 years old but 9.2 years for the rest of the population (United States Renal Data System, 2014).

Gastrointestinal (GI) symptoms are common among renal dialysis patients. The cause is multi-factorial, often due to a combination of dietary restrictions, lack of physical activity, side effects of medications, as well as effects of co-morbidities. Recent evidence suggests that patients with CKD have an altered gut microbiota which can drive metabolic abnormalities including uremic toxin production, inflammation and immunosuppression, which leads to further failure of the kidneys and CVD (Rossi *et al.*, 2015). As previously mentioned, constipation can cause serious side effects in renal dialysis patients and should therefore be avoided.

2.1.4 Definition, causes and prevalence of constipation

In order to assess constipation, a clear definition and diagnostic criteria must be used. Functional constipation can be defined simply as a functional bowel disorder that presents as persistently difficult, infrequent, or seemingly incomplete defecation,

which do not meet irritable bowel syndrome (IBS) criteria (Longstreth *et al.*, 2006). However, the term constipation means different things to different people, which makes comparing information from the literature difficult. For example, some people consider it normal to pass a stool three times a day while for others, three times a week is considered normal (Candy *et al.* 2015). This has resulted in different definitions of constipation as what is considered normal is different to different people.

The Rome III Criteria (Table 2.3) provides more in-depth diagnostic information which can be used as a measure by individuals to help define constipation. This criteria was originally established in Rome in 1991 from the consensus of an international committee with the goal of standardising criteria of functional gastrointestinal disorders including constipation (Drossman and Dumitrascu, 2006), and has since been updated three times.

Table 2.3 Rome III: Criteria Diagnosis of Chronic Functional Constipation[a]

1.Must include ≥2 of the following: - Straining during defecation[b] - Lumpy or hard stools[b] - Sensation of incomplete evacuation[b] - Sensation of anorectal blockage[b] - Manual manoeuvres to facilitate defecation[b] - Fewer than 3 bowel movements per week
2. Loose stools are not present without use of laxatives
3. Insufficient criteria for the diagnosis of irritable bowel syndrome

[a]Symptoms for previous 3 months (which need not be consecutive wks) with symptom onset > 6 months prior to diagnosis.
[b]At least 25% of defecations

In practice, the Rome III Criteria has limitations and the American College of Gastroenterology Chronic Constipation Task Force which reviewed the Rome Criteria

concluded it was too detailed for use in the primary setting. This was because the majority of primary physicians still emphasise constipation as being < 3 bowel motions per week, which is a dated measure of constipation (Wexner *et al.*, 2007). This measure on its own, captures only a small proportion of those with constipation, as many people pass more than 3 stools per week, but they still report difficultly (incomplete evacuation and straining) with stool passage . Therefore, to avoid any common misdiagnosis in the primary setting, health care professions must be encouraged to use the Rome III criteria in its full form.

Other than the Rome III criteria, the Bristol Stool Form Scale (BSFS) is a validated tool which uses stool consistency to assist in the diagnosis of constipation (Appendix D). The BSFS uses seven categories with stool images and descriptions that patients can use to classify their stool form. Stool form has been found to better correlate to objective measures of colonic transit compared to measuring stool frequency alone (Markland *et al.*, 2013). Although the Rome III criteria and BSFS are useful tools for measuring constipation, a common problem in the literature is using only stool frequency as a measure. Another problem in diagnosing constipation is the reliance on self-reporting of constipation, which is common in studies and is frequently assessed using retrospective questionnaires that depend on the patients abilities to recall symptoms. When self-reporting constipation, rates are usually higher, likely due to personal perception rather than the actual problem (Peppas *et al.*, 2008). Useful tools such as the BSFS or the Rome III criteria should be used in future research in combination with prospective, patient held diaries to reduce the effects of retrospective self-reporting of constipation.

The aetiology of constipation is often multifactorial and causes can be unclear (Wexner *et al.*, 2007). Lifestyle factors such as a low fibre diet, low fluid consumption and lack of exercise contributes to chronic constipation. Other than lifestyle related factors, neuronal disorders such as dementia, Parkinsons disease, multiple sclerosis and Hirschsprung disease can affect nerve impulses to the gut, inhibiting peristalsis. Psychological disorders such as depression can also be associated with constipation, as can endocrine and metabolic disorders such as diabetes, hyperparathyroidism and hypothyroidism (Candy *et al.*, 2015, Khan and Simon, 2010, Leung *et al.*, 2011). A wide

range of drugs can cause constipation, especially opioids (Iacono, 2008), as well as having impaired colonic muscle tone and pelvic floor muscles (Leung *et al.*, 2011).

Data from the literature regarding the prevalence of constipation in the general population differs. Large variations are likely due to the different methods used to measure constipation such as which version of the Rome scale was used (I, II or III), self-reporting questionnaires, or phone versus face to face based interviews (Peppas *et al.*, 2008, Quigley *et al.*, 2005). This is highlighted in one meta-analysis in which different diagnostic criteria were used on the same participants to reveal differing prevalence's of constipation: 14.2% with Rome II, 19.2% with Rome I and 29.5% when self-reporting (Peppas *et al.*, 2008). As shown by Peppas *et al.* (2008), the prevalence of constipation has been found to be lower in studies using the Rome II or III criteria (Suares and Ford, 2011a). The systematic review by Peppas *et al.* (2008) found mean rates of constipation in Europe to be 17.1%, which ranged from 5% to 35%. The mean value in Oceania was found to be 15.3% with values ranging from 4.3% in an elderly rest home to 30.7% in the general population of Sydney (Peppas *et al.*, 2008). Similar rates have been reported in North America (12-19%) (Higgins and Johanson, 2004). In a New Zealand study, 92 participants from a birth cohort (26 years) were questioned via a survey to determine the incidence of constipation. Results found that 19.9% suffered from constipation with one factor for increased odds being female gender (Talley *et al.*, 2004). Other studies (Markland *et al.*, 2013, Peppas *et al.*, 2008) have also found female gender to be associated with increased risk for constipation. Constipation is also more common in those of older age and in those with lower income (Dukas *et al.*, 2003, Quigley *et al.*, 2005, Suares and Ford, 2011b).

Eating a diet high in fibre may reduce the prevalence of constipation as fibre increases the bulk of a stool, putting pressure on the luminal wall promoting peristalsis (Frizelle and Barclay, 2007). However quality evidence is lacking due to how studies define constipation (Frizelle and Barclay, 2007). A prospective cohort study in 62,036 women aged 30 to 55 found that women in the highest quintile of fibre intake (median 20g/day) were significantly less likely to report constipation than those women in the lowest quintile of fibre intake (7g/day) (Dukas *et al.*, 2003). However, in this study constipation was defined retrospectively as <3 bowel movements per week, which is a

poor quality measure on its own. A cross-sectional study looking at 1705 Japanese dietetic students aged 18-20 years found no relationship between dietary fibre intake and constipation (Murakami *et al.*, 2006). However, this study was done by students ticking 'yes', 'sometimes' or 'no' from a questionnaire which is a poor quality measure as it relies on subject self-diagnosis of constipation. In a cross-sectional study by Markland *et al.* (2013) based on data from NHANES in the USA, significantly higher constipation rates in both genders were associated with the lowest quartile of dietary fibre intake (<10.1 g/day). An advantage of this study is that it used the BSFS to assess stool form, and defined constipation as having type 1 or 2 stools as the "usual or most common stool type". Overall, studies need to use validated tools to assess constipation to gain more reliable data.

Fluid intake in combination with dietary fibre is important to prevent constipation as water is absorbed by stools making them bulkier and softer, thus creating an easier passage through the intestines. Although there is no research to suggest improvements in constipation with fluid on its own without fibre, there is research however showing the benefits of fluid and fibre intake together on constipation. One randomised controlled trial RCT with 117 participants (aged 18-50 years) investigated whether fibre plus fluid intake reduced constipation compared to a high fibre diet alone. One group received a standard diet for 2 months providing around 25 g of fibre per day with *ad libitum* fluid intake. The other group received the standard diet and were instructed to drink 2L/day of mineral water. Results showed that both groups significantly increased their stool frequency from baseline. The high fibre and fluid group had a mean increase in stools per week of 2.4 which was significantly higher than the fibre group alone which had a mean increase of 1.3 stools per week ($P < 0.001$) (Anti *et al.*, 1998). In addition, multivariable analysis of data from the NHANES study found that low fluid intake was a predictor for constipation among women and men and univariate analysis of data found significantly higher rates of constipation in both genders at the lowest quartile of fluid intake (Markland *et al.*, 2013). Both of these studies however used < 3 bowel movements per week as diagnosis of constipation which is not the best measure of constipation when used on its own.

Several studies have shown that people who perform daily physical activity are less likely to suffer from constipation compared with those who don't exercise (Brown *et al.*, 2000, De Schryver *et al.*, 2005, Dukas *et al.*, 2003). An Australian cohort study involving 39,532 women found that across all age groups those women who were most physically active were less likely to report constipation compared to women who were the least physically active (Brown *et al.*, 2000). Similarly, a study by Dukas *et al.* (2003) found that women who reported daily physical activity had significantly lower prevalence of constipation than sedentary women. In a randomised controlled trial (RCT) using middle aged, sedentary, constipated men and women by De Schryver *et al.* (2005), one group was randomised to their normal lifestyle for 12 weeks, the other group was randomly assigned to a 12 week exercise programme. Those in the exercise group significantly decreased the fulfilment of the Rome I criteria compared to those maintaining a normal lifestyle. However, the NHANES study (Markland *et al.*, 2013) found no significant differences in constipation rates when related to vigorous physical activity . Vigorous physical activity was defined as any activity over the last 30 days for at least 10 minutes that caused heavy sweating or large increases in breathing or heart rate. The definition of vigorous physical activity of 10 minutes in the last 30 days is likely too little to encounter significant differences.

Constipation has been reported to cause considerable suffering. A reduction in quality of life (QOL) is widely reported in those with chronic constipation. In a 45 question survey on those pre-screened for constipation in a random sample of people from the USA, 52% reported symptoms affecting their QOL. Of this 52%, 71% reported bloating somewhat affecting their QOL, 65% reported abdominal discomfort, 63% infrequent bowel movements and hard stools and straining affecting 59% of respondents' QOL (Johanson and Kralstein, 2007). As well as abdominal discomfort, constipation can also cause nausea, faecal impaction, bowel perforation, bleeding, haemorrhoids, headaches, halitosis, restlessness and confusion (Candy *et al.*, 2015, Rao *et al.*, 2015). In a meta-analysis (Belsey *et al.*, 2010), mental and physical components of QOL scores were shown to be consistently impaired in constipated populations. The impact of constipation on QOL was found to be significant and comparable to other conditions such as allergies, musculoskeletal conditions and inflammatory bowel disease (Belsey

et al., 2010). Therefore, the treatment of constipation should be should be a priority as it is commonly associated with discomfort and a decreased QOL.

2.1.5 Constipation in Renal Dialysis Patients

In renal dialysis patients, constipation is very common. Variations in incidence within the dialysis population are likely dependent on the age of the population studied as well as the methods used to determine constipation. However, research studies consistently report constipation being higher in dialysis patients than in the general population, as well as higher rates in HD compared with PD patients. Studies reporting the prevalence of constipation in renal dialysis patients are shown in Table 2.4.

Table 2.4 Prevalence of constipation in renal dialysis patients

Study and clinical setting	Study design	Constipation criteria	Methodology	Major Findings
(Yasuda *et al.*, 2002) (Japan)	Multicentre comparative study	Via retrospective questionnaire of bowel habits over the last 12 months.	HD group (n =268), CAPD group (n =204) both asked about bowel frequency, stool consistency, straining and use of laxatives via a questionnaire	Frequency of constipation 28.9% in CAPD patients and 63.1% in HD patients. HD patients had 3.14 times the risk of constipation than CAPD patients
(Zhang *et al.*, 2013) Renal outpatient unit (Southeast China)	Cross sectional study	Self-reporting based on Rome III criteria via questionnaire	HD group (n =478), PD group (n =127) tested for constipation via questionnaire	Incidence of constipation 71.7% in HD patients and 14.2% in PD patients Relative risk for constipation 4.17 times higher in the HD compared to PD groups $p < 0.05$
(Wu *et al.*, 2004) Division of Nephrology Outpatients (Taiwan)	Controlled trial	Self-reported defecation frequency and use of laxatives	HD group (n =56), PD group (n =63) and healthy control group (n =25) tested for colonic transit time using radiopaque markers.	HD patients had significantly longer colonic transit time (43.0 ± 22.2 hours) compared to CAPD (32.7 ± 13.7 hours) and healthy controls (24.3 ± 11.9 hours) $p < 0.001$

HD = Haemodialysis
PD = Peritoneal dialysis
CAPD = Continuous ambulatory peritoneal dialysis

Yasuda *et al.* (2002) reported the frequency of constipation was 28.9% in 204 PD patients and 63.1% in 268 HD patients. Results were obtained via a questionnaire in which patients were asked about bowel frequency, stool consistency, straining and use of laxatives over the previous 12 months. An earlier study by the same authors found that 40% of HD patients (n =125) had to take laxatives for constipation compared to 16% of PD patients (Yasuda *et al.*, 1995). In a cross-sectional study of 605 (478 HD, 127 PD) Chinese dialysis patients, 71.7% of HD patients and 14.2% receiving PD reported constipation (Zhang *et al.*, 2013). In this study a questionnaire was used to evaluate constipation defined using the Rome III criteria. The previous studies were all based on self-reporting of constipation through retrospective questionnaires. Although these methods of measuring constipation are likely to produce unreliable results, the trend consistently shows high rates of constipation in this patient population. A study by Wu (2004) however, used objective measures by performing an abdominal x-ray following the ingestion of radiopaque dye for 6 days (Wu *et al.*, 2004). These results supported the results from previous studies of HD patients having significantly longer colonic transit times (43.0 ± 22.2 hours) than those on PD (32.7 ± 13.7 hours) or healthy controls (24.3 ± 11.9hours). The results also showed discrepancies between subjective reports of constipation and objective measures of total colonic transit times which highlights the limitations of self-reported constipation.

Due to the restrictions of the renal diet as discussed in Section 2.1.3, patients often cannot meet the dietary fibre recommendations of 25 g/day for women and 30 g/day for men (National Health and Medical Research Council, 2006). As a low fibre diet is often associated with constipation, patients with ESRF are therefore at even higher risk of developing constipation. In a cohort of American women on dialysis, mean fibre intake was found to be 10 g/day (Luttrell *et al.*, 2014) which is significantly lower than healthy women from a similar cohort (Therrien *et al.*, 2014). Low intakes of fibre were found in PD patients, where the mean intake of fibre

was 10g/day (Sutton *et al.*, 2001). In this study only 3 of the 34 patients (24 men, 10 women) achieved a fibre intake above 15 g/day. Supporting results were found using a food frequency questionnaire (FFQ) study carried out on 30 HD patients (15 men, 15 women), where fibre intake was found to be significantly lower in HD patients than matched controls who were not on dialysis (12 ± 6 g/day vs. 18 ± 11 g/day) (Kalantar-Zadeh *et al.*, 2002). In combination with a low dietary fibre intake, renal dialysis patients are often limited to 1000 ml/day of fluid. As discussed in Section 2.1.4., this fluid restriction in combination with a low fibre intake puts patients at increased risk of constipation. As PD patients usually have a greater allowance of fluid per day, this is a likely reason why constipation is more common in HD than PD patients.

As well as dialysis patients having lower dietary fibre and fluid intake, exercise levels in HD patients has also been found to be less than in healthy controls (Zamojska *et al.* 2006, Nowicki *et al.* 2010), thereby increasing their risk of constipation. Thirty four HD patients and 80 healthy sedentary individuals from San Francisco had their physical activity measured using a three dimensional accelerometer as well as with an activity questionnaire (Johansen *et al.*, 2000). Those on dialysis were found to have lower levels of physical activity than controls and this difference increased with increasing age. There is currently little evidence regarding physical activity levels of those who undergo PD. One study found HD patients took significantly less steps per day as measured with a pedometer compared to PD patients. (Cobo *et al.*, 2014). This was explained by HD patients being inactive on dialysis days which was not a constraint of PD patients and could be another contributing factor to the higher levels of constipation among HD patients.

Yasuda et al. (1995) suggested the reason for differences in rates of constipation between HD and PD patients could be due to the restriction of the potassium intake not being as strict as for HD patients. Dietary restriction of potassium limits the intake of many high fibre foods which

are high in potassium. This is supported by the later study by Yasuda et al. (2002) which found the potassium and fibre intakes respectively of PD patients (1.8 ± 0.5 g and 11.0 ± 4.0 g) to be significantly higher compared to HD patients (1.3 ± 0.5 g and 5.9 ± 2.7 g). These results suggest the lower incidence of constipation in PD patients compared to HD patients may be due to the increase in fibre in the PD diet and the increased physical activity in PD patients due to the ability to live a more mobile lifestyle.

For dialysis patients, phosphate binders are routinely prescribed as a way to decrease the amount of dietary phosphate absorbed by the body. However, phosphate binders have also been associated with constipation with reported increases in rates from between 6-14% (Iacono, 2008, Kazama, 2009). As chronic pain is very common in dialysis patients, the use of analgesia is also common. Constipation is a common effect of opiate based analgesia due to its effects on gastrointestinal motility. It has been reported that dialysis patients commonly use an average of 12 medications. This polypharmacy puts patients at increased risk of constipation, especially when a patient has numerous physicians for multiple co-morbidities, which is common in dialysis patients (Iacono, 2008).

In addition to dietary and medication factors, 35% of those who undergo renal dialysis in New Zealand are over the age of 65 (ANZDATA Registry Report, 2014). Since constipation increases with age, renal dialysis patients are therefore at increased risk as they age.

As with the general population, constipation has been shown to decrease QOL in the dialysis population. This highlights the importance of the treatment of constipation in this group. A self-administered form completed by renal dialysis patients found significantly lower mean values on the physical and mental component summary scales in the non-constipated group compared to a constipated group (Zhang *et al.*, 2013). Similarly in a CKD population, 128 HD, 55 PD and 50 pre-dialysis patients

completed two self-administered questionnaires measuring gastrointestinal (GI) symptoms and psychological general wellbeing (Strid *et al.*, 2002). Gastrointestinal symptoms were worse in all CKD patients compared to the general population, and a negative correlation between GI symptoms and psychological well-being was found in the CKD population. Symptom scores between HD, PD and pre-dialysis were not significantly different. As well as a decrease in QOL, constipation deprives those with ESRF the ability to excrete potassium through stools. Those with normal renal function excrete around 5-10% of their potassium load through the gut. In patients with ESRF, this is increased up to 25%. However, because potassium excreted through the gut is roughly proportionate to faecal output, constipation may put patients at risk of hyperkalaemia (Ahmed and Weisberg, 2001).

As well as a decrease in QOL, constipation can have serious consequences for PD patients, including an increased risk of peritonitis. Peritonitis can cause severe illness and discontinuation of PD and has been shown to occur more frequently when patients are constipated (Mitrović *et al.*, 2015). In a Turkish population it was found that patients with constipation were 2.2 times more likely to develop peritonitis than those without constipation (Keleş *et al.*, 2010). Bacterial overgrowth is common when intestinal motility is slowed, and this overgrowth increases the chance of bacterial translocation from the gut to the peritoneal cavity (Su *et al.*, 2012). As well as peritonitis, there have been rare reports of colon perforation in constipated PD patients as a result of straining during defecation (Nakamura *et al.*, 2004).

To conclude, rates of constipation within the ESRF population are high. Constipation within this population can be due to lifestyle reasons such as the difficulty in reaching recommended intakes for fibre and water as well as difficulty exercising. Old age and polypharmacy add to the risk. As constipation within this population causes a decrease in quality of life, an

increased risk of hyperkalaemia and increased risks of peritonitis, the treatment of constipation for patients with ESRF should be of priority.

2.2 Treatment of constipation

2.2.1 Dietary Measures

In constipated patients, measures to increase intake of dietary fibre are often recommended as a first line treatment (Eswaran *et al.*, 2013). Increasing dietary fibre through everyday foods can be affordable, well accepted and offer not only laxation benefits but also has been linked to lower rates of obesity, cardiovascular disease, diabetes and certain cancers (National Health and Medical Research Council, 2006). Studies which used food products to improve constipation are shown in Table 2.5.

Table 2.5 Summary of studies using food products in the treatment of constipation

Study and clinical setting	Constipation criteria	Methodology	Intervention/fibre dose/duration	No. In fibre arm	Treatment effect in fibre arm	No. In control arm	Treatment effect in control arm	In favour of fibre
(Hongisto *et al.*, 2006) secondary care outpatient setting (Finland)	Self-reported	Randomised two by two factorial design	Four diet groups: (i) rye bread +probiotic yoghurt (ii) rye bread (iii) probiotic yoghurt (iv) control Fibre, dose = 39.36 g 3 week intervention	15	1.3 mean stools per day	14	0.9 mean stools per day	Yes *P* = 0.001
(Sturtzel *et al.*, 2010) secondary care geriatric hospital (Austria)	Requiring laxative use	Controlled parallel intervention	5.2 g/day oat-bran mixed into common daily meals vs. control Fibre dose = 0.78 g/day 12 weeks	15	59% discontinued laxative use	15	8% increased laxative use	Yes *p* < 0.001
(Sairanen *et al.*, 2007) secondary care outpatient setting (Finland)	Self-reported	Randomised double blind crossover	260 g/day of yoghurt containing probiotic galactooligosaccharide (12 g/day), prunes (12 g/day) and linseed (6 g/day)/fibre compared to a control yoghurt 2 week baseline, 2 x 3 week interventions with 2 week washout period	43	8 bowel movements per week Ease of defecation 1.3 points 11 needed laxatives		7.1 bowel movements per week Ease of defecation 1.5 points 9 needed laxatives	Yes *p* = 0.011 Yes *p* =0.01 No
(Attaluri *et al.*, 2011) secondary care outpatient	Rome III	Single blind randomised crossover study	Prunes 50 g 2 x daily or psyllium 11 g 2 x daily Both having fibre = 6 g/day	Dried plums 40	3.6 ± 0.4 bowel movements/week	None	No control	Yes in favour of prunes *p* =0.001 for

Study and clinical setting	Constipation criteria	Methodology	Intervention/fibre dose/duration	No. In fibre arm	Treatment effect in fibre arm	No. In control arm	Treatment effect in control arm	In favour of fibre
setting (USA)			1 week baseline, 3 weeks each treatment with 1 week washout in between	Psyllium 40	Stool consistency 3.2 2.9 ± 0.3 bowel movements/week Stool consistency 2.8			bowel movements Yes in favour of prunes for consistency $p = 0.02$
(Cheskin *et al.*, 2009) Outpatient setting (USA)	Self-reporting Rome II via questionnaire	Placebo controlled randomised	8 oz prune juice 9 oz of apple juice with psyllium 9 oz of apple juice Each patient 2 weeks on each treatment	36 plum juice	1.3 ± 0.7 bowel movements/day Stool softness 0.74 ± 0.41	36 apple juice and psyllium	1.2 ± 0.7 bowel movements/day Stool softness 0.88 ± 0.5	No Yes $p = 0.02$
(Chan *et al.*, 2007) Gastroenterology outpatient clinic Hong Kong	Rome II criteria	Single centre case controlled study	2 kiwifruit per day in both constipated group and healthy control group 2 week baseline before 4 week intervention period	33 treatment group	Bowel movements per week 2.2 ± 2.6 during baseline *vs.* 4.4 ± 4.6 during intervention ($p = 0.013$) Number of days taking laxatives during baseline 2.2±2.5 vs. 0.8±1.5 during treatment $p = 0.003$ Total colonic transit time of 54.5 ± 29 hours during baseline vs. 39.6 ± 22 hours during treatment $p = 0.003$	22 control group	Bowel movements per week of 6.5 ± 1.6 during baseline *vs.* 7.1 ± 2.2 during intervention ($p = 0.31$) No laxatives needed in control group Total colonic transit time of 16.8 ± 23 during baseline vs. 14.1 ± 14 during treatment $p = 0.23$	No significance measured between groups

No. =number
Mean ± SD

Hongisto *et al.* (2006) used a fibre-rich bread and a probiotic to improve bowel function in patients self-reporting constipation. Rye bread (39 g/day fibre) consumption was found to shorten total intestinal transit time, increase faecal frequency, soften faeces and make defecation easier compared to low fibre bread (9 g/fibre day). The rye bread did however create significantly more gastrointestinal symptoms (mainly flatulence and bloating) than in the low fibre group. Interestingly, there were less gastrointestinal symptoms in the rye bread + probiotic yoghurt group compared with the rye bread group alone. This suggests that consumption of fibre may be better tolerated when taken in conjunction with a probiotic. Also of interest is the finding that the probiotic yoghurt tended to increase the effect of the rye bread on all bowel function variables. This highlights the potential of fibre in conjunction with probiotics to help ease constipation.

The use of dietary oat bran has been shown to reduce the use of laxatives in an elderly hospitalised population. A controlled parallel study in a constipated hospitalised geriatric population in Austria investigated whether the addition of oat bran to common daily meals would decrease laxative use. Thirty patients between the ages of 57-98 years were randomised into either the fibre intervention (5.1 g/day of fibre from oat bran) or a control group (standard diet) for 12 weeks. Results found that laxative use decreased by 59% in the fibre group and increased 8% in the control group (Sturtzel *et al.*, 2010).

In Finland, the use of prunes (12 g/day), linseed (6 g/day) and a prebiotic galacto-oligosaccharide (12 g/day) mixed with yoghurt was compared to a control yoghurt in a double blind, randomised, crossover design (Sairanen *et al.*, 2007). Forty-three elderly, constipated patients entered into the eight week study consisting of an initial two week run in period followed by a three week intervention, two week washout and subsequent three week intervention. Constipation was defined as <5 bowel motions per week or if patients complained of difficulty during defecation. Compared to the control yoghurt, the high fibre yoghurt was shown to significantly increase both frequency and ease of defecation. Although this study found significant results, the definition of constipation of <5 bowel motions per week is not in line with the Rome III

criteria. Also, there was no way to tell if the prunes, prebiotic or linseed were contributing to the laxative effect.

Prunes have been used as a treatment for constipation on their own compared to psyllium in a US study by Attaluri *et al.* (2011). Forty constipated patients meeting the Rome III criteria were randomised in a single blind cross over design to two three week treatment periods with a one week washout period in between. Fifty grams of prunes were eaten twice daily in one intervention (6 g fibre/day) and 11 grams of psyllium twice daily in the other (6 g fibre/day). Prunes significantly increased bowel motions per week compared to psyllium as well as improving stool consistency scores. Although straining at defecation was not different between the two treatments, both improved from baseline. The authors concluded that prunes are more effective in treating constipation than psyllium, and should be considered as a first line therapy. Other favourable results for prunes were found by Cheskin *et al.* (2009) in which prune juice was compared to psyllium mixed with apple juice and apple juice alone (control). Softer stools were found with prune juice compared to psyllium and the control. Prune juice was as likely as psyllium to provide relief from constipation within 24 hours of first use and both provided more instant relief than apple juice alone. However, there was no placebo for the prune juice and there was no washout period between treatments. Both studies using prunes were financially supported by prune companies which also may involve some bias. Although prunes can be beneficial in the general population, applying these findings to renal dialysis patients becomes difficult as prunes and prune juice are both high in potassium. The doses of prunes used in these studies would therefore not be recommended for renal dialysis patients.

The use of kiwifruit has also been shown to be effective in reducing the symptoms of constipation in constipated Chinese patients (Chan *et al.*, 2007). Eating two kiwifruit daily over a four week period was found to significantly increase bowel movements decrease laxatives used and decrease stool transit time compared to a baseline period. Advantages of this study included using a gastroenterologist to define constipation based on the Rome II criteria as well as using a prospective design where patients kept a daily log with stool frequency and consistency over the intervention period.

Objective measures of colonic transit time were also performed using radiopaque markers. Beneficial effects on bowel performance due to the consumption of kiwifruit were found using elderly subjects from New Zealand (Rush *et al.*, 2002). Although participants did not report constipation, consumption of one kiwifruit per 30 kg of body weight per day lead to significantly bulkier stools looser stools and produced more frequent bowel movements. The mechanism of kiwifruit on laxation is proposed to be via the enzyme actinidin as well as the dietary fibre in kiwifruit having an exceptionally high water holding capacity (Chan *et al.*, 2007, Rush *et al.*, 2002). Although there appears to be a benefit of kiwifruit consumption on laxation, kiwifruit are also high in potassium and it would not be recommended that dialysis patients eat two kiwifruit per day as was used in these studies.

These studies all show the potential of dietary fibre to help treat constipation. However, these studies use fibre from different sources, different doses (1-40 g/day) and the number of subjects in the fibre intervention groups were a low (14-40). How constipation is defined and the different primary outcome measures assessing constipation also make it difficult to compare studies. The difficulty in double blinding whole food products may make studies ineffective as participants are aware they are eating foods known to reduce constipation, thereby expecting certain results. Although the evidence surrounding the consumption of whole food products in reducing constipation is positive, large scale RCT's are needed with validated measures of constipation to gain more conclusive results.

2.2.2 Fibre supplementation

Fibre supplements are one way to increase dietary fibre in the diet. There are many varieties available on the market which usually come in powder form but can also be found within capsules. Fibre supplements are created through the processing of different plants or plant products isolating the fibre component. Fibre supplements can easily be incorporated into drinks and sometimes foods with the result of increasing dietary fibre in an individual's diet. Table 2.6 shows studies which used fibre supplementation as a method to improve bowel performance.

Table 2.6 Summary of studies using fibre supplements in the treatment of constipation

Study and clinical setting	Constipation criteria	Methodology	Intervention/fibre dose/duration	No. In fibre arm	Treatment effect in fibre arm	No. In control arm	Treatment effect in control arm	In favour of fibre
(Ashraf *et al.*, 1995) USA tertiary care	3 or less stools per week	Double blind	Psyllium 5 g 2 x daily 4 week placebo run in, 8 weeks treatment, 4 weeks placebo wash out	22	3.8 ± 0.4 bowel movements per week Stool consistency 3.2 ± 0.2	22	2.9 ± 0.1 bowel movements per week Stool consistency 3.8 ± 0.2	Yes $p < 0.05$ Yes $p < 0.05$
(Cheskin *et al.*, 1995)	Pelvic dysynergia	Single blind, randomised, placebo controlled crossover study	Psyllium 24 g per day or placebo for 1 month before crossing over	10	30.0 hours gut transit time 1.3 bowel movements per day	10	53.9 hours gut transit time 0.8 bowel movements per day	Yes $p < 0.05$ No $p > 0.05$
(Fenn *et al.*, 1986) UK primary care	Clinical diagnosis	Placebo controlled randomised single blind parallel	Psyllium 3.6 g three x daily or placebo for 2 weeks	104	86.5% Proportion with improvement in symptoms including: Stool consistency, number of stools formed, abdominal discomfort, pain at defecation	97	47.4% Proportion with improvement in symptoms including: Stool consistency, number of stools formed, abdominal discomfort, pain at defecation	Yes $p < 0.001$
(Nunes *et al.*, 2005) Brazil tertiary care	Less than 3 stools per week	Randomised placebo controlled double blind	Psyllium 10 g/day for 2 weeks or placebo	30	86.7% with normalisation in evacuation	30	30.0% with normalisation of evacuation	Yes $p < 0.05$

Study and clinical setting	Constipation criteria	Methodology	Intervention/fibre dose/duration	No. In fibre arm	Treatment effect in fibre arm	No. In control arm	Treatment effect in control arm	In favour of fibre
(López *et al.*, 2007) Spain, tertiary care	Rome II criteria	Prospective randomised double blind placebo controlled	Inulin and starch resistant maltodextrin 20 g/day or placebo for 20 days	15	35.7% straining during defecation	17	78.6% straining during defecation	Yes $p < 0.05$
(Marteau *et al.*, 2011) Eldery subjects aged 50-70	Rome criteria	Randomised, double blind, placebo controlled parallel study	Inulin 15 g/day versus placebo for 4 weeks	25	Softer stools and stool frequency Increased bowel motions per day Decreased defecation difficulty 2.45	25	Softer stools and stool frequency Increased bowel motions per day Decreased defecation difficulty 1.5	No P < 0.1 Yes $p < 0.01$ Yes $p < 0.01$
(Den Hond *et al.*, 2000) Belgium – healthy free living volunteers	Low stool frequency (1 stool every 2-3 days)	Double blind, placebo controlled, crossover	Inulin 5 g 3 x daily for 1 week, placebo for 1 week, 1 week washout period in between	6	4.0 ± 0.4 stools per week	6	6.1 ± 1.0 stools per week	Yes $p = 0.02$
(Dahl *et al.*, 2005) Institutionalised adults bound to wheelchairs, Canada	Institutionalised wheelchair bound with low stool frequency	Double blind cross over	15 g/day of inulin and placebo each for 3 weeks each	15	9.7 ± 3.4 bowel movements /21 days 26 ± 7.4 weighted bowel movement frequency	15	10.0 ± 3.9 bowel movements/21 days 23 ± 6.4 weighted bowel movement frequency	No $p > 0.05$ Yes $p < 0.01$

Study and clinical setting	Constipation criteria	Methodology	Intervention/fibre dose/duration	No. In fibre arm	Treatment effect in fibre arm	No. In control arm	Treatment effect in control arm	In favour of fibre
					6.8 ± 2.3 enema administrations/ 21 days		7.9 ± 2.3 enema administrations/21 days	Yes $p < 0.01$
(Takahashi *et al.*, 1994) Free living healthy Japanese women	Self-reported constipation	Prospective, open label, single treatment arm, three phase study	PHGG 11 g/day for 3 weeks and 2 x 3 week control periods	15	0.63 ± 0.05 faecal frequency per day 6.4 ± 0.1 faecal pH 71.3 ± 1.0% faecal moisture	15	0.46 ± 0.03 faecal frequency/day 6.9 ± 0.1 faecal pH 69.1 ± 1.0% faecal moisture	Yes $p <0.05$ Yes $p < 0.05$ Yes $p < 0.05$
(Polymeros *et al.*, 2014) Outpatient setting, Greece	Rome III criteria	Prospective, open label, single treatment arm, two phase study	PHGG 5 g/day for 4 weeks after a 2 week run in period	39	45.63 ± 37.27 hours colonic transit time 4.75 bowel movements per week 3.7 Bristol Stool Form Scale	39	57.28 ± 39.25 hours colonic transit time 1.5 bowel movements per week 1.8 Bristol Stool Form Scale	Yes $p =0.026$ Yes $p < 0.001$ Yes $p < 0.001$

No. =number
Mean ± SD
PHGG = Partially hydrolysed guar gum

2.2.2.1 Psyllium husk

Psyllium husk (also Ispaghula husk) is the outer coat of the psyllium seed from the plant Plantago Ovata. It is a soluble, gel forming, viscous fibre source which is intermediately fermentable (Rao *et al.*, 2015). It is readily available in New Zealand from supermarkets and pharmacies and is currently the only dietary fibre supplement funded on the PHARMAC schedule. Psyllium is a stool softener and works by retaining water in the stool. Psyllium husk in the treatment of constipation has been well studied and many RCT's, have been carried out compared to placebo (Ashraf *et al.*, 1995, Cheskin *et al.*, 1995, Fenn *et al.*, 1986, Nunes *et al.*, 2005, Tomas-Ridocci *et al.*, 1992). All studies used patients who suffered from chronic constipation with the treatment period varying between two and eight weeks. The majority of studies used 10 g of psyllium fibre/day, although Cheskin *et al.* (1995) used 24 g/day. Results of these studies all found significant differences in one or more of the following variables compared to placebo: increase in stool frequency per week, decrease in gut transit time, increase in stool weight, ease of defecation, improved stool form and lesser abdominal pain/discomfort. In addition, a systematic review by Frizelle and Barclay (2007), found psyllium to increase stool frequency after two weeks in adults with chronic constipation when compared to placebo.

Psyllium husk has also found to be beneficial when compared to other common laxatives such as lactulose and docusate. One review (Rouse *et al.*, 1990) found consumption of seven g/day of psyllium increased the frequency of bowel movements after four weeks compared with 30 ml/day of lactulose. Psyllium also had the benefit of having fewer reported cases of abdominal pain than lactulose. Similarly, docusate (stool softening laxative) was compared to psyllium in a double blind study involving 170 patients with chronic constipation (McRorie *et al.*, 1998). Patients were randomised into one of two groups being either psyllium fibre in addition to a docusate placebo or a docusate laxative in addition to a psyllium placebo. Compared to baseline, psyllium was found to be more effective at increasing stool weight, stool water content and stool output than docusate sodium. In the 2 week treatment, bowel

movement frequency was significantly higher in treatment week 2 for psyllium with no differences between treatments in the first week

Although there is good evidence supporting psyllium at improving symptoms in patients with chronic constipation, its use has limitations when applied to the renal dialysis population. The majority of studies use 10g/day of psyllium mixed with 750 ml of water. As renal dialysis patients are advised to restrict their fluid intake to generally 1L, needing 750 ml of water per day for the intake of a fibre supplement is not ideal as it allows for little other fluid intake.

2.2.2.2 Inulin

Inulin is also a soluble fibre, but unlike psyllium it is non-gelling and highly fermentable in the large bowel. It escapes digestion and enters the large intestine largely intact, where it is then fermented by intestinal bacteria. Inulin is found naturally in various plants, but it is best isolated industrially from the root of the chicory plant (Marteau *et al.*, 2011). Through RCT's, inulin has been found to reduce symptoms of constipation with multiple studies all showing the beneficial effects of inulin in constipated subjects when compared to placebo (Dahl *et al.*, 2005, Den Hond *et al.*, 2000, López *et al.*, 2007, Marteau *et al.*, 2011). These studies found ingestion of 13-20 g of inulin per day over 2-4 week periods led to improvements in stool frequency and a reduction in defecation difficulties such as straining, incomplete evacuation and rectal obstruction. Recently, scientific opinion was published by the European Food Safety Authority (2015) which gave scientific substantiation to the health claims of inulin. The panel concluded that inulin contributes to the maintenance of normal defecation by increasing stool frequency if 12 or more grams per day are consumed.

As well as the benefits of reducing constipation symptoms, inulin is also a prebiotic (Marteau *et al.*, 2011). Prebiotics stimulate the growth of intestinal bacteria such as bifidobacteria and lactobacillus. These bacteria ferment fibre in the gut forming short chain fatty acids (SCFAs) which serve as fuel for the local gut lining and may regulate cellular processes (Stewart *et al.*, 2009). The SCFAs may decrease luminal pH, therefore inhibiting growth of potentially pathogenic bacteria (Noack *et al.*, 2013). The

consequential increase in bacterial mass can increase stool weight, stimulate bowel movements and create an osmotic effect which increases water content in the colon (Macfarlane *et al.*, 2006). These properties help explain the mechanism by which inulin can be useful in the treatment of constipation.

2.2.2.3 Partially hydrolysed guar gum

Partially hydrolysed guar gum (PHGG) is a soluble, highly fermentable non-gelling fibre produced through controlled breakdown of guar gum. PHGG is sold as a dietary fibre supplement and can be easily incorporated into liquids and foods. As well as inulin, PHGG is also a prebiotic which feeds 'good' bacteria in the gut, lowering the pH of the intestinal lumen and producing health promoting SCFAs (Noack *et al.*, 2013).

Two studies have shown that consumption of PHGG reduces bowel symptoms in constipated subjects. Takahashi *et al.* (1994) gave 11 g/day of PHGG to 15 constipated women over a 3 week period. Compared to a control period where habitual diet was followed, PHGG caused an increased frequency of defecation, and an increase in faecal water content compared to the control period. In a more recent study, 5 g/day of PHGG was given to 39 constipated participants over a 4 week period. Compared to a control period, colonic transit time was significantly reduced, bowel movement frequency significantly increased, stool form improved and the number of bowel movements with straining decreased, number of days with laxative intake and abdominal pain also decreased (Polymeros *et al.*, 2014). Although these studies found favourable results, both were open-label studies which meant participants knew exactly what they were taking and neither was placebo controlled. To further investigate the use of PHGG in the treatment of constipation, placebo controlled RCT's are needed.

2.2.2.4 Wheat dextrin

As with inulin and PHGG, wheat dextrin is a non-gelling soluble fibre which mostly escapes digestion until being highly fermented in the large bowel (Stewart *et al.*, 2009). It escapes digestion due to its structure having many α-1.6 linkages and non-digestible glucoside linkages. Wheat dextrin is extracted from wheat starch in a multi-

step industrial process (van den Heuvel *et al.*, 2005).Thus far, no research has been carried out investigating the ability of wheat dextrin to reduce the effects of constipation. However, wheat dextrin like inulin and PHGG is a known prebiotic with beneficial properties. Wheat dextrin is fermented in the large bowel, producing SCFAs, lowering the pH of the colon and adjusting the colonic environment (Hobden *et al.*, 2013, Noack *et al.*, 2013, Pasman *et al.*, 2006). The study by Hobden *et al.* (2013) used a validated gut model system to establish the impact of wheat dextrin on the gut microbiota. The use of 14 g/day of wheat dextrin resulted in significant increases in total bacteria in vessels simulating the transverse and distal colon especially of those bacteria types Clostridium cluster XIVa and Roseburia genus. These bacteria types are key producers of SCFAs, especially butyrate which has protective and metabolic benefits. The beneficial effects of butyrate include being an energy substrate for colonocytes, having a beneficial trophic effect on gut epithelium as well as having protective properties against colon cancer which is more prevalent in the distal colon (Hobden *et al.*, 2013).

Of the SCFAs produced by the fermentation of wheat dextrin, butyrate is not only the preferred energy substrate for colonic epithelial cells but in animal studies it has also been shown to excite neurons of the GI tract causing colonic circular smooth muscle contraction (Soret *et al.*, 2010). In support of this, colonic fermentation of undigested starch in humans has been shown to produce an increase in high amplitude propagated contractions of the colon (Jouët *et al.*, 2011). These increased contractions were in parallel to increases in SCFA production, a lowering of colonic pH as well as colonic distension resulting from the production of gas during fermentation (Jouët *et al.*, 2011). This supports one mechanism of how wheat dextrin may accelerate colonic transit thereby reducing constipation. In conjunction, soluble fibre is thought to increase stool bulk through an increase in biomass which produces softer stools. This further strengthens the possible use of wheat dextrin as a potential treatment for constipation.

As well as its potential laxative effect, wheat dextrin has been proposed to have other beneficial health effects as a prebiotic. Ingestion of 14 g/day of wheat dextrin over a nine week period in overweight subjects was shown to significantly increase satiety,

reduce energy intake, reduce body weight and improve body composition compared to placebo (Guérin-Deremaux *et al.*, 2011, Guérin-Deremaux *et al.*, 2013). The satiating effect of wheat dextrin may be due to its effect in elevating synthesis of the anorexigenic gut hormones glucagon-like peptide 1 and peptide YY and decreasing synthesis of the orexigenic gut hormone ghrelin (Hobden *et al.*, 2013).

Wheat dextrin is well tolerated at large doses with one study finding it well tolerated at 30 and 45 g/day until doses of 60g/day were reached when some bloating and flatulence occurred (Pasman *et al.*, 2006, van den Heuvel *et al.*, 2004). An in vitro study by Noack *et al.* (2013) found that compared to PHGG and inulin, wheat dextrin produced the least gas during fermentation at 8, 12, and 24 hours. In conjunction, wheat dextrin produces gradual and consistent SCFAs compared to inulin which produces rapid peaks (Stewart *et al.*, 2009). The gradual SCFA production following wheat dextrin consumption is likely to correspond to less bloating and flatulence and is one possible reason why wheat dextrin is better tolerated than inulin.

Although no studies have investigated the use of wheat dextrin as a fibre supplement for the possible treatment for constipation, it does have viable potential mechanisms of action. Along with its other health benefits described earlier and the fact that it is well tolerated makes the research of wheat dextrin in reducing constipation worthwhile.

2.2.3 Laxatives

Laxatives can be used in the treatment of constipation but may have side effects; the efficacy of some laxatives have not been established (Jones *et al.*, 2002). Lactulose and laxsol are both commonly used laxatives in the Northland District Health Board (New Zealand) as well as by patients who undergo renal dialysis.

Lactulose is an osmotic laxative which increases the water content of stools, thereby increasing faecal volume and softness. It is fermented in the intestines producing carbon dioxide and hydrogen, resulting in acidification of the stools (Candy *et al.*, 2015). Irritation of the colon wall then promotes peristalsis. Lactulose comes as a

sweet liquid and is subsidised on the PHARMAC schedule with a patient prescription. Systematic reviews indicate that lactulose has beneficial effects on laxation when compared to placebo. This evidence has been considered superior by Leung *et al.* (2011) and graded as an 'A' recommendation by the American College of Gastroenterology Chronic Constipation Taskforce (Quigley *et al.*, 2005) meaning its use is supported by two or more RCT's with adequate sample size and methodology without conflicting evidence from other trials. However, lactulose can cause unpleasant side effects such as electrolyte abnormalities, altered bowel flora, bloating, flatulence, and excessive diarrhoea (Ruston *et al.*, 2013).

Laxsol, another laxative commonly used in Northland DHB is made from docusate sodium and senna. Docusate sodium is a synthetic detergent which decreases surface tension allowing water to interact more effectively with stools. Senna is a stimulant laxative which works by irritating the nerve endings of the colon, stimulating peristalsis and decreasing water absorption from the lumen (Leung *et al.*, 2011, Woolery *et al.*, 2008). Research on docusate sodium versus placebo is limited and results are variable (Quigley *et al.*, 2005). A systematic review in critically ill, palliative, constipated patients found the use of docusate to be based on inadequate evidence and concluded that more RCT's are needed to determine the efficacy of its use to treat constipation (Hurdon *et al.*, 2000). In a well-designed RCT, psyllium was found to be more effective than docusate sodium as a laxative (McRorie *et al.*, 1998). An active control of placebo with the addition of senna has also been found to have no significant effect on stool frequency, volume or consistency than docusate plus senna (Tarumi *et al.*, 2013). In support of these mixed results, a review by Leung *et al.* (2011) reported a moderate recommendation for the use of docusate sodium as a laxative. Similarly, a systematic review by the American College of Gastroenterology Chronic Constipation Taskforce found insufficient data to make a recommendation on the efficacy of stool softeners such as docusate sodium as a treatment in patients with chronic constipation (Quigley *et al.*, 2005).

Senna, the other active ingredient in laxsol has been used for over 100 years, but surprisingly there are no well-designed RCT's comparing its effects to placebo. There

are however, older studies which show its benefit in constipated subjects when used with psyllium (Marlett *et al.*, 1987, Passmore *et al.*, 1993). The use of senna as a laxative was given a recommendation of moderate by Leung *et al.* (2011). However, side effects have been reported such as abdominal discomfort, electrolyte imbalances, allergic reactions and hepatotoxicity (Ruston *et al.*, 2013). There has also been debate in the literature about the potential long term use of senna increasing the risk of developing colon cancer. Although human studies are insufficient, Leung *et al.* (2011) states that when the evidence is combined it does not support a role of senna in causing colon cancer in rats or humans.

Therefore the efficacy of docusate sodium and senna for the use in the treatment of constipation is mixed. In combination, side effects can occur and the long term effects are unknown. Although lactulose has good evidence behind its use, side effects for patients can be unpleasant. An alternative treatment to constipation involving a gentle fibre supplement is therefore likely to be welcomed.

2.3 Treatment of constipation in renal dialysis patients

2.3.1 Dietary Measures

While increases in fibre and fluid through dietary measures should be the first intervention to reduce constipation, this is often ineffective in renal dialysis patients. Increasing dietary fibre in renal dialysis patients has proven to be difficult even when patients are given lists of high fibre food with preferable potassium and phosphate profiles (Sutton *et al.*, 2014). This has been shown in a study by Sutton *et al.* (2014) where patients on PD could not significantly increase their dietary fibre intake when encouraged to do so. Subjects were given food lists which contained foods with 2 grams of fibre and asked to increase the fibre in their diet by 2-4 g/day (to avoiding bloating and discomfort) until an extra 12 g/day was added. It was found that as a whole the group did not manage to increase the amount of fibre in their diet and the authors concluded that it is difficult to increase and maintain fibre intake through dietary means in PD patients (Sutton *et al.*, 2014). The reasons behind not being able

to add fibre to the diet as recommended by health care professionals was investigated in a survey of 90 elderly (mean age 77.4 years) living in Adelaide, South Australia (Annells and Koch, 2003). Reasons found were availability of preferable fruit due to season, cost and 'living on a pension,' co-morbidities such as diabetes restricting fruit and diverticulitis restricting intake of dried fruit and nuts, not being used to planning and cooking meals especially for widowers and trying dietary measures suggested that have no effect on constipation. Sutton *et al.* (2007) suggested factors contributing to poor fibre intake in PD patients may be poor appetite, feeling full from the dialysate and the conflict between a recommended high fibre diet and so many high fibre foods being rich in potassium and phosphate. These factors are relevant to the renal dialysis population who are frequently not only elderly, but often from a low socioeconomic background.

Other trials have also shown that giving dietary advice to patients who undergo dialysis is ineffective at adjusting patients' energy intake. A prospective, randomised controlled trial in 55 PD patients was carried out in the UK assessing whether offering dietary advice was effective in adjusting patients' energy intake. The study found that protein and energy intakes did not change in either the control or treatment group despite receiving dietetic advice. The study concluded that patients not meeting their dietary targets did not adjust their intake to match advice given by a dietitian. This inability to change suggests that subjects may be eating to the limit of their appetite (Sutton *et al.*, 2007b).

Taking into account the above findings, alternatives to dietary approaches are needed for renal dialysis patients in order to increase their fibre intake. Incorporating a fibre supplement into the diet of these patients may offer a solution. Studies using fibre supplements to improve bowel performance in renal dialysis patients are shown in Table 2.7.

Table 2.7 Summary of studies using fibre supplements in the treatment of constipation in renal dialysis patients

Study and clinical setting	Constipation criteria	Methodology	Intervention/fibre dose/duration	No. In fibre arm	Treatment effect in fibre arm	No. In control arm	Treatment effect in control arm	In favour of fibre
(Sutton *et al.*, 2007a) PD patients (UK)	Those using laxatives from review of patient notes	Prospective, open label, three phase study	1st establishing bowel habits and laxative use for 4 weeks, 2nd using a PHGG supplement 12 g/day for 4 weeks, 3rd truing to increase dietary fibre via modifying food intake	23	17/23 replaced all laxatives with PHGG supplement	No control	No comparison to 1st four weeks	No testing for significance
(Sutton *et al.*, 2014) Multi unit study (UK)	Those using laxatives 4 or more times per week	Randomised, placebo controlled parallel group design	1st 4 week observation stage to establish bowel habits and laxative use followed by 12 g/day of PHGG supplement or placebo for 4 weeks	11	38% laxative decrease	10	3% laxative increase	No $p > 0.05$
(Wang *et al.*, 2001) HD patients (Taiwan)	Chronic constipation – not specified	Controlled intervention study	Firstly 2 week basal period before 30 g/day of isomaltose-oligosaccharide for 4 weeks	20	76.3% ± 30.9% increase in bowel movements compared to baseline	20	Increases in bowel movements were compared to baseline data	Yes $p > 0.05$
(Meksawan *et al.*, 2014) PD patients (Thailand)	Chronic constipation – not specified	Randomised, double blind, placebo, crossover study	Either 30 days of 20 g/day of fructo-oligosaccharide or placebo for 30 days, 2 week washout before the opposite treatment.	9	10.5 ± 2.0 frequency of defecation per week	9	6.2 ± 1.4 frequency of defecation per week	Yes $p < 0.005$

No. = number
Mean ± SD
PHGG = partially hydrolysed guar gum

2.3.2 Inulin

As discussed in Section 2.2.2.2, there is evidence to show that inulin can reduce constipation. In addition, since inulin does not need to be taken with water, is odourless, tasteless and can be successfully dissolved into food, this makes inulin a suitable candidate for the prevention/treatment of constipation in renal dialysis patients. However, currently there is no research using only inulin to improve bowel health and/or constipation in the renal dialysis population. There is however evidence of using inulin (15 g/day) combined with muffins containing pea hull fibre (10 g/day) to significantly increased stool frequency compared to placebo in patient with CKD with a GFR < 50 (Salmean *et al.*, 2015). Although this study found increases in stool frequency with an increase in fibre intake, the control period used different quantities of placebo versus inulin and the control period was 2 weeks compared to the treatment period of 6 weeks. Further research is needed which isolates inulin as a potential fibre source to reduce constipation in the renal dialysis population. Unfortunately inulin is not available in New Zealand, which negates any current benefit of research involving inulin to our target population.

2.3.3 Partially hydrolysed guar gum

As PHGG does not need to be taken with fluid, it is an ideal option for increasing dietary fibre in renal dialysis patients. Two studies based in the United Kingdom have specifically looked at the use of PHGG to reduce constipation in PD patients (Sutton *et al.*, 2007a, Sutton *et al.*, 2014). In the study by Sutton *et al.* (2007a), of 23 PD patients, consumption of an average of 12 g/day of a PHGG fibre supplement for 4 weeks resulted in 17 trial participants completely stopping their laxative use and two reducing laxative use by 50% . Most patients consumed the supplement in hot or cold drinks or mixed in with soft foods. The study also reported that 15 patients thought the supplement gave the best results in terms of stool form as well as better results in terms of reducing side effects such as bloating, flatulence and abdominal cramps. It was also reported that 14 patients preferred using the supplement rather than laxatives. However, this study was not placebo controlled, so it cannot be categorically

stated that improvements were due to the PHGG supplement alone rather than due to a placebo effect. Similarly, a study by Maeda *et al.* (2012) found consumption of 10 g/day of PHGG decreased constipation scores in 35 patients on maintenance dialysis, however, this study was also not placebo controlled. However the later study by Sutton *et al.* (2014) was placebo controlled and randomly assigned 31 PD patients to either a high fibre diet group, a PHGG fibre supplement group or a placebo group. Results reported a 38% decrease in laxative use when 12 grams of a PHGG was consumed compared to a 16% decrease in laxative use on a high fibre diet and 3% increase on placebo. Subjects from the high fibre diet group and fibre supplement group showed a decrease in hard and ideal stool types over the intervention period and an increase is loose stools. These studies give some support to PHGG being effective in reducing laxative use compared to placebo. PHGG would therefore be of interest to use in the renal dialysis population to help reduce constipation. However, as with inulin, there are currently no PHGG supplements readily available in New Zealand.

2.3.4 Wheat Dextrin

To date, no studies have been reported using wheat dextrin to treat constipation within the renal dialysis population, or within the non-renal population. However, as discussed in section 2.2.2.4, the mechanisms of action of wheat dextrin indicate it has the potential to improve bowel health and stimulate bowel movements. Wheat dextrin, like inulin and PHGG does not need to be taken with water. It is odourless, tasteless, does not thicken, can be mixed into foods and has low amounts of potassium and phosphate. These properties, in combination with wheat dextrin being readily available from supermarkets and pharmacies in New Zealand, make it an ideal candidate to potentially reduce constipation within the renal dialysis population within New Zealand.

2.3.5 Other Fibre Products

Isomalto-oligosaccharide (IMO) and fructo-oligosaccharide (FOS) are both fermentable soluble fibres which have prebiotic properties and have been found to increase stool

frequency and mass in an elderly population (Yen *et al.*, 2011). IMO has also been used in the treatment of chronic severe constipation in HD patients (Wang *et al.*, 2001). Twenty patients consumed 30 g/day of IMO for 4 weeks. An increase in bowel movements, and an improvement in constipation in 76.3% of patients was found when compared to baseline data, however this study was not placebo controlled. In a small study by Meksawan *et al.* (2014), nine PD patients with constipation were randomly assigned to receive either 20 g/day of FOS or placebo for 30 days before being switched to the placebo after a 14 day washout period. Results found FOS increased stool frequency as well as stool form compared to the placebo. As IMO and FOS do not require water to be taken, they have a place in future research in dialysis patients, however currently these products are not readily available in New Zealand.

2.3.6 Non-fibre treatments

A variety of other products have been used in renal dialysis patients in order to reduce constipation. Polyethylene glycol (PEG) is an osmotic laxative which was used in 21 CAPD patients who reported constipation (Mimidis *et al.*, 2005). All patients reported improvements in stool frequency, stool form and reported less blood in stools as well as less painful defecation (Mimidis *et al.*, 2005). However, this study was not placebo controlled and PEG is only prescribed under special authority in New Zealand. Olive oil and flaxseed oil have also been used to potentially reduce constipation in HD patients. In a study by Ramos *et al.* (2015), 50 constipated HD patients were randomly assigned in a double blind manner to receive mineral oil, olive oil or flaxseed oil for 4 weeks. Constipation scores all significantly improved from baseline for all three oils with the study concluding that olive oil and flaxseed oil were both comparable to mineral oil in the treatment of constipation. However since constipation is due to patients self-reporting, a psychological effect due to the expectation of treatment cannot be excluded. As olive oil and flaxseed oil are likely easily incorporated into the diet of renal dialysis patients, more research involving this method of treating constipation would be beneficial.

2.4 Conclusion

Constipation among those on renal dialysis is common. It causes a decrease in QOL and has serious consequences, especially for PD patients. Its treatment in the non-dialysis population involves an increase in dietary fibre, fluid and physical activity. However, due to the lifestyle associated with dialysis and the dietary restrictions involved, these methods are often unsuccessful. The use of laxatives is therefore common treatment, however they can have side effects and the efficacy of the use of some has not yet been established. An alternative treatment is therefore necessary. Fibre supplements have been shown to be successful in the treatment of constipation in non-dialysis populations. However their use in the renal dialysis population is limited and the fibre supplement currently subsidised with a prescription is not suitable for renal dialysis patients. There is however a wheat dextrin supplement available in New Zealand that can be tolerated by renal dialysis patients. However, this supplement needs to be tested to see if it is of benefit in treating constipation in the renal dialysis population.

Chapter Three

3.0 Methodology

3.1 Study Design

A single blind, randomised and cross-over design was used to conduct this pilot study (Figure 3.1). Each subject served as their own control. Subjects were blinded as to which treatment they were receiving, either the placebo or wheat dextrin fibre supplement.

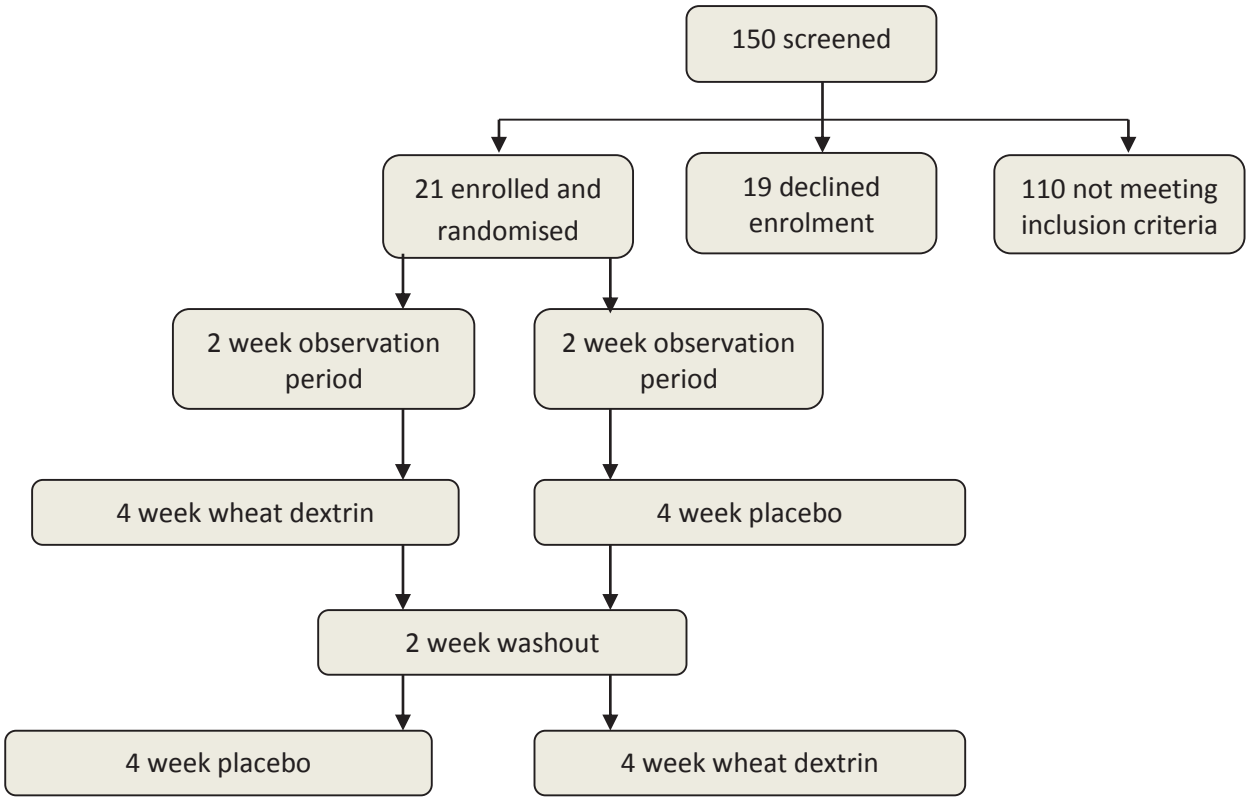


Figure 3.1 Diagram showing study enrolment and design

3.2 Intervention Materials: Treatment and placebo

The treatment product was a 100% wheat dextrin fibre supplement (Benefiber®, Novartis Consumer Health, Australasia Pty Ltd). The study was not supported by or for the benefit of Novartis. The product is an odourless, tasteless, white powder which can easily be mixed into foods and drinks Wheat dextrin is a branched glucose polymer composed of indigestible (1–2), (1–3), and (1–6) bonds, and as a result is primarily indigestible, with only 10–15% being degraded in the small intestine by host enzymes, 76% being fermented in the colon, and the remainder being excreted in the faeces (Stewart *et al.* 2009) The placebo used was 100% maltodextrin. Maltodextrin differs from wheat dextrin as it is completely hydrolysed in the small intestine not reaching the small large bowel and therefore not being fermented. Maltodextrin is fully hydrolysed due to its structure having very few indigestible linkages. The nutrition information of each product is shown in Table 3.1. Like wheat dextrin, this is a white odourless powder. The maltodextrin had a slight sweet taste and did not dissolve in cold liquids as easily as the wheat dextrin product. To prevent the subjects from detecting the sweeter flavour of the placebo, they were given a list of recommended ways to add both the treatment and placebo to their existing diets (Appendix A). Unlike wheat dextrin, the placebo is fully hydrolysed into glucose units before reaching the large bowel, thus not acting as a dietary fibre. Both supplements were packaged into the same white, unmarked containers, labelled only with a colour code so subjects could identify what supplement to take over the correct time period.

Table 3.1 Nutrition information of the wheat dextrin fibre supplement and maltodextin placebo.

	Quantity at maximum dosage per day (22 g)	
	Wheat dextrin (Treatment Product)	**Maltodextrin (Placebo)**
Energy	240 kJ	945 kJ
Protein	Less than 1 g	Less than 1 g
Fat, total	Less than 1 g	Less than 1 g
-saturated	Less than 1 g	Less than 1 g
Carbohydrate	4 g	57 g
- **Sugars**	Less than 1 g	28 g
Dietary Fibre, total	22.5	Less than 1 g
-soluble	22.5	Less than 1 g
Sodium	38 g	Nil
Potassium	Nil	Nil
Phosphates	Nil	Nil

3.3 Ethics approval

The study protocol was approved by the New Zealand Health and Disability Ethics Committee Northern B (application 13/NTB/46) (Appendix H). Northland District Health Board also gave permission for this study to take place and approval from the renal department was sought to recruit patients from the renal wards in the NDHB. Approval from NDHB Maori Research Review Committee was also obtained. The study has also been registered in the Australian New Zealand Clinical Trials Registry (Registration Number: ACTRN12615000363583).

3.4 Participants

Based on other research in similar groups, thirty subjects were deemed sufficient to achieve significant results (Sutton *et al*. 2015). Although unlikely, based on previous recruitment experience, more than thirty subjects would be recruited if there were

eligible and willing patients. By the end of recruitment, twenty-one volunteers with chronic kidney disease stage five provided written consent to participate in the study (Appendix B). Participants were then randomly assigned to receive either the fibre supplement or placebo first.

Inclusion criteria were patients over 18 years of age who:

- were undergoing either HD or PD,
- were prescribed laxatives.

Exclusion criteria were those patients who:

- do not take laxatives,
- have dementia,
- are due to have surgery in the next three months,
- are already taking fibre supplements,
- are using opioids,
- have coeliac disease.

3.5 Recruitment

All patients in the NDHB either undergoing HD or PD were screened by the research team via a review of patient notes on the renal ward of Whangarei Hospital. A list of eligible patients was compiled taking into account the inclusion and exclusion criteria. HD patients were then approached by the primary researcher while on the ward for dialysis. These wards consisted of the renal units in Whangarei Hospital, Bay of Islands Hospital and Kaitaia Hospital. Some PD patients were recruited at Whangarei Hospital during a PD information session. During this session the primary researcher presented a brief overview of the purpose of the study, exclusion and exclusion criteria, the importance of the study and what would be involved for participants. All other PD patients, were sent an information sheet in the post (Appendix C). These patients were then followed up with a phone call asking if they were interested in taking part in the study or if they had any questions regarding the study. All participants received a

complete written explanation of the investigation (Appendix G) and gave informed written consent before beginning the study.

3.6 Experimental Procedures

The study lasted 12 weeks overall. Once patients had given informed consent, they were either given in person or sent via the post, all the paperwork for the study as well as the intervention products (both treatment and placebo) for the entire 12 week procedure. All subjects were blinded to the treatment and placebo as well as the meaning of the colour coding except knowing in what order (1st or 2nd stage) to consume the supplement. The multi-site nature of the study and vast geographic locations of participants made this the only logistical solution. Subjects received an envelope containing all the information and forms needed for the observation stage of the study, with a date on the front of when it should be opened. Participants also received two boxes containing the two colour coded supplements and forms needed, as well as the dates of when to open each box dependent on whether subjects were randomised to receive the placebo or fibre supplement first.

Once the study was underway, subjects underwent a two week observation stage as described in Section 3.7. In the third week, subjects were randomly assigned to receive either wheat dextrin or placebo for four weeks. The following two weeks were a washout period. In the following 4 weeks, participants switched treatments.

Subjects were encouraged to add both the wheat dextrin and placebo into the diet in the same way with the help of an instruction sheet (Appendix A). Subjects were instructed to increase the dose of the powders from two scoops (8.8 g) on day 1-3 to four scoops per day (17.6 g) on days 4-6 to five scoops per day (22 g) from day seven onwards. The maximum dose of five scoops providing 22 g/day of soluble fibre. The slow increase in dosage was necessary to avoid bloating, flatulence and abdominal discomfort. Daily doses were split into morning and night, with the maximum dose being instructed at three scoops in the morning and two in the evening. Although subjects were encouraged to take the maximum dose, those that could not manage to take the full, maximum supplement dose had the opportunity to take less. All subjects

followed a free diet throughout the study period but were instructed not to start any new dietary regime whilst on the study.

Instructions on how subjects could reduce their laxative use were also included on the instruction sheet (Appendix A). Bowel motions were said to be too loose if greater than five on the BSFS. If stools did become too loose subjects taking 15 mL of lactulose per day were advised to stop taking lactulose altogether. Those taking 30 mL of lactulose per day were advised to cut back to 15 mL per day for three days, then if stools were still greater than five on the BSFS subjects were advised to stop altogether. If stools were above five, those taking one tablet of laxsol per day were advised to stop taking them completely. Those taking two tablets per day were advised to cut down to one per day. If the subject's stools were still greater than five after three days they were advised to cut out laxsol completely. Those taking three laxsol tablets per day were advised to reduce the dose by one tablet every three days until stool consistency was improved (BSFS 3 or 4).

Routine weekly phone calls were made to each subject so any questions could be answered and to remind them of the study protocol.

3.7 Measurements

The two week observation period consisted of subjects recording daily dose and frequency of any laxatives they took. Stool form was also recorded every time a subject passed a stool using the BSFS (Appendix D). The BSFS assigns a numerical rating to stools from 1 (hard) to 7 (watery). This information was recorded in a patient held record as in the study by Sutton *et al.* (2014) (Appendix E). The two 4 week supplement phases consisted of the same recordings as the observation stage with the addition of recording the amount of supplement or placebo taken per day in both the morning and evening. This was recorded by participants in terms of the number of scoops of the product taken. This was again recorded in a patient held record. Anytime during the last three days of each stage (observation, wheat dextrin or placebo), subjects were instructed to fill in a quality of life (QOL) survey. The Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire is a brief but comprehensive

questionnaire consisting of 28 points assessing the domains of physical discomfort, psychosocial discomfort, worries and concerns, and satisfaction (Appendix F). The physical discomfort domain assesses bloating, feelings of being heavy, feeling of unable to defecate and how often physical discomfort is felt. The psychosocial discomfort assesses embarrassment, eating habits and changes in routine due to constipation. The worries and concerns domain assesses irritability, stress, obsessing, self-confidence and worries about constipation. The satisfaction domain assesses satisfaction in terms of how happy the subjects are with their treatment for constipation, their bowel transit time and frequency of bowel movements. At the conclusion of each stage in the study, the patient held records and QOL surveys were requested to be returned via post to Whangarei Hospital. A pre-paid, addressed envelope was provided to each subject at each stage to make this process as easy as possible.

3.8 Data handling and analysis

Once all the data were received, it was entered into Microsoft Excel spreadsheets. Data were entered for each subject for each week of each study stage and was taken from the patient held records and QOL questionnaires for each participant form each stage of the study. For the observation stage, data from over the two weeks was combined to give a weekly average of that stage. For the wheat dextrin and placebo stages, four time points (one for each of weeks one to four) were recorded in the spreadsheet. A fifth time point for the wheat dextrin and placebo stage was also recorded. This was an average calculated across weeks 3 and 4 and was calculated for each variable. This fifth time point was created as it was a time in which subjects were most likely taking the full dose of supplement. It also takes data across a two week period which takes a larger representation of subjects bowel habits.

Data entered into the spreadsheet for the observation stage and each time point of the wheat dextrin and placebo stages were as follows:

- Stool frequency per week was calculated by counting the number of times a stool was passed for each participant.

- The average stool form per week was calculated for each participant by taking the sum of all the stool types produced in a week and dividing this by the stool frequency for that week.
- The percentage of ideal stools passed per week was calculated by counting the number of stools passed which were classed as ideal (between 3 and 5 on the BSFS). This was then divided by the stool frequency for that week and recorded as a percentage.
- The amount of lactulose in mL per week was calculated by taking the sum of mL taken by each participant for each week.
- The number of laxsol tablets used per week was calculated by taking the sum of laxsol tablets taken by each participant for each week.
- The number of occasions laxatives were used per week was calculated by taking the sum of the number of times laxatives were taken by each participant for each week. This measure was irrespective of dose and type of laxative taken.
- The amount of powder consumed in grams per week was calculated by taking the product of the number of scoops taken per week and grams per scoop (4.4 g). This applied to the wheat dextrin and placebo stages only.
- The data from the QOL questionnaires were split into four domains based on the instructions in the PAC-QOL Information booklet. The four domains were physical discomfort (Q1-4), psychosocial discomfort (Q5-12), worries and concerns (Q13-23), and satisfaction (Q24-28). Each question gave an option to answer on a Likert Scale of 0 to 4. In the first three domains, a lower score indicated better QOL. In the satisfaction domain, a higher score indicated better QOL. Questions 24-28 in this domain were therefore reversed as instructed in the PAC-QOL Information booklet. The average score of each domain for each participant at each stage was calculated and entered into the spread sheet. An overall QOL score for each participant at each stage was then calculated by taking the average of all four domains.

3.9 Statistical analysis

All data was entered in to statistical package for social sciences (SPSS) for Windows software (version 22.0, Armonk, NY: IBM Corp).

All variables were tested for normality using the Kolmogorov-Smirnov and Shapiro Wilk test and for homogeneity using the Levenes test. If data was non-normally distributed it was log transformed in an attempt to obtain normality. Normally distributed data was expressed as means ± SD, data that was log transformed to obtain normality was expressed as geometric means [95% CI] and data that could not be log transformed to obtain normality was not normally distributed and expressed as median (25^{th}, 75^{th} percentiles). A *P* value of less than 0.05 was considered to be statistically significant.

As data from stool frequency, stool form, % of ideal stools, laxsol use, total laxative use and QOL measures was normally distributed, comparisons were made using analysis of variance with repeated measures. As data from lactulose use and amount of powder was non-normally distributed, it was compared using Friedmans analysis of variance.

Correlation was assessed by using Pearson's correlation coefficient (2 tailed). Pearson r^2 was used to represent the proportion of the variability in one variable that is explained by the other. Bivariate correlations were used unless there was suspicion that other variables may be having a confounding effect. In this case, a partial correlation was carried out.

Chapter Four

4.0 Results

The results of the current pilot study are presented in the following order: firstly the subject demographics and reasons for participant withdrawal will be shown, followed by the results broken into sections based upon each variable measured. The amount of wheat dextrin or placebo powder used by each subject is shown first to establish whether the amount of powder consumed was similar between each subject and each stage of the study. This will be followed by an assessment of laxative use, including the amount of lactulose and laxsol used as well as the total number of times laxatives were taken. The results of stool frequency in terms of how many stools were passed per week will then be explored. This will be followed by stool form including any changes in the percentage of stools that were of ideal form over the different stages of the study. Measures of quality of life of subjects over the different stages of the study and correlations between different variables will conclude the results section. The results will be presented as the differences within each variable by comparing the three stages of the study being the observation (OBS) stage, wheat dextrin (WD) stage and placebo (PB) stage. As the number of subjects who returned a full set of results was low (n =7), the results will also explore the independent effects of the WD and PB on individual subjects. Presenting the results in this way may give some insight into whether certain individuals responded favourably to the WD and/or if some had a response to the PB.

4.1 Demographics of subjects and subject withdrawals

Screening for potential subjects to take part in this cross-over intervention study took place across several sites in the Northland District Health Board in the months of March and April 2015. These sites were Whangarei Hospital, Bay of Islands Hospital and Kaitaia Hospital. In total, 150 patient's notes were screened by the lead investigator for inclusion criteria. Those screened were patients who were receiving

either haemodialysis or peritoneal dialysis. From the screening process, 40 (26.7%) of the 150 patients met the inclusion criteria and were invited to participate in the study via either a phone call, letter in the mail, or at a group meeting. An information sheet (Appendix G) was either handed to, or posted to each potential subject and they were given time to ask any questions. Of the 40 eligible patients, 19 declined enrolment and 21 consented to enrol into the study (Appendix B).

From the initial enrolment, subjects withdrew (n =14) throughout the study for various reasons. Figure 4.1 shows the screening process and study trial with withdrawals at certain time points.

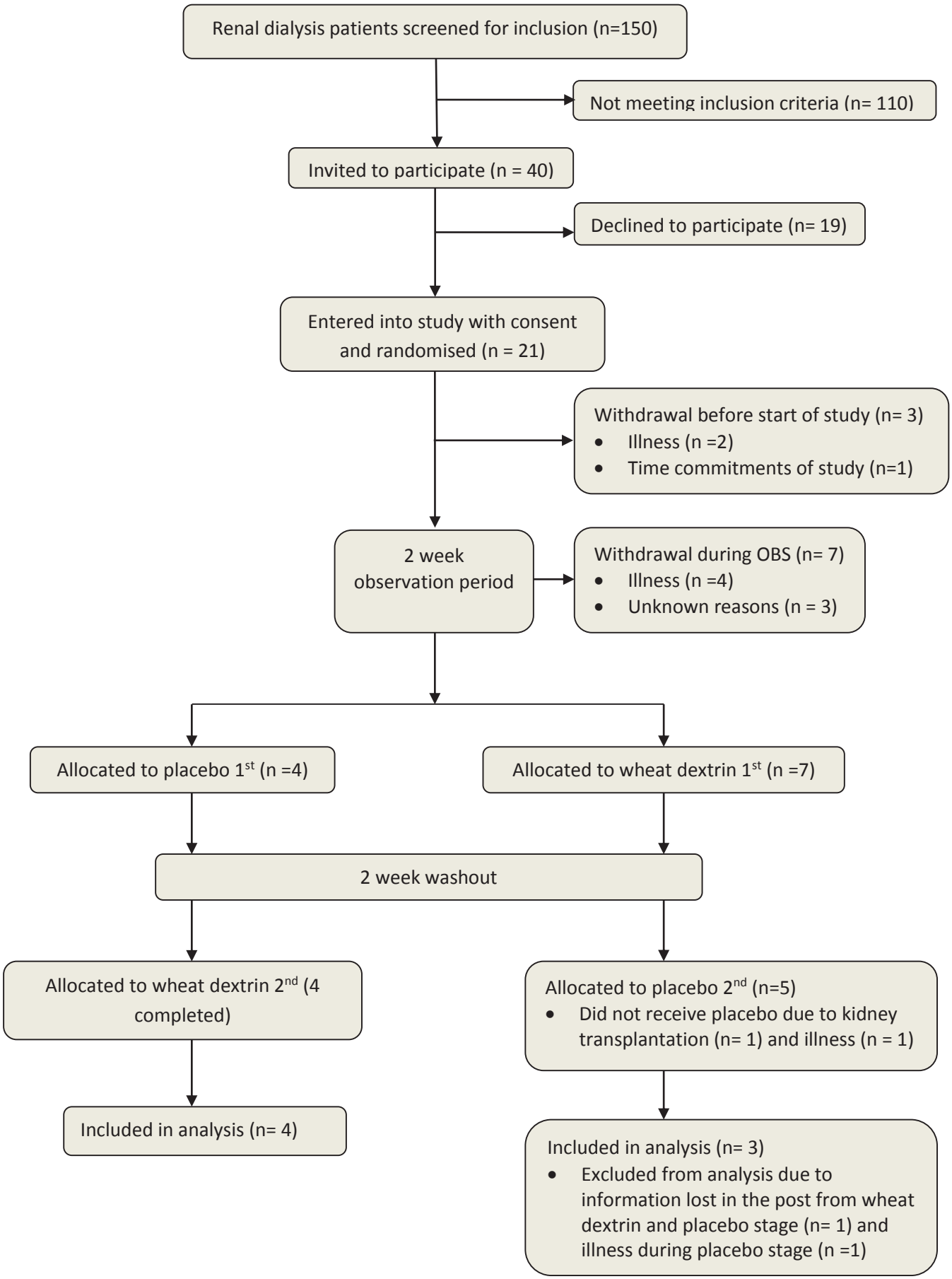


Figure 4.1 Flow diagram showing subject screening, recruitment, inclusion and withdrawal

After consenting to participate in the study, two subjects withdrew prior to the start date due to illness, and one due to the inconvenience of the amount of time the study was due to take. During the OBS stage, four subjects withdrew due to illness unrelated to the study and three withdrew due to unspecified reasons. Due to geographical limitations, subjects were randomised and given all study resources for the entire 12 week period. Of those recruited into the trial, a greater number of withdrawals occurred from the group allocated to consume the placebo first, thus there was an uneven number of subjects consuming the WD (n =7) or PB (n =4) first (see Figure 4.1). As subjects were acting as their own controls with a washout period between, this should not have affected the outcomes of the study. One subject withdrew during the first testing stage due to having a kidney transplant and one due to illness. One subject withdrew during the 2nd stage due to an illness unrelated to the study. Two of the subjects records were lost in the mail. After subject withdrawal, seven subjects completed all stages of the study. The age, gender and ethnicity of the seven subjects who completed the trial and are included in the analysis, are shown in Table 4.1.

Table 4.1 Demographics of subjects who completed all stages of the study

Characteristics (n =7)		**Values**
Age		68.1 ± 14.8*
Ethnicity	NZ European	4 (57.1%)#
	NZ Maori	3 (42.9%)#
Gender	Male	4 (57.1%)#
	Female	3 (42.9%)#
Mode of dialysis	HD	2 (28.5%)#
	PD	5 (71.5%)#

*mean ± SD
Count (frequency)

From Table 4.1 it can be seen that there are approximately even numbers of NZ European and NZ Maori as well as male and female subjects who completed the trial. There were more PD patients (n =5, 71.4%) than HD patients (n =2, 28.6%). Table 4.2 below shows the characteristics of those 14 subjects withdrawing from the study after recruitment. These subjects' results are not included in the analysis. However, it is useful to consider the demographics of this group in case it may confer any useful information for future trial recruitment processes.

Table 4.2 Demographics of subjects who withdrew from the study

Characteristics (n =14)		Values
Age		61.6 ± 11.91*
Ethnicity	NZ European	5 (35.7%)#
	NZ Maori	9 (64.3%)#
Gender	Male	6 (42.9%)#
	Female	8 (57.1%)#
Mode of dialysis	HD	8 (57.1%) #
	PD	6 (42.9%)#

*mean ± SD
Count (frequency)

4.2 Quantity of intervention product (wheat dextrin) or placebo product (maltodextrin) used by subjects during the study

This section of the results will be focused on the quantity of WD and PB supplement consumed by each subject over each of the four week periods during both the WD and PB stages of the study. Subjects were instructed to increase both their WD and PB use to the required level during week one and then maintain their use over the following three weeks. During the first week, the amount of supplement the subjects were instructed to take was equal to 101.2 g/week or 14.5 g/day. During the following three weeks the amount of supplement instructed to take was equal to 154 g/week or 22 g/day (Appendix A). Table 4.2 shows the quantity of WD and PB that each subject actually consumed respectively over each week of the study in both study periods.

Table 4.2 Amount of WD and PB consumed by each subject over the study period

	Wheat dextrin (g/week)				Placebo (g/week)			
Subject	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**
1	101.2	154	145.2	136.4	95	154	154	154
2*	83.6	8.8	17.6	17.6	57.2	101.2	92.4	83.6
3	145.2	154	154	154	100	154	118.8	154
4	92.4	136.4	83.6	110	105	154	154	96.8
5	96.8	140.8	154	132	154	154	132	154
6	110	154	154	154	35	154	154	154
7	23	154	154	154	ND	ND	150	154
Mean	108 ± 19.2	149 ± 8.07	141 ± 28.2	140 ± 17.7	111 ± 37.1	145 ± 21.6	137 ± 24.2	135 ± 31.4

ND = No data
Mean ± SD
Wk = week
Weeks 2-4 maximum amount of 22g/day = 154 g/week
*Values for subject two are excluded from the means

From Table 4.2 it can be seen that not all subjects consumed the recommended maximum dose of 154 g/week from weeks two to four. Subject two in particular, consumed low quantities throughout the WD study period. In order to gain a better insight into the consumption patterns of WD per week by each subject the same results of WD intake per week, are presented graphically (Figure 4.2).

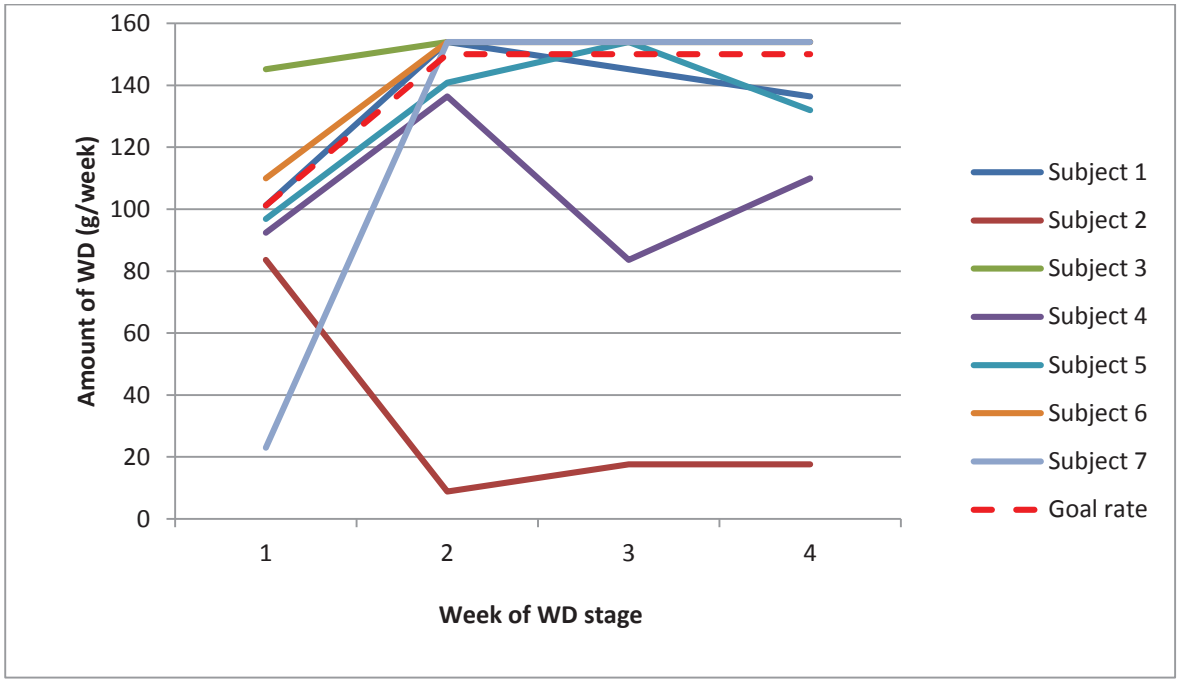


Figure 4.2 Quantity of WD supplement consumed each week by each subject

From Figure 4.2 it can be seen that with the exception of subject two, each subject shows an increase in the level of consumption of WD from week one to two. All subjects except subject two and four then maintained a high dose of between 130g to 150g of WD fibre supplement per week for the remainder of the WD stage. Subject four still managed to consume on average over 100 g of WD per week. In contrast, subject two started with the recommended dose for the first week but instead of building up the dose, the level of consumption fell to just under 20 g/week. Due to the small quantity of supplement consumed by subject two compared with other subjects, the results from subject 2 will be excluded in any central tendency measure for variables in the WD stage as well as being excluded during any significance testing.

Figure 4.3 shows the quantity of PB supplement consumed by each subject during each week of the PB stage of the trial. Each subject increased their supplement use from week 1 to week 2 with the exception of subject five, who started with the highest recommended dose (154 g/week). All subjects then maintained a dose above 100 g/week except for subject 2. As with the WD stage, subject two consumed considerably less PB than all other subjects. Data from subject two will therefore be removed from further analysis as previously mentioned due to non-compliance.

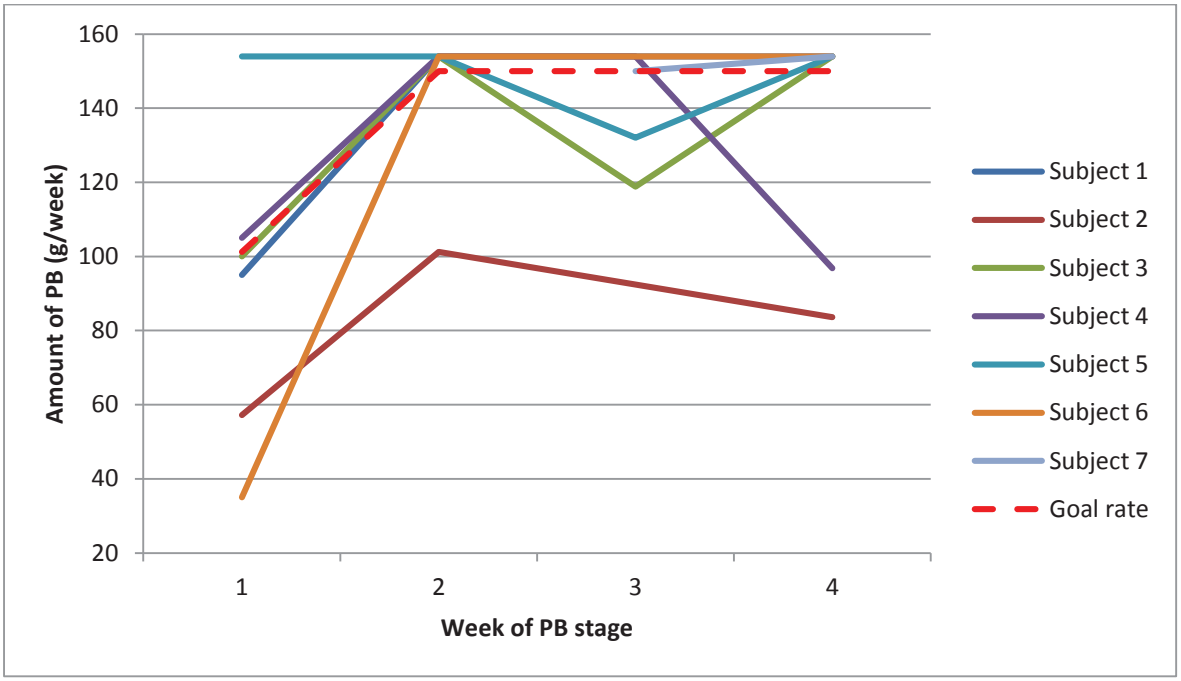


Figure 4.3 Quantity of PB supplement consumed each week by each subject

Overall, there were no significant differences in the quantity of supplement consumed per week between the wheat dextrin and placebo stage at any time point. There was however a trend (p =0.058) that the quantity of wheat dextrin and placebo consumed was less during the first week than any of the following three weeks (Figure 4.4).

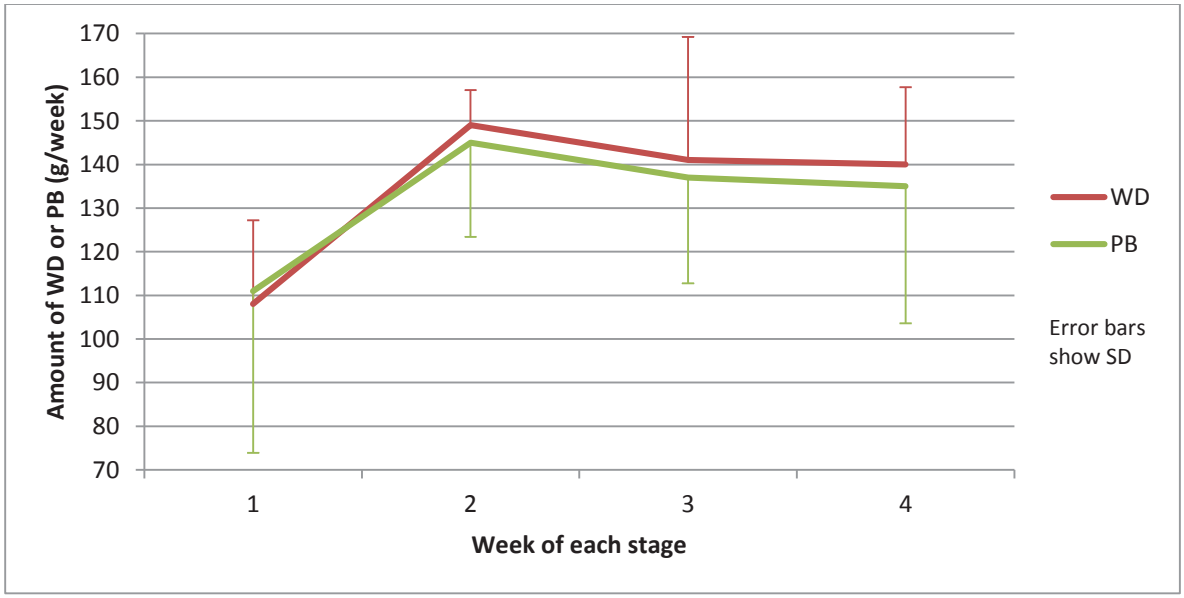


Figure 4.4 Mean quantity (g) of supplement consumed per week in both WD & PB supplementation stages of the trial (n =6)

This was to be expected due to the subjects being given an instruction sheet on how to increase the dose over the first week and then maintain a higher dose over the following three weeks of the trial. This trend can be seen in Figure 4.4 which shows the median quantity of supplement taken per week during both the WD and PB stages of the trial. After the first week of both the OBS and WD stage, there is a clear increase in supplement intake, the amount of supplement then reduced slightly in weeks 3 & 4 of both the WD and PB stages.

4.3 Laxative use over the course of the study

It is common for renal patients to be prescribed laxatives due to the high prevalence of constipation within this population. Constipation can lead to peritonitis in PD patients and temporary discontinuation of dialysis, therefore it is important to prevent constipation whenever possible. Monitoring the laxative use of each subject was important to determine if consuming the supplement could result in a reduction in laxative use. The volume (mL) of lactulose used per week and number of laxsol tablets used per week was compared in the OBS, WD and PB stages. The total number of times both lactulose and laxsol were used was combined to give a weekly total of the number of occasions laxatives were used per week. The values for these measures for each week of the study are shown in Table 4.3.

Table 4.3 Lactulose, laxsol and total number of times laxatives were used during the OBS, WD and PB stages (n =6)

	OBS	Wheat dextrin					Placebo					*p* value
		Wk 1	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 3&4**	**Wk1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 3&4**	
Lactulose use (mL/wk)	5.00 (0.00, 50.0)	0.00 (0.00, 37.5)	10.0 (0.00, 62.5)	0.00 (0.00, 40.0)	0.00 (0.00, 45.0)	10.0 (0.00, 50.0)	0.00 (0.00, 55.0)	10.0 (0.00, 47.5)	0.00 (0.00, 40.0)	30.0 (0.00, 80.0)	15.0 (0.00, 60.0)	0.694
Laxsol use (tabs/wk)	6.36 ± 8.18	7.50 ± 7.01	7.00 ± 5.18	4.33 ± 3.84	5.22 ±5.21	4.78 ± 3.64	1.67 ± 2.42	3.67 ± 4.32	1.24 ± 3.30	3.86 ± 3.89	4.07 ± 3.52	0.204
Total no. x laxatives used/week	6.07 ± 5.47)	6.37 ± 5.21	6.00 ± 3.96	4.56 ± 4.10	5.22 ± 5.17	4.89 ± 4.23	3.0 ±4.29	4.67 ± 5.05	4.57 ± 4.69	4.86 ± 5.15	4.71 ± 4.88	0.299

Mean ± SD
Median (25^{th}, 75^{th} percentile)
OBS = Weekly average of both observation weeks combined
Wk = week
Wk 3&4 = weekly average of weeks 3&4 combined
P value is significant if < 0.05
no. = number

The amount of laxsol (p =0.204) and lactulose, (p =0.694) used did not differ significantly between the OBS and WD stage, OBS and PB stage or WD and PB stage. When lactulose and laxsol use were combined, the total number of times that laxatives were used per week was not significantly different between the OBS and WD stage, OBS and PB stage or WD and PB stage (p = 0.299).

It is useful to examine each subject's laxative use individually in order to determine whether individual subjects were able to reduce their laxative use when using either the WD or the PB supplement. In order to do this, laxative intake data from the OBS stage and a weekly average of weeks 3&4 for the WD and PB stages were compared for each subject (Figure 4.5).

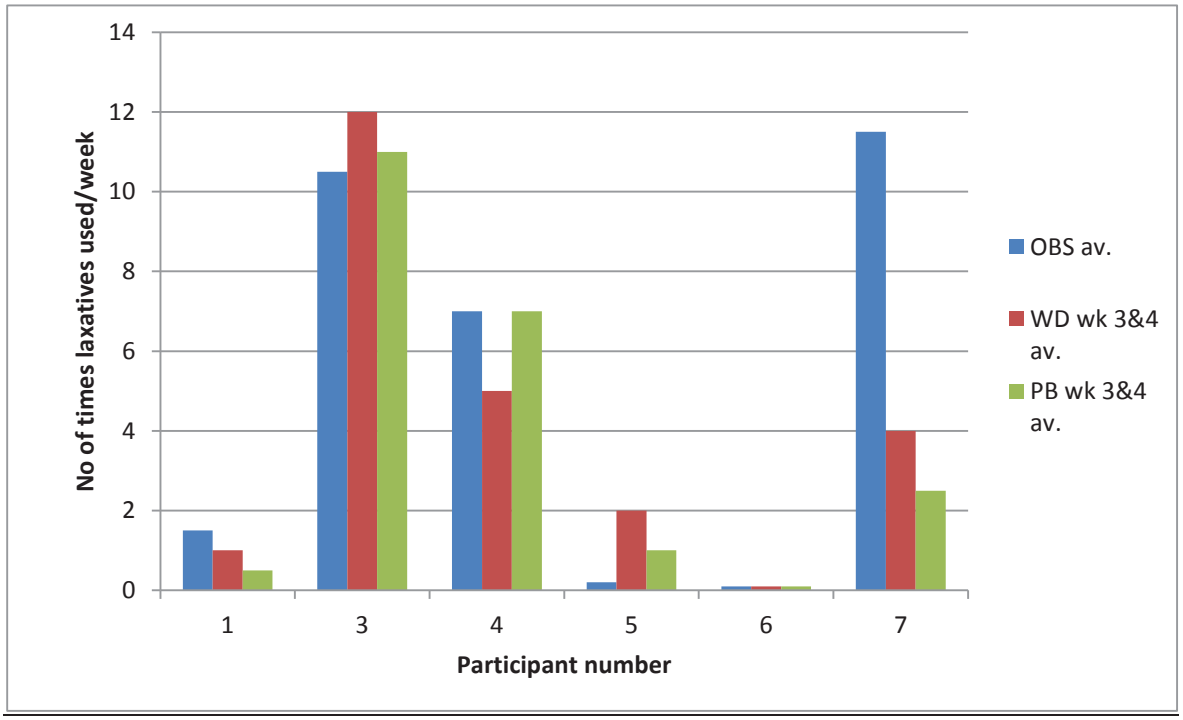


Figure 4.5 Number of times laxatives were used per week over each phase of the study for each subject

From Figure 4.5 we would expect to see laxative use being less in the WD stage compared to both the OBS and PB stages if WD is able to improve bowel performance. This result can be seen in subject four who managed to reduce their laxative use during the WD stage (5 times/week) compared to both the OBS (7 times/week) and PB

stages (7 times/week). This shows WD reducing laxative use in one subject compared to placebo. Subject seven reduced total laxative use from 11.5 times/week in the OBS stage to 4 times/week in the WD stage and 2.5 times/week in the PB stage. This shows both WD and PB working to reduce laxative use compared to the OBS stage. Subjects one, three and five showed reduced laxative use with the placebo, however these reductions were minimal (approximately one less occasion per week) so has little clinical relevance. Overall, no subjects could completely replace their laxatives with WD or PB supplementation. Wheat dextrin may have the ability to reduce laxative use in some patients; however, it is difficult to come to any conclusion with a limited number of subjects.

4.4 Stool frequency

Stool frequency is the number of times stools were passed over a certain time period. In the current study, stool frequency is expressed as the number of stools passed per week. When comparing changes in mean scores for stool frequency, there were no significant differences between the OBS and WD stage, OBS and PB stage or WD and PB stage (p =0.653). As there were no significant differences in stool frequency between any stages of the study, data from individual subjects were explored to see if some subjects had increases in stool frequency when consuming either the WD or PB compared to the OBS stage. Table 4.4 shows the stool frequency for each subject as well as weekly mean values for each week of the study in the OBS, WD and PB stages.

Table 4.4 Weekly stool frequency for each subject and mean weekly values of stool frequency in the OBS, WD and PB stages

	OBS	Wheat dextrin				Placebo			
Subject		**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**
	Number of stools passed per week								
1	2	1	1	3	2	2	2	2	3
2*	8	9	8	11	11	12	10	13	15
3	8.5	6	7	7	7	10	6	6	6
4	13	11	12	9	13	9	12	7	10
5	11	7	5	4	7	14	14	8	11
6	4	7	14	14	14	7	5	5	5
7	12.5	12	7	8	9	ND	ND	5	9
Mean	8.42 ± 4.19	7.33 ± 3.93	7.67 ± 4.72	7.50 ± 3.94	8.87 ± 4.41	8.40 ± 4.39	7.80 ± 5.01	5.50 ± 2.07	7.33 ± 3.14

Values represent the Mean ± SD.
ND = No data
Wk = week
OBS = Weekly average of both observation weeks combined
*Values for subject two are excluded from mean

Fluctuations in stool frequency occurred in many individual subjects with some showing increases with the WD and some showing increases with the PB. When stool frequency data is presented graphically for each individual it can be seen that subjects had differing responses to the supplementation with WD and PB (Figures 4.6-4.12).

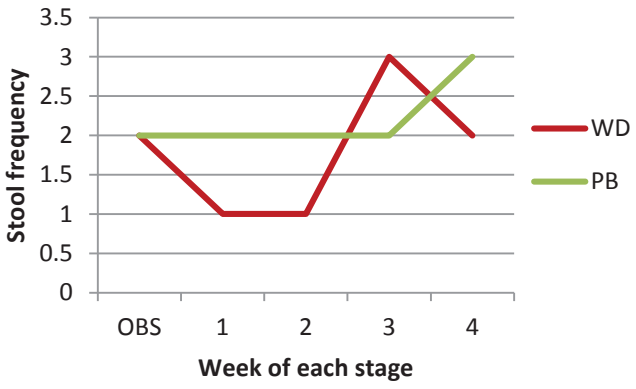


Figure 4.6 Stool frequency for subject 1 over all stages of the study

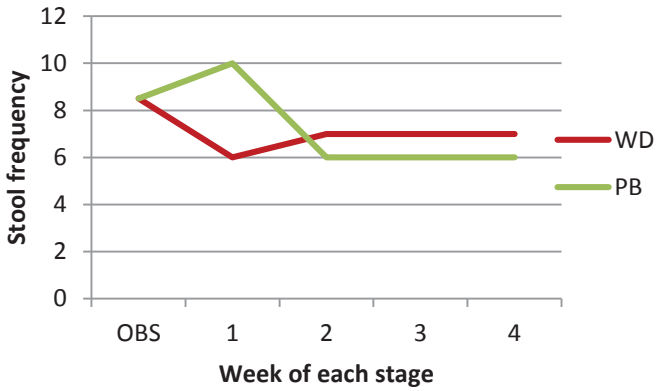


Figure 4.7 Stool frequency for subject 3 over all stages of the study

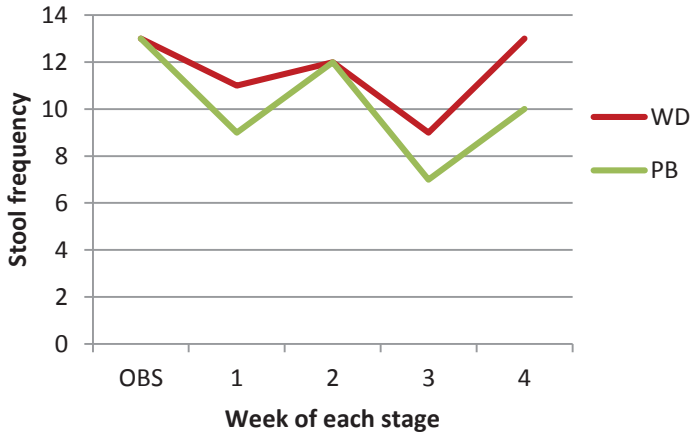


Figure 4.8 Stool frequency for subject 4 over all stages of the study

In subjects one, three and four (Figures 4.6, 4.7 and 4.8 respectively), very little change in stool frequency was observed over either the WD or PB supplementation periods. Therefore, consumption of WD or PB does not appear to improve bowel function in these subjects.

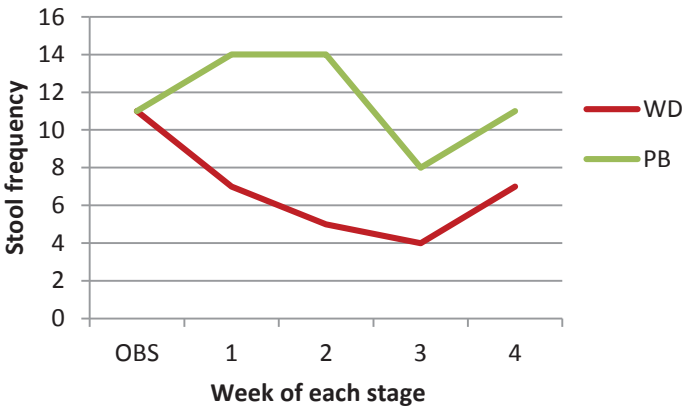


Figure 4.9 Stool frequency for subject 5 over all stages of the study

Subject five had a reduction in stool frequency during the WD supplementation stage, from 11 stools/week during the OBS stage, to 7 seven stools/week by week four of WD supplementation (Figure 4.9). Placebo supplementation did not have an effect on stool frequency after four weeks with stool frequency remaining at 11/week after four weeks of taking the PB.

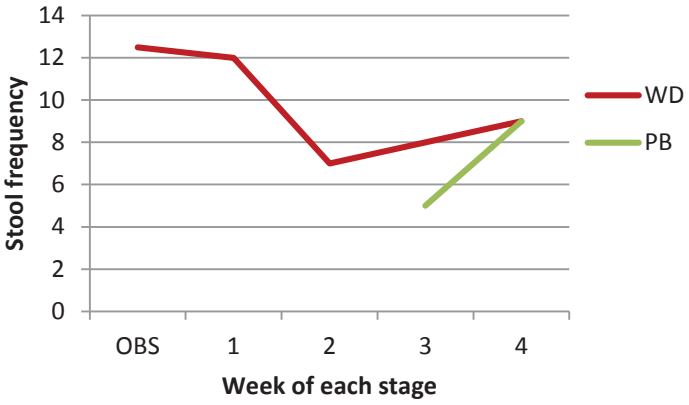


Figure 4.10 Stool frequency for subject 7 over all stages of the study

Subject seven, similar to subject five showed a decrease in stool frequency during the WD stage of the trial, from 12.5 stools/week in the OBS stage to nine stools/week, by week four in the WD supplementation stage (Figure 4.10). Participant seven had no stool frequency data for weeks one and two of the PB supplementation stage. However, the stool frequency data that is available for weeks 3 & 4 is lower that of the OBS stage, suggesting that PB supplementation may decrease stool frequency in subject seven.

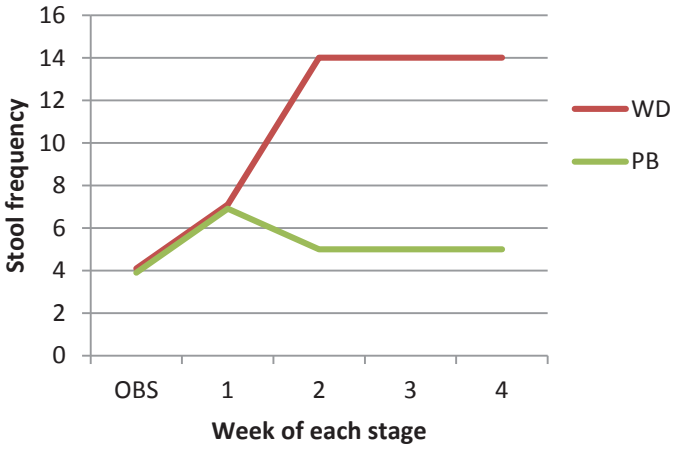


Figure 4.11 Stool frequency for subject 6 over all stages of the study

Subject six showed positive results of WD supplementation increasing stool frequency. Stool frequency increased from an average of four stools/week during the OBS stage, to 14 stools/week in weeks two, three and four (Figure 4.11). Subject six showed a small increase in stool frequency while consuming the PB supplement, with stool frequency increasing from four stools /week during the OBS period to five stools/week.

As WD had a clear effect of increasing stool frequency compared to the OBS and PB stage in one subject (Figure 4.12), it may be that WD can work to increase stool frequency in some individuals but not others.

4.5 Stool Form

Stool form was measured using the Bristol stool form scale (BSFS) with one on the scale being the hardest stools and 7 on the scale being the loosest (Appendix D). The ideal stool type on the BSFS is between 3 and 5. The percentage of ideal stools formed per week was determined to see if either WD or PB supplementation could act as a stool normaliser, by creating a greater percentage of ideal stools compared to the OBS stage. The mean weekly values for stool form and percent of ideal stool form are shown in Table 4.5.

Table 4.5 Mean weekly values for stool from and percent of ideal stools for the OBS, WD and PB stages (n =6)

	OBS	Wheat dextrin					Placebo					*p* value
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 3&4	Wk1	Wk 2	Wk 3	Wk 4	Wk 3&4	
Stool form	3.7 ± 1.2	4.0 ± 1.2	4.2 ± 1.0	3.8 ± 0.6	3.9 ±0.7	3.8 ± 0.5	3.6 ± 0.7	3.6 ± 0.7	4.2 ± 0.9	3.9 ± 0.4	4.1 ± 0.52	0.549
% of ideal stools*	60.8 ± 31.4	66.3 ± 36.9	80.1 ± 36.6	86.2 ± 18.5	89.9 ± 16.6	88.1 ± 12.7	79.7 ± 21.7	83.0 ± 17.7	82.4 ± 22.5	90.9 ± 11.7	84.3 ± 16.8	0.253

Mean ± SD
OBS = Weekly average of both observation weeks combined
Wk 3&4 = weekly average of weeks 3&4 combined
Wk = week
p value is significant if < 0.05
*3-5 on Bristol stool form scale

The mean weekly scores for stool form were not significantly different between the OBS and WD stages, OBS and PB stages or WD and PB stages (*p* =0.549). This shows that stools did not get any looser or harder between stages of the study. The percentage of ideal stool types (3-5 on the BSFS) also did not significantly differ between the OBS and WD stages, OBS and PB stages or WD and PB stages (*p* = 0.253). From Table 4.5, it can be seen that the number of ideal stools in the WD stage

increases gradually from 61.0% in the OBS stage to 89.1% by week four. In the PB stage, percent of ideal stools increases gradually from 61.0% in the OBS stage to 90.9% by week four. This appears as though the percentage of ideal stools formed increases over the study period in both the WD and PB stages.

However, results for individual subjects need to be analysed to determine whether there were some subjects who clearly responded to either the WD supplementation or the PB supplementation compared to the OBS stage. Of those subjects who completed all stages of the study, there were some who had stools which were more ideal in the WD and/or PB stage in comparison to the OBS stage (Figure 4.15).

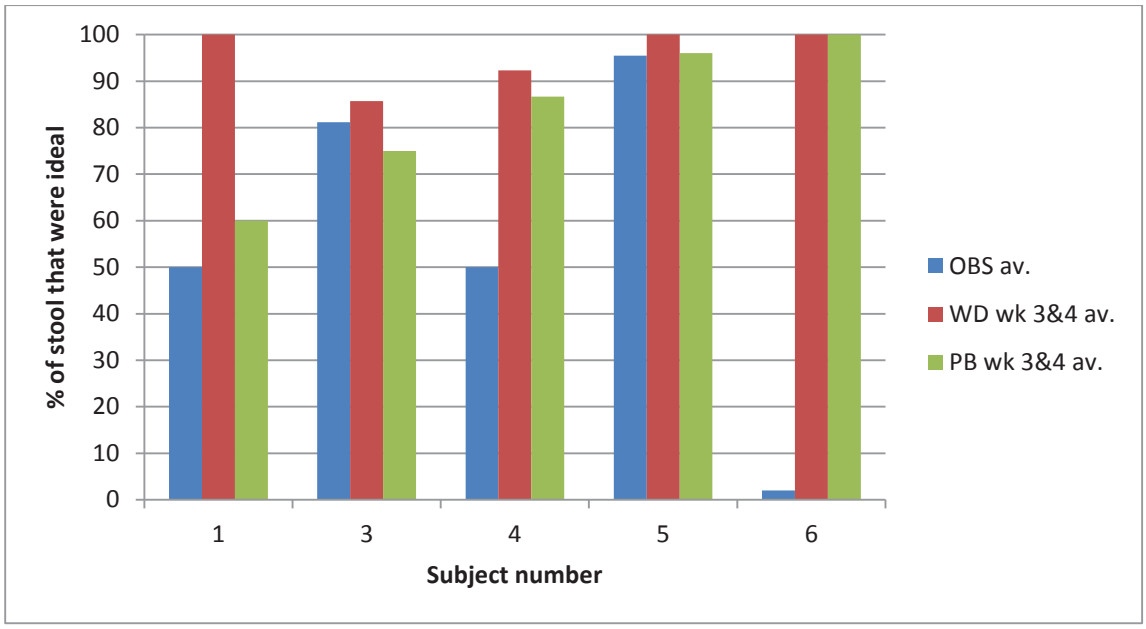


Figure 4.12 Percent of stools that were ideal (BSFS 3-5) for each subject over all three stages of the study.

If we consider a 20% change from OBS to be clinically relevant, then subjects 1, 4, 6 and 7 all met this criteria for WB and/or PB supplementation. The percent of ideal stools formed increased by 100%, 85% and 100% between the OBS and WD stage in subjects 1, 4, and 6 respectively. The percent of ideal stools formed also increased in the same subjects by 20%, 73% and 100% respectively and for subject 7 by 33% in response to supplementation with PB. Subjects 3 and 5 showed little change in percent

of ideal stool types between the stages of the study. When analysing individuals results, benefits of both WD and PB can be found in terms of being a stool normaliser.

4.6 Quality of life

The 28 question Quality of Life (QOL) questionnaire (Appendix 6) was completed by each subject during one of the last three days of each stage of the study. The questionnaire consisted of 28 questions designed to assess the effect constipation had on the patient's QOL during the two weeks immediately prior to completing the questionnaire. The QOL questionnaire is designed to be assessed in four different domains (QOL categories) as shown in Table 4.6 below (see Section 3.7 for explanation of domains). Table 4.6 shows the mean scores for QOL across the different domains during all stages of the study. The average value of the four domains was used to determine an overall QOL measure. Scores ranged from one being the best QOL to seven being the worst QOL.

Table 4.6 Quality of life scores for the four domains as experienced by subjects at each stage of the study (n =6)

Domain	Observation	Wheat dextrin	Placebo	*p* value
Physical discomfort	0.93 ± 0.75	1.00 ± 0.82	0.57 ±0.62	0.270
Psychosocial discomfort	0.79 ± 0.52	0.80 ± 0.61	0.46 ± 0.44	0.171
Worries and concerns	0.91 ± 0.76	0.87 ± 0.64	0.75 ± 0.61	0.632
Satisfaction	1.69 ± 0.91	1.94 ± 0.71	1.57 ± 0.87	0.291
Overall of all 4 domains	1.08 ± 0.65	1.15 ± 0.58	0.84 ± 0.59	0.181

Values are mean ± SD
A lower value = better quality of life

The mean scores of the QOL survey were not significantly different between the OBS and WD stage, OBS and PB stage or WD and PB stage for physical discomfort (p =0.270), psychosocial discomfort (p =0.171), worries and concerns (p =0.632), satisfaction (p =0.291), or overall quality of life (p =0.181). Although no significance was found, looking at the results of individual subjects from the overall QOL domain from each stage shows interesting results (Figure 4.13).

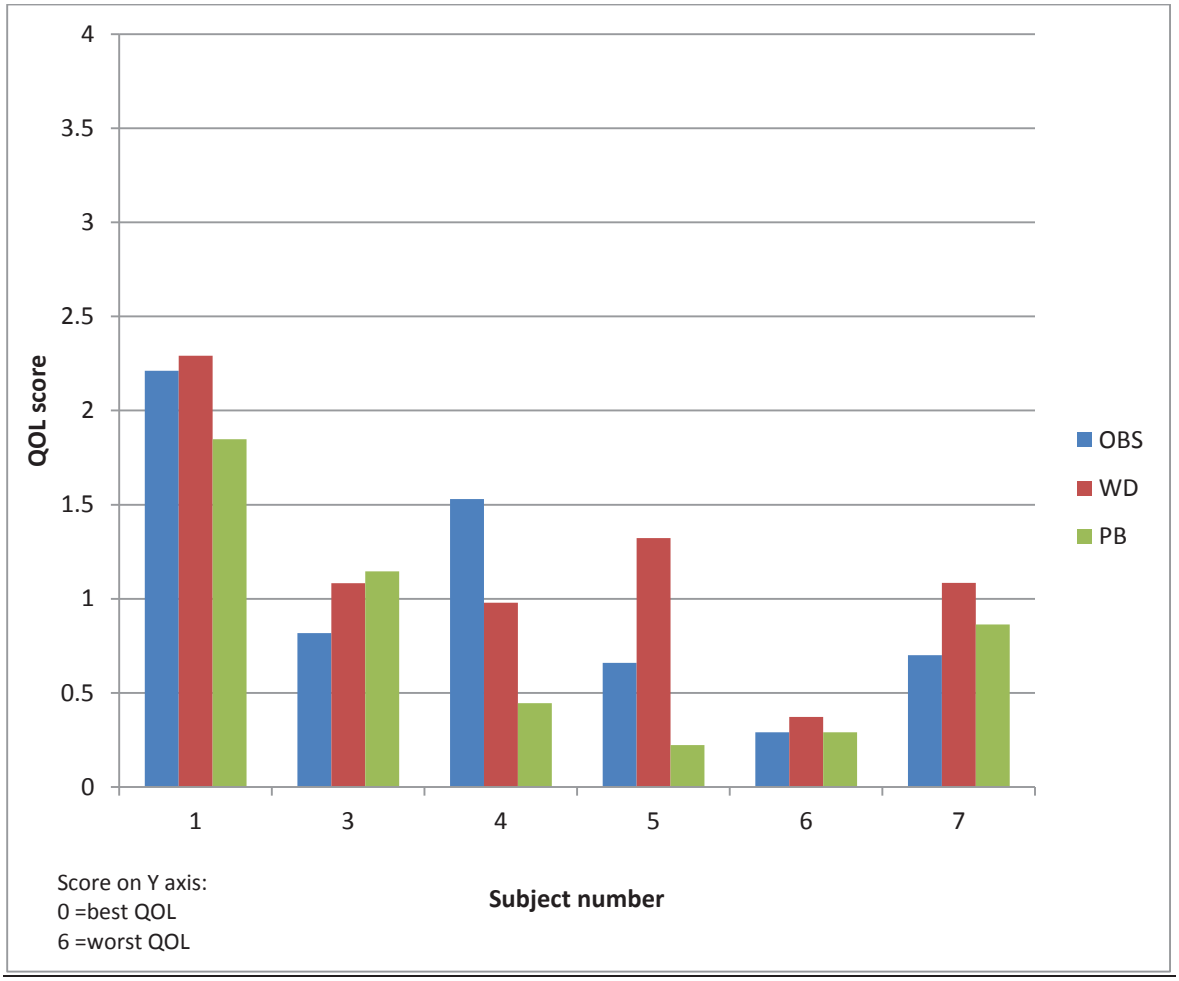


Figure 4.13 Overall QOL scores for each subject in each stage of the study (n =6)

If we take a change in QOL score of 20% to be relevant, compared to the OBS stage, overall QOL in the WD stage improved in subject 4 but was worse in subjects 3, 5, 6 and 7. When comparing the OBS and PB stage, overall QOL scores improved in the PB stage by more than 20% in subjects 1, 4 and 5, but were worse in subjects 3 and 7. When comparing the overall QOL scores of the WD and PB stages, scores were at least 20% worse in the WD stage in subjects 1, 4, 5, 6 and 7 (83% of subjects) compared to the PB stage. Overall, it appears WD does not improve QOL scores in individual subjects.

4.7 Correlations between different variables measured

Correlations were carried out to see if there were any relationships between the variables measured in the current study. This gives insight into relationships which may be of interest to study in the future. The correlations were carried out using data from a weekly average of weeks 3&4 of the WD stage combined. Throughout the correlation section this time point will be called week 3&4. This time point was chosen as it covers a greater time period, gathering a larger representation of the results. It also encompasses the time at which subjects were instructed to take the full dose of WD and had already been consuming the fibre supplement for two weeks and hence should have become accustomed to taking it. The number in the text boxes show which data points belong to which subject.

The stool frequency of weeks 3&4 of the WD stage was compared to all five QOL measures to determine if there was a relationship between the variables. There was found to be significant correlations between stool frequency and QOL domains, with the physical discomfort domain (Figure 4.14) correlation being the strongest (r = -.900, n =7, *p* =0.001) followed by the worries and concerns domain (r =-.835, n =7, *p* =0.005).

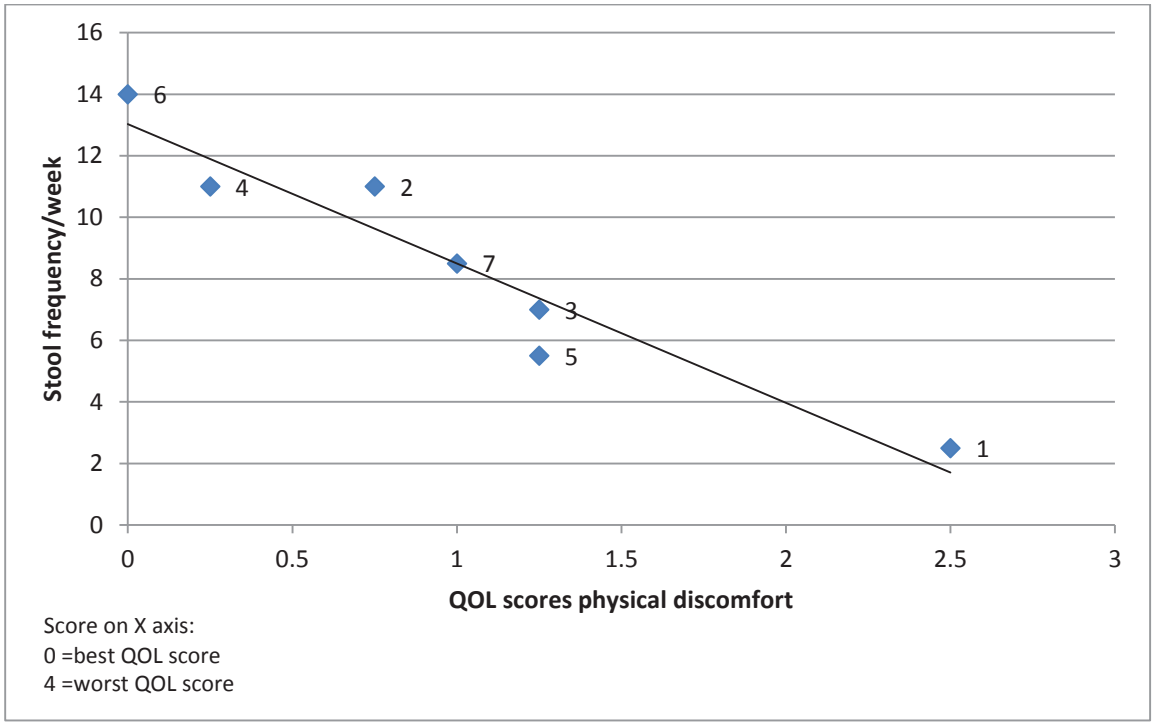


Figure 4.14 Correlation of weekly average of stool frequency from weeks 3&4 of the WD stage and quality of life physical discomfort domain (n =7)

From Figure 4.14 above, it can be seen that as stool frequency increases, QOL scores improve. There was also a non-significant correlation between stool frequency and the psychological dysfunction domain (r =-.601, n =7, *p* =0.087). After performing partial correlations, there was no significant correlation between stool frequency and worries & concerns when controlling for physical dysfunction (r =-.106, n =7, *p* =0.802) or between stool frequency and physical dysfunction when controlling for worries and concerns (r =-.617, n =7, *p* =0.103). This shows that the QOL domains are related and that as stool frequency increases, an associated improvement in quality of life scores occurs.

Due to the relationships that exist between the different QOL domains, it is not surprising that a significant negative correlation also exists with stool frequency and overall quality of life (r =-.785, n =7, *p* =0.012) as shown in Figure 4.15.

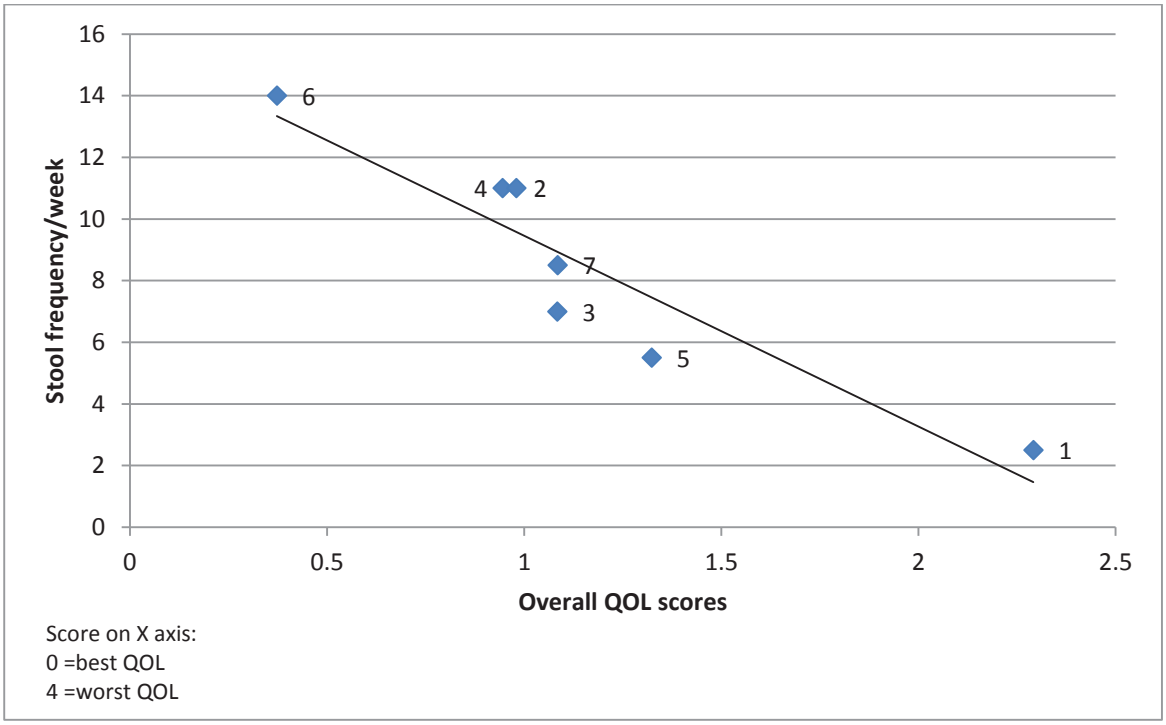


Figure 4.15 Correlation of weekly average stool frequency from weeks 3&4 of the WD stage combined and overall quality of life (n =7)

From Figure 4.15 above, it can be seen that as stool frequency increases, it is associated with improvements in overall quality of life scores.

Of interest was a relationship found between the variables stool form and stool frequency. A non-significant negative correlation (r = -.699, n =7, *p* =0.081) was found between stool frequency and stool form in weeks 3&4 of the WD stage (Figure 4.16).

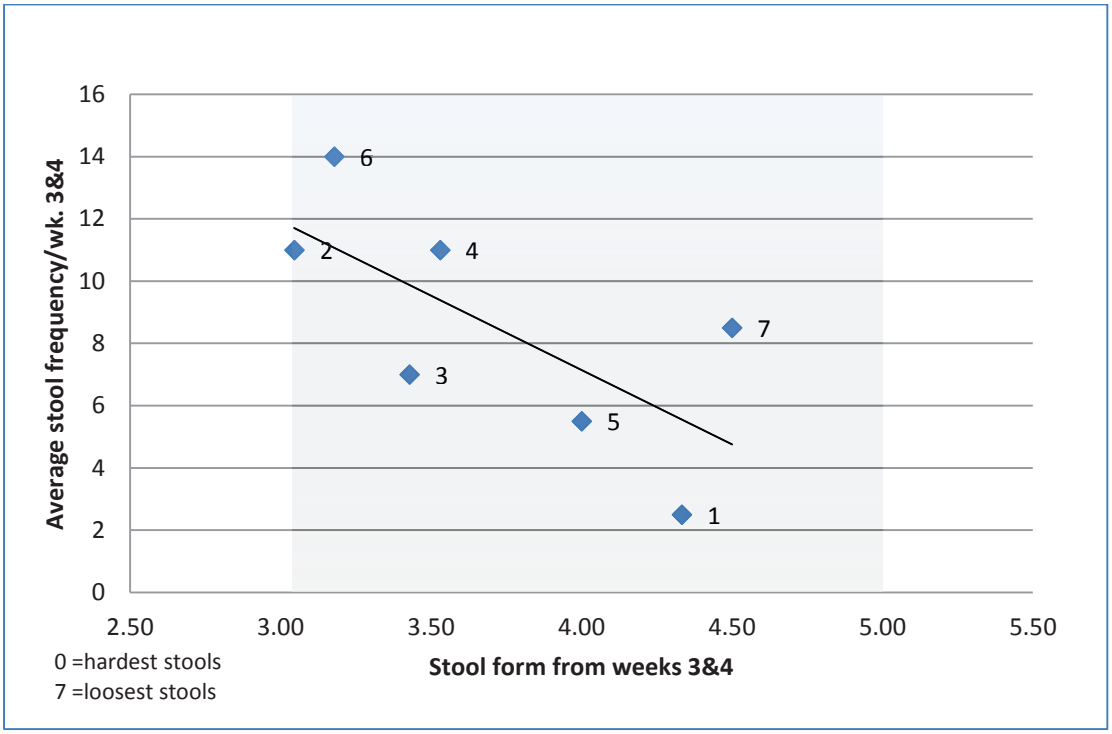


Figure 4.16 Correlation of weekly average of stool frequency from weeks 3&4 of the WD stage and stool form from the same period (n =7). The shaded region represents the ideal stool form range.

From Figure 4.16 above, although stool are still within the normal range (3-5 as highlighted), it appears that as the stool form becomes looser (i.e. higher form number), it is associated with passing fewer stools per week.

A correlation using the number of times laxatives were used revealed interesting results when relating it to the percent of stools which were ideal (Figure 4.17).

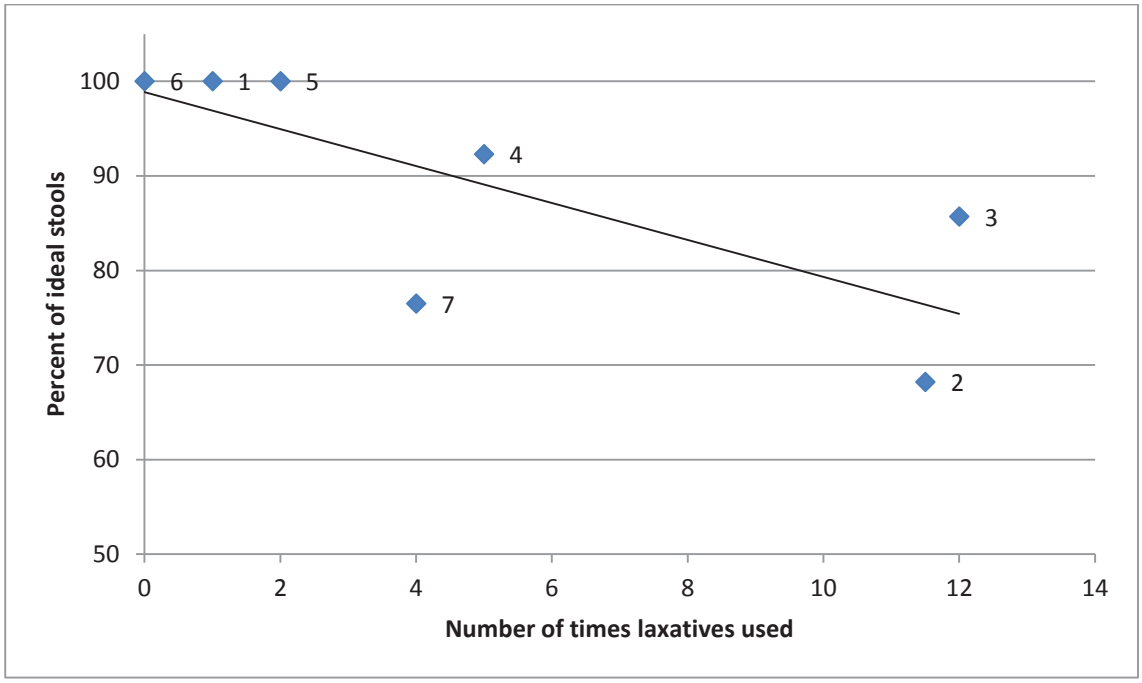


Figure 4.17 Correlation between the total number of laxatives used and percent of stools formed that were ideal in the combined weekly average from weeks 3&4 of the WD stage (n =7)

It appears that as the number of times laxatives are used increases, the percent of ideal stools formed decreases. This is shown by a significant negative correlation (r =-.698 n =7, *p* =0.036) between the percent of stools formed that were ideal and the number of times laxatives were used in weeks 3&4 of the WD stage.

Chapter Five

5.0 Discussion

The aim of this pilot study was to examine the effectiveness of a wheat dextrin fibre supplement on bowel performance in free living patients who are currently receiving either peritoneal or haemodialysis within the Northland DHB. Constipation is very common in renal dialysis patients due to a low intake of dietary fibre, physical inactivity, fluid restrictions and polypharmacy. Constipation within this population can have serious consequences making its treatment important. Current practice for management of constipation in renal dialysis patients in Northland DHB involves prescribing laxatives and attempting to alter dietary fibre intake through dietary measures. However due to dietary restrictions of many fruits, vegetables and whole grains, and the side-effects of using laxatives, an alternative treatment is necessary as ad hoc increases in dietary fibre (and associated water requirements) is not always feasible. Ideally, a fibre supplement would be available to these patients which is low in potassium and phosphate with no fluid requirements for ingestion. PHARMAC does have a psyllium based fibre supplement which is available at a subsidised rate. However, this needs to be consumed with 750 mL of fluid per day and is therefore not suitable for renal dialysis patients. A wheat dextrin fibre supplement is available in New Zealand and can be mixed into food therefore requiring no water. It also does not contain any potassium or phosphate. This makes a wheat dextrin fibre supplement ideal for renal dialysis patients as a way to increase their fibre intake in an attempt to improve bowel performance. This pilot study is the first to explore whether wheat dextrin can be used to improve bowel performance in renal dialysis patients.

5.1 Characteristics of participants

The dialysis patients participating in this study were of NZ European (57.1%) and NZ Maori (42.9%) descent. From the 150 patients screened for inclusion, 49% identified as being of Maori decent. Those who participated in the study are therefore representative of the ethnic makeup of dialysis patients within the Northland DHB.

According to the NZ census 2013, 76% of the population of Northland identified with NZ European and 32% identified as Maori (Statistics New Zealand, 2013). The reason for a higher number of Maori renal patients compared to the population as a whole is due to a higher proportion of Maori having end stage renal failure (1326 per million) compared to New Zealand as a whole (877 per million) (ANZDATA Registry Report, 2014). The age of the subjects in the current study (68.1 ± 14.8 years) was also in line with data from ANZDATA which shows the most common age bracket for those on dialysis in NZ to be between 55 and 64 years (ANZDATA Registry Report, 2014) . The proportion of HD and PD subjects is not representative of the population. According to ANZDATA, 34% of those on dialysis in NZ undergo PD and 66% undergo HD (ANZDATA Registry Report, 2014). This compares to 28.5% on HD and 71.5% on PD in the current study. In the Northland DHB, PD patients are prescribed laxatives more frequently than HD patients due to the consequences of constipation on those undergoing PD being potentially more dangerous than those on HD. Due to the recruitment criteria stating subjects must currently be taking laxatives, it is therefore not surprising that the number of PD patients was greater than HD patients. The gender of those who participated in the study was approximately split evenly between male (57.1%) and female (42.9%). This is representative of those who undergo renal replacement therapy in NZ with males (58%) being slightly higher than females (42%) (National Renal Advisory Board, 2006).

5.2 Amount of wheat dextrin and placebo used during the study

This study found no significant differences between the quantity of wheat dextrin powder and maltodextrin placebo powder consumed between any weeks of the WD or PB stages. Subjects were instructed to increase the dose of supplement over the first week of each stage (Appendix 1) to adapt to the fibre and avoid bloating and flatulence (van den Heuvel *et al.*, 2004), which has been associated with large immediate doses of soluble fibre (Chutkan *et al.*, 2012). A mean of 108 grams of WD was consumed by subjects in the first week of the WD stage followed by 149, 141 and 140 grams in weeks 2, 3 and 4 respectively. A mean of 111 grams of PB was consumed by subjects in the first week of the PB stage followed by a mean of 145, 137 and 135 grams per week

for weeks 2, 3 and 4 respectively. It is therefore surprising that no significant result was found between the quantity of powder consumed in week one of each stage compared to weeks two, three and four of each stage.

The small sample size of seven subjects may not have been large enough to detect any significant differences in the quantity of powder consumed during each stage. Although no significant differences were detected, it is clear when looking at the results that subject two consumed far less WD supplement than the rest of the subjects. As there has been shown to be a dose response relationship between the quantity of WD consumed and the amount of beneficial fermentation products , it is likely this subject did not receive the full benefit of the WD (van den Heuvel *et al.*, 2005). Data from subject two was therefore excluded from all values of central tendency due to non-compliance, as the lack of WD consumed would be likely to affect all other measures in the study. During weekly phone conversations, subject two reported limiting the quantity of supplement consumed due to the fear of needing to evacuate the bowels while taking public transport to and from dialysis sessions. The same fear reduced supplement intake in subject two due to the perceived risk of needing to temporarily stop dialysis to use the bathroom. This subject reported having their bowels working to their liking by having what they believed to be the right combination of laxatives and certain fruit and they had a fear of altering this. As this patient group has a history of constipation, it may be that many were adverse to change and were resistant to using the recommended amount of supplement. This may have been a reason why the amount of supplement consumed in the study varied between individuals.

Another reason individuals did not manage to consume the recommended amount of supplement was due to illnesses disrupting the study routine. One subject in the analysis missed taking the PB for two weeks due to a hospital admission while others were excluded from analysis due to large gaps in taking the supplement due to illness. Data from the USA Renal Data System found 1.73 hospital admissions per patient per year for HD and 1.61 admissions per year for PD patients (Saran *et al.*, 2015). This is in comparison to 0.23 hospitalisations per person per year for NZ in general in 2012/2013 showing the increased hospital admissions in the renal dialysis patients (Ministry of

Health, 2015c). In addition, the current study was carried out over the winter months of May, June, July and August. The winter months in New Zealand are known to increase hospital admissions which would have increased the chance of hospital admissions and associated disruptions in the study group (Gosai and Salinger, 2007).

5.3 Laxative use

There were no differences in the quantity of lactulose (p =0.694) or laxsol (p =0.204) used or the total number of times laxatives were used (p =0.299) between any weeks when comparing the OBS and WD stages, OBS and PB stages or WD and PB stages. The average number of times laxatives were used was 4.89 ± 4.23 in weeks 3&4 of the WD stage and 4.71 ± 4.88 in weeks 3&4 of the PB stage compared to 6.07 ± 5.47 in the OBS stage. From observing the results of individual subjects, subject seven reduced their total laxative use from the OBS stage (11.5 times/week) to 4 times/week in the WD stage and 2.5 times/week in the PB stage. This shows both WD and PB working to reduce laxative use compared to the OBS stage. Subject five however was the only subject who showed an observed benefit of WD compared to PB. Subject five managed to reduce their laxative use to five times per week in the WD stage from seven times per week in the OBS stage and seven times per week in the PB stage. Therefore WD may have the ability to reduce laxative use in some patients.

Other studies using renal patients with similar methods to the current study have clearly shown reductions in laxative use when patients consumed a soluble fibre supplement. Partially hydrolysed guar gum (PHGG) was found to replace all prescribed laxatives in 17 of 23 peritoneal dialysis (PD) patients and reduce laxative use by 38% in PD patients when compared to a placebo (Sutton *et al.*, 2007a, Sutton *et al.*, 2014). In non-dialysis patients, PHGG was found to significantly reduce laxative use from three days per week in a control period to zero days per week during PHGG treatment (Polymeros *et al.*, 2014). Inulin has also been successful in decreasing enema and laxative use in non-renal, institutionalised adults by 13% compared to a control period (Dahl *et al.*, 2005).

Both studies by Sutton *et al.* (2007 & 2014) used similar methods as the current study such as using free living patients, the supplement period lasted four weeks and the amount of fibre consumed was on average 12 g/day (20 g/day in the current study). Like in the current study, the BSFS was used as a guide of when to cut down laxative use. Differences in results between both Sutton studies and the current study may be due to the low subject numbers in the current study (n =7) compared to the Sutton (2007) (n =23) and Sutton (2014)(n =31) studies respectively. Research data has already shown the efficacy of PHGG as a successful treatment of constipation in terms of increasing stool frequency, stool water weight, stool form and reducing colonic transit time (Polymeros *et al.*, 2014, Takahashi *et al.*, 1994). However, the same improvements have not been researched using wheat dextrin. Due to the effects on bowel performance, PHGG may be superior to wheat dextrin in its ability to reduce laxative use. However the current study is the first to look at the possibility of using wheat dextrin to reduce laxative use. As PHGG is not available in New Zealand, further studies using wheat dextrin are warranted to determine whether it can be used to reduce laxative use in a greater number of individuals.

5.4 Stool frequency

The current study found no differences in stool frequency between the OBS, WD or PB stages (p =0.653). Although wheat dextrin has not been used in other studies to increase stool frequency, other soluble fibres have been found to increase stool frequency. Psyllium has been used most in research regarding increasing stool frequency. Increases in stool frequency of 0.9 stools per week have been found using 10g of psyllium per day compared to increases of 0.2 stools per week using placebo (Ashraf *et al.*, 1995). Although psyllium is a soluble fibre, it increases stool frequency due to its gel forming properties which holds water, softening stools and increasing stool bulk (McRorie and Fahey, 2013). Inulin, PHGG and wheat dextrin however work by a different mechanism. They are all non-gelling, soluble fibres which mostly escape digestion to be fermented in the large bowel. They are all probiotics which when fermented produce health promoting short chain fatty acids (SCFA's), lowering the pH of the intestinal lumen (Noack *et al.*, 2013). Both inulin and PHGG have been shown to

increase stool frequency with PHGG increasing stool frequency from 1.5 stools per week to 4.75 stools per week in constipated otherwise healthy adults over a four week period (Polymeros *et al.*, 2014). In healthy adults with a low stool frequency, 15g of inulin per day for 2 weeks increased stool frequency by 2.5 stools per day compared to placebo (Den Hond *et al.*, 2000). Both inulin and PHGG work by increasing stool bulk through an increase in biomass, producing softer stools. In addition, the production of SCFA's, especially butyrate, excites neurons of the GI tract causing colonic circular smooth muscle contractions (Soret *et al.*, 2010) as well as creating an increase in high amplitude propagated contractions of the colon (Jouët *et al.*, 2011). Wheat dextrin has similar mechanisms of action (Hobden *et al.*, 2013, Noack *et al.*, 2013, Pasman *et al.*, 2006) and is therefore likely to increase stool frequency.

Although overall no significant differences were found in stool frequency between the three study stages, subject six did have an increase from four stools/week in the OBS stage, to an average of five stools/week in week 3&4 of the PB stage to an average of 14 stools/week in the WD stage. Based on this result, WD may have an effect on increasing stool frequency in some subjects but not in others. Different results between individuals may be explained by variations in gut microbiota between individuals as fermentation of a dietary fibre may depend not only on the properties of the fibre but also on the composition of the gut microbiota (Stewart *et al.*, 2009). In the study by Stewart *et al.* (2009) *Lactobacillus reuteri* which naturally exists in the human digestive tract was added to yoghurt and was found to alter the fermentation profile of inulin but not wheat dextrin. Although wheat dextrin was not affected by *Lactobacillus reuteri*, other microbiota may have preferentially fermented WD as *Lactobacillus reuteri* did with inulin. Since bacteria preferentially ferment different types of soluble fibres and people have differing microbiota, it is logical that fibre supplements will work best in certain people with the most appropriate microflora. Having a larger sample size would be necessary in the future to investigate whether wheat dextrin could have an effect on stool frequency in more individuals.

5.5 Stool form

The current study found no significant differences in stool form (p =0.549) or percentage of ideal stools formed (p =0.253) between any weeks when comparing the OBS and WD stage, OBS and PB stage or WD and PB stage Although no significant differences were found in the current study, other studies using soluble fibre did find significant differences in stool form compared to a control. Improvements were found using PHGG (Polymeros *et al.*, 2014), psyllium (Ashraf *et al.*, 1995, McRorie *et al.*, 1998), galacto-oligosaccharide (GOS) (Sairanen *et al.*, 2007) and fructo-oligosaccharide (FOS) (Meksawan *et al.*, 2014). The main difference between these studies and the current study is the number of subjects. In the other studies that found significant differences, in all but one of the studies, the minimum number of subjects used was 22 compared to the current study in which only seven completed the trial, one of whose data could not be included due to non-compliance. The one study that used fewer subjects (n =9) was that of Meksawan *et al.* (2014) which had a similar design to the current study. This was a randomised, double blind, placebo controlled study in which PD patients received 20 grams of FOS or placebo for 30 days with a 14 day washout period between. This study found improvements in stool form from type one (hard) in the placebo to type four (ideal) during the treatment period. It is possible fructo-oligosaccharide may be superior to wheat dextrin in improving stool form. However, when looking at the current study, ideal stools formed did increase by more than 20% in subjects 1, 4, 6 and 7 (67% of subjects) from the OBS stage to week 3&4 of the WD and PB stages. Soluble fibre has been shown to act as a stool normaliser in other studies, especially in those using subjects with irritable bowel syndrome (IBS) (Chutkan *et al.*, 2012). As with IBS, renal dialysis patients can often have stools which are either below (hard) or above (loose) the ideal stool form due to the unpredictability of using laxatives to avoid constipation (Sutton *et al.*, 2014). This unpredictability of laxatives may be a reason for the significant negative correlation found in the current study between the percentage of ideal stools and number of times laxatives were used. Although wheat dextrin did not show qualities as a stool normaliser compared to placebo, it did show increases in ideal stool percentage when compared to the OBS

stage in some subjects. This may be due to wheat dextrin's effect in producing a high amount of short chain fatty acids (SCFA) (Stewart *et al.*, 2009). A high SCFA absorption is associated with a high water and salt absorption which may reduce the incidence of diarrhoea (van den Heuvel *et al.*, 2005). Due to this mechanism of action, further research looking at wheat dextrin as a stool normaliser involving more subjects would be of interest.

Of interest in the current study was a correlation found between the variables stool form and stool frequency (n =7, p =0.081). It appears that as stool form becomes greater (i.e. stools become looser), it is associated with passing fewer stools per week. This is the opposite to what we would expect with hard stools usually being associated with fewer stools due to a long gut transit time and loose stools being associated with an increase in stools due to a faster gut transit time (Markland *et al.*, 2013). One possible reason for the unexpected correlation in the current study may be because the average stool form for each subject in the correlation was between a narrow range of 3 and 4.5 on the BSFS. These stool types are considered normal (between 3 and 5), not loose, or hard. This result therefore has no clinical relevance as the stool form is within a narrow, healthy range. We would expect that with more subject numbers, there would be more chance of obtaining results in stool form outside the normal range which would likely affect the correlation, potentially reversing it.

5.6 Quality of life

The current study found no significant differences in quality of life (QOL) between any weeks when comparing the OBS and WD stage, OBS and PB stage or WD and PB stage. This finding was across all QOL domains including physical discomfort (p =0.270), psychosocial discomfort (p =0.171), worries and concerns (p =0.632), and satisfaction (p =0.291). It is not surprising that no significant results for QOL were found as there were no significant findings for stool frequency, stool form or laxative use which are known to affect QOL. From subject reports over the phone, there was some difficulty in adding both the WD and PB powders to foods and drinks due to the large volume of powder needed. Keeping a record of bowel habits, laxative use and supplement taken for a 10 week period was also reported to be difficult for some subjects. These two

difficulties experienced may have impacted on QOL during the study as well as compliance. However the protocol was the same for both the WD and PB stage and no one stage was reported by subjects as being more or less difficult than the other. Although not significant, compared to the OBS stage, overall QOL scores were more than 20% worse in the WD stage in subjects 3, 5, 6, and 7. In addition, QOL scores were more than 20% worse in the WD stage than the PB stage in subjects 1, 4, 5, 6 and 7. Quality of life scores in the WD stage appear to be consistently worse than QOL scores in both the OBS and PB. This may be due to a possible increase in gas production which can occur when fermentable soluble fibres are consumed. Wheat dextrin is known to produce less gas and more consistently over time than inulin and PHGG (Noack *et al.*, 2013, Stewart *et al.*, 2009). However, wheat dextrin still produces significantly more flatulence than a maltodextrin placebo taken at doses of 30 g per day but not at doses of 15 g per day (van den Heuvel *et al.*, 2004). With subjects taking on average just over 20 g per day in the current study, an increase in flatulence is possible, which may explain a tendency for poorer QOL scores while taking wheat dextrin compared to placebo. Although it appears QOL scores were negative for the WD stage, scores of all subjects except one were under 1.5 on the Likert scale which has a range of zero to four with four being the worst QOL (Section 4.6, Figure 4.13). This puts these scores into perspective on a scale which has the potential for much larger variations in QOL. A larger sample size would increase the chances of establishing whether wheat dextrin has an effect on QOL.

No previous interventions have investigated whether a fibre supplement can improve QOL in constipated subjects. A patient perspective on constipation by Johanson and Kralstein (2007) did find that of 268 patients who were taking fibre supplements, 64% were not completely satisfied with the ability of fibre to improve their QOL. However, if a fibre supplement can reduce constipation in a controlled intervention, improvements in QOL would be expected due to constipation being associated with a decreased QOL in the renal dialysis (Strid *et al.*, 2002, Zhang *et al.*, 2013) and general population (Belsey *et al.*, 2010, Johanson and Kralstein, 2007). This is in line with findings in the current study which found that as QOL scores improved, it was significantly correlated with increases in stool frequency. This is highlighted in subject

two who had the worst overall QOL score as well as the lowest stool form of 2.5 stools per week which meets part of the ROME III criteria for constipation. Due to the ease of administration of the QOL survey, it would be valuable for future fibre studies to investigate if reductions in measures of constipation are associated with improvements in QOL.

5.7 Individual subject's data

Since improved bowel function can manifest in a number of ways, it is important to consider all of the measures together to assess the impact of wheat dextrin and placebo in bowel performance in individual subjects.

Subject 1: When subject one consumed the WD supplement, their percent of ideal stools were 100% better compared to OBS and PB stages. Their stool frequency was relatively unchanged, as was their laxative use. Their overall QOL scores, although within a narrow range on the scale (1.75 – 2.25 / 4.0), were still more than 20% better in the WD stage compared to PB. Due to the large increases in stool form in this subject and negligible changes in other results, it appears that wheat dextrin may be beneficial in improving bowel performance for this subject.

Subject 3: For subject three, their percent of ideal stools were relatively unchanged between the three stages of the study, as was their laxative use. Stool frequency for subject three declined slightly over both the WD and PB stages compared to the OBS stage. Their overall QOL scores were again within a narrow range (0.75 – 1.1 / 4.0) but were still 20% worse in the PB stage and WD stage compared to the OBS stage. It appears that supplementation with either the WD or PB was not beneficial in improving bowel performance for subject three.

Subject 4: For subject four, their percent of ideal stools improved by 80% between the OBS and WD stage and 75% between the OBS and PB stages. Laxative use declined by 31% during the WD stage compared to the PB and OBS stages. Stool frequency was mostly unchanged in the WD or PB stage compared to the OBS stage. Subject four's overall QOL scores were within a narrow range (0.45 – 1.6 / 4.0) but were 33% better in the WD stage compared to the OBS stage and 71% better between the OBS stage

compared to the PB stage. Due to the clear reduction in laxative use compared to the OBS and PB stages in this subject, with negligible changes in other results compared to placebo, it appears that wheat dextrin may be beneficial in improving bowel performance for subject four.

Subject 5: The percent of ideal stools for subject five were relatively unchanged between the three stages of the study as was their laxative use. Stool frequency for subject five declined slightly during the WD stage compared to placebo and remained the same between OBS and PB. Subject five's QOL scores were within a narrow range (0.2 – 1.4 / 4.0), but were 133% worse during the WD stage than the OBS stage and 67% better in the PB stage compared to the OBS stage. It appears that WD is not beneficial for subject five due to worsening overall QOL scores, slight reduction in stool frequency and no other changes.

Subject 6: For subject six the percent of ideal stools increased from 0% in the OBS stage to 100% in both the WD and PB stages. Laxative use was nil throughout all study stages. Stool frequency showed a clear improvement with WD (14 stools/week) compared to both OBS (4 stools/week) and PB (5 stools/week). Overall QOL scores were within a narrow range (0.3 – 0.4 / 4.0) and showed no change between stages. It appears that wheat dextrin may be beneficial in improving bowel function for subject 6 due to clear increases in stool frequency compared to PB with no other significant results compared to PB.

Subject 7: For subject seven, the percentage of ideal stools increased 33% from the OBS to PB stage, but did not increase between the OBS and WD stage. Laxative use declined from 11.5 times per week in the OBS stage to 4 times per week during the WD stage and 2.5 times per week in the PB stage. Stool frequency declined from 12.5 stools per week in the OBS stage to nine stools per week in the WD stage and to 9 stools per week in the PB stage. Overall QOL scores were again within a narrow range (0.7 – 1.1 / 4.0), but were still 57% worse in the WD stage compared to the OBS stage and 42% worse in the PB stage compared to the OBS stage. It appears that the PB is beneficial in improving stool form when compared to WD in subject seven. Although both the WD and PB were able to reduce laxative use compared to the OBS stage, the

PB created the greatest reduction. Overall, it appears that PB supplementation was more beneficial in improving bowel function than the WD in subject seven.

When observing individual data, it appears as though wheat dextrin is beneficial in improving at least one aspect of bowel performance for three of the six subjects who completed the study. As mentioned in Section 5.4, a reason for positive results in a select group may be due to individual subject's differing gut microbiota which may help them preferentially ferment wheat dextrin (Stewart *et al.*, 2009). Having a larger sample size would be necessary in the future to investigate whether wheat dextrin could have an effect on stool frequency in more individuals.

Chapter Six

6.0 Conclusion

6.1 Research problem and aims of the research study

Renal dialysis patients often suffer from constipation with reported rates from across the world varying between 14% and 71% (Wu *et al.*, 2004, Yasuda *et al.*, 2002, Yasuda *et al.*, 1995, Zhang *et al.*, 2013) . The reason for the high prevalence is often multifactorial, including polypharmacy, dietary restrictions causing a low fibre intake, low fluid intake and low rates of exercise (Iacono, 2008, Johansen *et al.*, 2000, Luttrell *et al.*, 2014). Constipation within this group is associated with a decreased QOL as well as specific complications such as peritonitis in PD patients (Mitrović *et al.*, 2015, Strid *et al.*, 2002, Zhang *et al.*, 2013). The treatment of constipation in renal dialysis patients is therefore of great importance. Currently, the primary treatment involves the use of laxatives, however, laxatives can create unpredictable stools, cause unpleasant side effects and the long term effects are not known (Jones *et al.*, 2002, Ruston *et al.*, 2013). Therefore an alternative solution is necessary. Fibre supplementation can be used to reduce constipation (Eswaran *et al.*, 2013), however the current fibre subsidised supplement available in NZ requires the addition of water for its consumption and effectiveness. This type of product is therefore not suitable for renal patients who are normally on a fluid restriction. Wheat dextrin is a soluble fibre supplement that does not need to be taken with water and has a minimal potassium and phosphate content, making it ideal for renal dialysis patients. Although other soluble fibre supplements such as inulin and PHGG have been shown to reduce constipation (European Food Safety Authority, 2015, Polymeros *et al.*, 2014), they are not available for use in NZ. Wheat dextrin is the only soluble fibre supplement readily available in New Zealand. There is a paucity of data regarding the effects of wheat dextrin to reduce constipation. This has led to the aim of the current pilot study to examine the effectiveness of a wheat dextrin fibre supplement on bowel performance

in free living patients who are currently receiving either peritoneal or haemodialysis in the Northland District Health Board.

6.2 The main findings of the research study

The objectives of this study were to determine whether the introduction of a wheat dextrin fibre supplement to the diet of free living patients on dialysis in Northland DHB will improve bowel performance, reduce laxative use, and improve quality of life.

Improvements in bowel performance were measured using stool form and stool frequency. Neither of these measures was significantly different between the OBS, WD or PB stages. However, one subject did show a clear benefit of WD increasing stool frequency compared to PB. When stool form was expressed as percentage of ideal stools, it appeared that both the wheat dextrin and placebo had a stool normalising effect from 60.8% of stools being ideal in the OBS stage to 88.1% by the end of the WD stage and 84.3% by the end of the PB stage. This increase in percent ideal stool type was clearly demonstrated by two subjects for both PB and WD, one subject for PB only and one subject for WD only. Overall there is not clear evidence that the objective of wheat dextrin improving bowel performance has been met. There is however some evidence of wheat dextrin improving bowel performance in some individuals. This finding warrants further investigation of the current objective using a study with more subjects.

No significant differences were found between laxsol use, lactulose use and the number of occasions laxatives were used between the OBS, WD or PB stages. One subject did reduce their laxative use by 31% in the WD stage compared to the OBS and PB stages. The objective of whether wheat dextrin can reduce laxative use in renal dialysis patients was not met. However, as it was shown to be effective in one subject, further investigation into this objective is warranted using a larger number of subjects.

There was also no significant difference in QOL between the OBS, WD, or PB stages of the study. Although not significant, the analysis of overall QOL scores in individual subjects showed 83% of subjects had QOL scores which were at least 20% worse in the

WD stage than in the PB stage. Although this result appears negative for WD, taking into account where all the scores lie on the Likert scale puts this result into perspective. With the exception of one subject, QOL scores for individuals in all stages were very low being between zero and 1.5 on a four point Likert scale (with a lower score being a better QOL). Further studies using more subjects are needed to determine if WD supplementation has an effect on QOL in renal dialysis patients.

In summary, the introduction of a wheat dextrin fibre supplement to the diet of free living patients on dialysis in Northland DHB found that wheat dextrin may work to improve bowel performance in some individuals. Although statistically, no significant differences were found in any of the objectives measured, observing data from individual subjects showed WD may improve stool frequency and stool form and reduce laxative use compared to placebo in some individuals. If this individual effect is dependent on individuals gut microflora, further research should be repeated using a larger sample size in order to show the efficacy of wheat dextrin on improving bowel performance.

6.3 Strengths

This is the first study to determine the effectiveness of a wheat dextrin fibre supplement on bowel performance in renal dialysis patients. Other studies have used PHGG, IMO and FOS fibre supplements with similar aims to the current study (Meksawan *et al.*, 2014, Sutton *et al.*, 2007a, Sutton *et al.*, 2014, Wang *et al.*, 2001). This study however has the strength of being specific to the New Zealand population as wheat dextrin is the only readily available soluble fibre supplement in New Zealand. The study gives insight into the use of wheat dextrin for renal dialysis patients who are a population in need and have no alternative fibre supplement to use.

Another strength of the study was the study design. Firstly, the study used a placebo so that subjects in the study were not biased towards the treatment. The placebo was well matched to the wheat dextrin supplement, and any differences were minimised by encouraging the addition of both powders to certain food types (Appendix A). Secondly, the study used a cross over design where subjects were their own controls.

This study design reduces the influence of cofounding covariates and reduces the number of subjects needed to find statistical significance; the latter being especially important in the current study considering the small number of potential subjects. Thirdly, the study used prospective, patient-held records as a way of recording bowel habits. Other studies have used retrospective questionnaires in order to report constipation, which depends on the patient's ability to recall symptoms and bowel habits (Dukas *et al.*, 2003, Zhang *et al.*, 2013). The use of the patient-held record clearly outlined what to record and the prospective aspect increased the chance of accurate recordings as it did not rely on memory.

6.4 Limitations

The major limitation of the study was the inability to recruit subjects as well as retain subjects throughout the study period. Having a larger number of subjects complete the study would have increased the chance of finding significant differences in the results. One reason for having difficulty recruiting subjects was due to the area the study was carried out in. Northland District Health Board is a relatively small DHB, servicing 169, 053 patients over a large geographic area (Ministry of Health, 2015b). Auckland DHB on the other hand services 482, 015 patients over a much smaller geographic area (Ministry of Health, 2015a). This gives a smaller potential patient pool to recruit from in Northland as well as increased difficulty of physically contacting patients for recruitment and follow up. It is also common for renal dialysis patient to have co-morbidities and already have demanding lifestyles due to their medical commitments such as dialysing and taking multiple medications. For these reasons, patients may have been more likely to decline to participate in further clinical interventions due to their current commitments. Although initially 21 subjects signed up for the study, only seven produced sufficient results to be included in the analysis, and of these one was removed for non-compliance. This high rate of withdrawal within the various intervention stages was due to illnesses and hospital admissions which are generally high amongst the renal dialysis patient group (Saran *et al.*, 2015). Two withdrew prior to the start of the study due to illness and four subjects withdrew due to illness during the OBS stage. One subject withdrew during the first four week stage due to having a

kidney transplant, two other subjects had data missing due to being admitted to hospital and one other withdrew in the first four week stage due to general illness. The study period being over the winter months may also have increased the chance of patient illness (Gosai and Salinger, 2007). As the study was conducted over a 12 week period, this may have been too long a time period for many to commit to. This may have caused potential subjects to reject the invitation as well as those originally recruited to withdraw. Over the study period, one subject withdrew due to time commitments and four other due to unknown reasons.

Another limitation was the study involving laxative use which makes it difficult to determine whether the results were due to the laxatives taken, or the wheat dextrin or placebo consumed or a combination of both. Although instructions were given for subjects to adjust their laxative use as their stool form changed (Appendix A), these instructions may have been confusing for some and difficult to follow accurately over time. In combination, subjects are prescribed laxatives in order to avoid constipation. Therefore it is likely subjects would have been trying to form the ideal stool and have a comfortable stool frequency before the beginning of the study as well as during the OBS stage. It then makes results of stool form and frequency in the OBS stage difficult to compare to the WD and PB stages.

As this study was the first to look at whether wheat dextrin could improve bowel performance, it would have been worthwhile to use constipated, otherwise healthy subjects who are not taking laxatives. This would have excluded any confounding factors caused by laxative use and isolated the potential of wheat dextrin to improve bowel performance. If wheat dextrin was found to improve bowel performance and/or reduce constipation, it would then be wise to move to a more complex patient group.

6.5 Use of the findings of this research study

Due to the lack of significant results in the current study, there are few recommendations that can be made in regards to the consumption of the wheat dextrin fibre supplement. It appears as though some subjects in the study were able to increase their stool frequency using wheat dextrin compared to placebo, others were able to decrease their laxative use and many were able to improve their stool form. However, the same can be said with the placebo. It is therefore not possible to confidently make recommendations regarding any benefits of wheat dextrin affecting components of bowel performance. However, as wheat dextrin has known mechanisms that can improve bowel health, it is likely that the studies limitations are reasons for finding no significant results. As wheat dextrin is the only soluble fibre supplement available on the market for renal dialysis patients, it would be wise for individual patients to try a wheat dextrin fibre supplement as it may elicit positive results on bowel performance and/or bowel health. The main use of the results and experiences from this pilot study will be in making recommendations regarding future research in this area as described in Section 6.6 below.

6.6 Recommendations for future research

- Similar, blinded studies should be used with a larger number of subjects in order to have the chance of obtaining significant results. Using a DHB with a larger pool of potential recruits in a smaller geographic area would be ideal (e.g. Auckland, Waitemata or Counties DHB).
- Investigating the effects of wheat dextrin using constipated, otherwise healthy subjects who are not taking laxatives would be beneficial. This would isolate wheat dextrin as a potential supplement to improve bowel performance without having laxatives use as a confounding variable.
- If wheat dextrin was found to be beneficial in constipated otherwise healthy individuals, it would then be wise to tests its effectiveness in renal dialysis patients.

- Further research should be carried out using wheat dextrin as a stool normaliser in those with diarrhoea and constipation. Those with combination IBS would be ideal as this subtype of IBS is associated with both constipation and diarrhoea.
- Adding the supplement to a food vehicle such as yoghurt would be an easier way for subjects to consume the fibre daily. This would also be an easy way to create a placebo and likely be better accepted by subjects in a long term intervention study. It would also be beneficial to collect subjective information from subjects regarding the best foods to add wheat dextrin to.
- Probiotics have recently been used to improve constipation (Dimidi *et al.*, 2014). Of interest would be the use of a probiotic with a prebiotic fibre supplement to see if there is a synergistic effect. Adding a prebiotic yoghurt to the above recommendation would be a practical way to include both pre and probiotics in a study.

Although the results of this pilot study were not significant, some individuals did appear to have improvements in bowel performance following the consumption of a wheat dextrin fibre supplement, which warrants further research. This study has highlighted some of the difficulties in carrying out such a trial in renal dialysis patients, and these should be taken into account when designing future trials in this population. Using a randomised placebo controlled study design without a crossover would be beneficial if a larger number of subjects could be recruited. Randomising subjects into two groups (age and sex matched) who each underwent a two week OBS stage (baseline) followed immediately by either a four week treatment period in one group or four week placebo period in the other. This would reduce the study time and subject burden, thus increasing the chance of recruiting and maintaining more subjects. It would be beneficial to repeat the study using the same dose of 20 g/day, as in the current study, over a similar time frame (4 weeks) but with the dose delivered in a food vehicle such as yoghurt. This would likely further encourage participation and compliance due to the acceptability of a food product such as yoghurt. Using the above study design with constipated otherwise healthy patients who do not take laxatives would also be

beneficial. Then if positive results were found, further investigation into the use of wheat dextrin in renal dialysis patients would be recommended.

References

Ahmed, J. & Weisberg, L. S. Hyperkalemia in dialysis patients. Seminars in dialysis, 2001. Wiley Online Library, 348-356.

Annells, M. & Koch, T. 2003. Constipation and the preached trio: diet, fluid intake, exercise. *International journal of nursing studies,* 40**,** 843-852.

Anti, M., Lamazza, A., Pignataro, G., Pretaroli, A., Armuzzi, A., Pace, V., Valenti, A., Leo, P., Iascone, E. & Castelli, A. 1998. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. *Hepatogastroenterology,* 45**,** 727-732.

Anzdata Registry Report 2014. Australia and New Zealand Dialysis and Transplant Registery Report. 35 ed. Adelaide.

Ash, S., Campbell, K., Maclaughlin, H., Mccoy, E., Chan, M., Anderson, K., Corke, K., Dumont, R., Lloyd, L. & Meade, A. 2006. Evidence based practice guidelines for the nutritional management of chronic kidney disease. *Nutrition & Dietetics,* 63**,** S33-S45.

Ashraf, W., Park, F., Lof, J. & Quigley, E. 1995. Effects of psyllium therapy on stool characteristics, colon transit and anorectal function in chronic idiopathic constipation. *Alimentary pharmacology & therapeutics,* 9**,** 639-647.

Astor, B. C., Muntner, P., Levin, A., Eustace, J. A. & Coresh, J. 2002. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). *Archives of internal medicine,* 162**,** 1401-1408.

Attaluri, A., Donahoe, R., Valestin, J., Brown, K. & Rao, S. 2011. Randomised clinical trial: dried plums (prunes) vs. psyllium for constipation. *Alimentary pharmacology & therapeutics,* 33**,** 822-828.

Australian Bureau of Statistics 2013. Australian Health Survey. Biomedical Results for Chronic Diseases. Canberra: ABS.

Belsey, J., Greenfield, S., Candy, D. & Geraint, M. 2010. Systematic review: impact of constipation on quality of life in adults and children. *Alimentary pharmacology & therapeutics,* 31**,** 938-949.

Brown, W. J., Mishra, G., Lee, C. & Bauman, A. 2000. Leisure time physical activity in Australian women: relationship with well being and symptoms. *Research quarterly for exercise and sport,* 71**,** 206-216.

Candy, B., Jones, L., Larkin, P. J., Vickerstaff, V., Tookman, A. & Stone, P. 2015. Laxatives for the management of constipation in people receiving palliative care. *The Cochrane Library*.

Chan, A., Leung, G., Tong, T. & Wong, N. 2007. Increasing dietary fiber intake in terms of kiwifruit improves constipation in Chinese patients. *World Journal of Gastroenterology,* 13**,** 4771.

Cheskin, L. J., Kamal, N., Crowell, M. D., Schuster, M. M. & Whitehead, W. E. 1995. Mechanisms of constipation in older persons and effects of fiber compared with placebo. *Journal of the American Geriatrics Society,* 43**,** 666-669.

Cheskin, L. J., Mitola, A. H., Ridoré, M., Kolge, S., Hwang, K. & Clark, B. 2009. A naturalistic, controlled, crossover trial of plum juice versus psyllium versus control for improving bowel function. *The Internet Journal of Nutrition and Wellness,* 7.

Chutkan, R., Fahey, G., Wright, W. L. & Mcrorie, J. 2012. Viscous versus nonviscous soluble fiber supplements: Mechanisms and evidence for fiber-specific health benefits. *Journal of the American Academy of Nurse Practitioners,* 24**,** 476-487.

Cobo, G., Gallar, P., Gama-Axelsson, T., Di Gioia, C., Qureshi, A. R., Camacho, R., Vigil, A., Heimbürger, O., Ortega, O. & Rodriguez, I. 2014. Clinical determinants of reduced physical activity in hemodialysis and peritoneal dialysis patients. *Journal of nephrology***,** 1-8.

Combe, C., Mccullough, K. P., Asano, Y., Ginsberg, N., Maroni, B. J. & Pifer, T. B. 2004. Kidney Disease Outcomes Quality Initiative (K/DOQI) and the Dialysis Outcomes and Practice Patterns Study (DOPPS): Nutrition guidelines, indicators, and practices. *American Journal of Kidney Diseases,* 44, Supplement 2**,** 39-46. Available: DOI http://dx.doi.org/10.1053/j.ajkd.2004.08.010.

Dahl, W. J., Whiting, S. J., Isaac, T. M., Weeks, S. J. & Arnold, C. J. 2005. Effects of thickened beverages fortified with inulin on beverage acceptance, gastrointestinal function, and bone resorption in institutionalized adults. *Nutrition,* 21**,** 308-311.

Davison, S. N. & Jhangri, G. S. 2005. The impact of chronic pain on depression, sleep, and the desire to withdraw from dialysis in hemodialysis patients. *Journal of pain and symptom management,* 30**,** 465-473.

De Schryver, A. M., Keulemans, Y. C., Peters, H. P., Akkermans, L. M., Smout, A. J., De Vries, W. R. & Van Berge-Henegouwen, G. P. 2005. Effects of regular physical activity on defecation pattern in middle-aged patients complaining of chronic constipation. *Scandinavian journal of gastroenterology,* 40**,** 422-429.

Den Hond, E., Geypens, B. & Ghoos, Y. 2000. Effect of high performance chicory inulin on constipation. *Nutrition Research,* 20**,** 731-736.

Dimidi, E., Christodoulides, S., Fragkos, K. C., Scott, S. M. & Whelan, K. 2014. The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. *The American journal of clinical nutrition,* 100**,** 1075-1084.

Drossman, D. A. & Dumitrascu, D. L. 2006. Rome III: New standard for functional gastrointestinal disorders. *Journal of Gastrointestinal and Liver Diseases,* 15**,** 237.

Dukas, L., Willett, W. C. & Giovannucci, E. L. 2003. Association between physical activity, fiber intake, and other lifestyle variables and constipation in a study of women. *The American journal of gastroenterology,* 98**,** 1790-1796.

Eknoyan, G., Lameire, N., Barsoum, R., Eckardt, K.-U., Levin, A., Levin, N., Locatelli, F., Macleod, A., Vanholder, R., Walker, R. & Wang, H. 2004. The burden of kidney disease: improving global outcomes. *Kidney international,* 66**,** 1310-4. Available: DOI 10.1111/j.1523-1755.2004.00894.x.

Eswaran, S., Muir, J. & Chey, W. D. 2013. Fiber and functional gastrointestinal disorders. *The American journal of gastroenterology,* 108**,** 718-727.

European Food Safety Authority 2015. Scientific opinion on the substantiation of a health claim related to" native chicory inulin" and maintenance of normal defecation by increasing stool frequency pursuant to Article 13.5 of Regulation (EC) No 1924/2006. *EFSA Journal,* 13.

Fenn, G., Wilkinson, P., Lee, C. & Akbar, F. 1986. A general practice study of the efficacy of Regulan in functional constipation. *The British journal of clinical practice,* 40**,** 192.

Findlay, M. & Isles, C. 2015a. Haemodialysis. *Clinical Companion in Nephrology.* Springer.

Findlay, M. & Isles, C. 2015b. Peritoneal Dialysis. *Clinical Companion in Nephrology.* Springer.

Foley, R. N., Parfrey, P. S. & Sarnak, M. J. 1998. Epidemiology of cardiovascular disease in chronic renal disease. *Journal of the American Society of Nephrology: JASN,* 9**,** S16-23.

Frizelle, F. & Barclay, M. 2007. Constipation in adults. *Clinical evidence,* 2007.

Gosai, A. & Salinger, J. 2007. How is climate linked to respiratory infections in Auckland. *Water and Atmosphere,* 14**,** 22-23.

Guérin-Deremaux, L., Pochat, M., Reifer, C., Wils, D., Cho, S. & Miller, L. E. 2011. The soluble fiber NUTRIOSE induces a dose-dependent beneficial impact on satiety over time in humans. *Nutrition research,* 31**,** 665-672.

Guérin-Deremaux, L., Pochat, M., Reifer, C., Wils, D., Cho, S. & Miller, L. E. 2013. Dose-response impact of a soluble fiber, NUTRIOSE®, on energy intake, body weight and body fat in humans. *Global Epidemic Obesity,* 1**,** 2.

Hallan, S. I., Ritz, E., Lydersen, S., Romundstad, S., Kvenild, K. & Orth, S. R. 2009. Combining GFR and Albuminuria to Classify CKD Improves Prediction of ESRD. *Journal of the American Society of Nephrology,* 20**,** 1069-1077. Available: DOI 10.1681/asn.2008070730.

Hedayati, S. S., Bosworth, H. B., Briley, L. P., Sloane, R. J., Pieper, C. F., Kimmel, P. L. & Szczech, L. A. 2008. Death or hospitalization of patients on chronic hemodialysis is associated with a physician-based diagnosis of depression. *Kidney international,* 74**,** 930-936.

Herzog, C. A., Asinger, R. W., Berger, A. K., Charytan, D. M., Díez, J., Hart, R. G., Eckardt, K.-U., Kasiske, B. L., Mccullough, P. A., Passman, R. S., Deloach, S. S., Pun, P. H. & Ritz, E. 2011. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International,* 80**,** 572-586. Available: DOI 10.1038/ki.2011.223.

Higgins, P. D. & Johanson, J. F. 2004. Epidemiology of constipation in North America: a systematic review. *The American journal of gastroenterology,* 99**,** 750-759.

Hobden, M. R., Martin-Morales, A., Guérin-Deremaux, L., Wils, D., Costabile, A., Walton, G. E., Rowland, I., Kennedy, O. B. & Gibson, G. R. 2013. In Vitro Fermentation of NUTRIOSE® FB06, a Wheat Dextrin Soluble Fibre, in a Continuous Culture Human Colonic Model System.

Hongisto, S., Paajanen, L., Saxelin, M. & Korpela, R. 2006. A combination of fibre-rich rye bread and yoghurt containing Lactobacillus GG improves bowel function in women with self-reported constipation. *European journal of clinical nutrition,* 60**,** 319-324.

Hurdon, V., Viola, R. & Schroder, C. 2000. How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *Journal of pain and symptom management,* 19**,** 130-136.

Iacono, S. A. 2008. Medication side effects: barriers to the management of fluid intake. *Dialysis & Transplantation,* 37**,** 196-201.

Inker, L. A., Astor, B. C., Fox, C. H., Isakova, T., Lash, J. P., Peralta, C. A., Kurella Tamura, M. & Feldman, H. I. 2014. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 63**,** 713-35. Available: DOI 10.1053/j.ajkd.2014.01.416.

Johansen, K. L., Chertow, G. M., Ng, A. V., Mulligan, K., Carey, S., Schoenfeld, P. Y. & Kent-Braun, J. A. 2000. Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney international,* 57**,** 2564-2570.

Johanson, J. & Kralstein, J. 2007. Chronic constipation: a survey of the patient perspective. *Alimentary pharmacology & therapeutics,* 25**,** 599-608.

Jolly, S., Chatatalsingh, C., Bargman, J., Vas, S., Chu, M. & Oreopoulos, D. 2001. Excessive weight gain during peritoneal dialysis. *The International journal of artificial organs,* 24**,** 197-202.

Jones, M. P., Talley, N. J., Nuyts, G. & Dubois, D. 2002. Lack of objective evidence of efficacy of laxatives in chronic constipation. *Digestive diseases and sciences,* 47**,** 2222-2230.

Jouët, P., Sabaté, J. M., Coffin, B., Lémann, M., Jian, R. & Flourié, B. 2011. Fermentation of starch stimulates propagated contractions in the human colon. *Neurogastroenterology & Motility,* 23**,** 450-e176.

Kalantar-Zadeh, K., Ikizler, T. A., Block, G., Avram, M. M. & Kopple, J. D. 2003. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *American Journal of Kidney Diseases,* 42**,** 864-881. Available: DOI http://dx.doi.org/10.1016/j.ajkd.2003.07.016.

Kalantar-Zadeh, K., Kopple, J. D., Deepak, S., Block, D. & Block, G. 2002. Food intake characteristics of hemodialysis patients as obtained by food frequency questionnaire. *Journal of Renal Nutrition,* 12**,** 17-31.

Kalantar-Zadeh, K., Regidor, D. L., Kovesdy, C. P., Van Wyck, D., Bunnapradist, S., Horwich, T. B. & Fonarow, G. C. 2009. Fluid retention is associated with cardiovascular

mortality in patients undergoing long-term hemodialysis. *Circulation,* 119**,** 671-679.
Kalantar-Zadeh, K., Tortorici, A. R., Chen, J. L. T., Kamgar, M., Lau, W.-L., Moradi, H., Rhee, C. M., Streja, E. & Kovesdy, C. P. 2015. Dietary Restrictions in Dialysis Patients: Is There Anything Left to Eat? *Seminars in Dialysis,* 28**,** 159-168. Available: DOI 10.1111/sdi.12348.
Kazama, J. J. 2009. Oral phosphate binders: history and prospects. *Bone,* 45**,** S8-S12.
Keleş, M., Cetinkaya, R., Uyanik, A., Acemoğlu, H., Eroğlu, F. & Uyanik, M. H. 2010. Peritoneal dialysis-related peritonitis: an analysis of risk factors in Northeast Anatolia*. *Turkish Journal of Medical Sciences,* 40**,** 643-650.
Khan, F. & Simon, C. 2010. Constipation in adults. *InnovAiT: The RCGP Journal for Associates in Training,* 3**,** 279-284.
Khoueiry, G., Waked, A., Goldman, M., El-Charabaty, E., Dunne, E., Smith, M., Kleiner, M., Lafferty, J., Kalantar-Zadeh, K. & El-Sayegh, S. 2011. Dietary intake in hemodialysis patients does not reflect a heart healthy diet. *Journal of Renal Nutrition,* 21**,** 438-447.
Kimmel, P. L. 2002. Depression in patients with chronic renal disease: what we know and what we need to know. *Journal of psychosomatic research,* 53**,** 951-956.
Leung, L., Riutta, T., Kotecha, J. & Rosser, W. 2011. Chronic constipation: an evidence-based review. *The Journal of the American Board of Family Medicine,* 24**,** 436-451.
Levey, A. S., Eckardt, K.-U., Tsukamoto, Y., Levin, A., Coresh, J., Rossert, J., De Zeeuw, D., Hostetter, T. H., Lameire, N. & Eknoyan, G. 2005. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney international,* 67**,** 2089-100. Available: DOI 10.1111/j.1523-1755.2005.00365.x.
Longstreth, G. F., Thompson, W. G., Chey, W. D., Houghton, L. A., Mearin, F. & Spiller, R. C. 2006. Functional bowel disorders. *Gastroenterology,* 130**,** 1480-1491.
López, R. J., Martínez, G. A., Luque, A., Pons, M. J., Vargas, A. A., Iglesias, J., Hernández, M. & Villegas, J. 2007. [The effect of a fibre enriched dietary milk product in chronic primary idiopatic constipation]. *Nutricion hospitalaria,* 23**,** 12-19.
Luttrell, K. J., Beto, J. A. & Tangney, C. C. 2014. Selected Nutrition Practices of Women on Hemodialysis and Peritoneal Dialysis: Observations From the NKF-CRN Second National Research Question Collaborative Study. *Journal of Renal Nutrition,* 24**,** 81-91.
Lynch, K. E., Lynch, R., Curhan, G. C. & Brunelli, S. M. 2011. Prescribed Dietary Phosphate Restriction and Survival among Hemodialysis Patients. *Clinical Journal of the American Society of Nephrology,* 6**,** 620-629. Available: DOI 10.2215/cjn.04620510.
Macfarlane, S., Macfarlane, G. & Cummings, J. T. 2006. Review article: prebiotics in the gastrointestinal tract. *Alimentary pharmacology & therapeutics,* 24**,** 701-714.
Maeda, H., Uemura, T., Nasu, M., Iwata, N., Yoshimura, J. & Sakai, S. 2012. PARTIALLY HYDROLYZED GUAR GUM INTAKE AMELIORATES CONSTIPATION, IMPROVES NUTRITIONAL STATUS AND REDUCES INDOXYLSULFURIC ACID IN DIALYSIS PATIENTS. *Kidney Research and Clinical Practice,* 31**,** A53.
Markland, A. D., Palsson, O., Goode, P. S., Burgio, K. L., Busby-Whitehead, J. & Whitehead, W. E. 2013. Association of low dietary intake of fiber and liquids with constipation: evidence from the National Health and Nutrition Examination Survey. *The American journal of gastroenterology,* 108**,** 796-803.
Marlett, J. A., Li, B., Patrow, C. J. & Bass, P. 1987. Comparative laxation of psyllium with and without senna in an ambulatory constipated population. *The American journal of gastroenterology,* 82**,** 333-337.
Marteau, P., Jacobs, H., Cazaubiel, M., Signoret, C., Prevel, J.-M. & Housez, B. 2011. Effects of chicory inulin in constipated elderly people: a double-blind controlled trial. *International journal of food sciences and nutrition,* 62**,** 164-170.

Mcrorie, J., Daggy, B., Morel, J., Diersing, P., Miner, P. & Robinson, M. 1998. Psyllium is superior to docusate sodium for treatment of chronic constipation. *Alimentary Pharmacology and Therapeutics,* 12**,** 491.
Mcrorie, J. W. & Fahey, G. C. 2013. A review of gastrointestinal physiology and the mechanisms underlying the health benefits of dietary fiber: Matching an effective fiber with specific patient needs. *Clinical Nursing Studies,* 1**,** p82.
Meksawan, K., Chaotrakul, C., Leeaphorn, N., Gonlchanvit, S., Eiam-Ong, S. & Kanjanabuch, T. 2014. EFFECTS OF FRUCTO-OLIGOSACCHARIDE SUPPLEMENTATION ON CONSTIPATION IN ELDERLY CONTINUOUS AMBULATORY PERITONEAL DIALYSIS PATIENTS. *Peritoneal Dialysis International***,** pdi. 2014.00015.
Merkus, M. P., Jager, K. J., Dekker, F. W., De Haan, R. J., Boeschoten, E. W. & Krediet, R. 1999. Physical symptoms and quality of life in patients on chronic dialysis: results of The Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD). *Nephrology Dialysis Transplantation,* 14**,** 1163-1170.
Mimidis, K., Mourvati, E., Kaliontzidou, M., Papadopoulos, V., Thodis, E., Kartalis, G. & Vargemezis, V. 2005. Efficacy of polyethylene glycol in constipated CAPD patients. *Peritoneal dialysis international,* 25**,** 601-603.
Ministry of Health. 2015a. *Auckland DHB* [Online]. Available: http://www.health.govt.nz/new-zealand-health-system/my-dhb/auckland-dhb [Accessed 21st September 2015].
Ministry of Health. 2015b. *Northland DHB* [Online]. Available: http://www.health.govt.nz/new-zealand-health-system/my-dhb/northland-dhb/population-northland-dhb [Accessed 21st September 2015].
Ministry of Health 2015c. Publicly funded hospital discharges - 1 July 2012 to 30 June 2013. Wellington: Ministry of Health.
Mitrović, M., Majster, Z., Damjanović, T., Janković, A., Bajčetić, S., Popović, J., Đurić, Ž., Đorđević, T., Đurić, P. & Todorov, V. 2015. THE PREVALENCE, SEVERITY AND DIVERSITY OF GASTROINTESTINAL SYMPTOMS IN HEMODIALYSIS AND PERITONEAL DIALYSIS PATIENTS. *Nephrology Dialysis Transplantation,* 30**,** iii612-iii612.
Murakami, K., Okubo, H. & Sasaki, S. 2006. Dietary intake in relation to self-reported constipation among Japanese women aged 18–20 years. *European journal of clinical nutrition,* 60**,** 650-657.
Nakamura, H., Kitazawa, K., Kato, K., Inada, Y., Kato, N., Takahashi, M., Uekusa, T., Mitsugu, A. & Sugisaki, T. 2004. Stercoral perforation of the sigmoid colon in a patient undergoing CAPD: case report. *Peritoneal dialysis international,* 24**,** 399-401.
National Health and Medical Research Council. 2006. *Nutrient reference values for Australia and New Zealand – Dietary Fibre* [Online]. Available: https://www.nrv.gov.au/nutrients/dietary-fibre [Accessed July 14 2015].
National Kidney Foundation 2013. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements,* 3**,** 1-150.
National Kidney Foundation. 2015a. *Global Facts: About Kidney Disease* [Online]. Available: https://www.kidney.org/kidneydisease/global-facts-about-kidney-disease#_ENREF_1 [Accessed 10 December 2015].
National Kidney Foundation. 2015b. *How your kidneys work* [Online]. Available: https://www.kidney.org/kidneydisease/howkidneyswrk#signs [Accessed July 13 2015].
National Kidney Foundation. 2015c. *Potassium and your CKD Diet* [Online]. Available: https://www.kidney.org/atoz/content/potassium [Accessed May 15 2015].
National Renal Advisory Board 2006. New Zealand's Renal Services: Towards a national strategic plan. Ministry of Health.
Noack, J., Timm, D., Hospattankar, A. & Slavin, J. 2013. Fermentation Profiles of Wheat Dextrin, Inulin and Partially Hydrolyzed Guar Gum Using an in Vitro Digestion

Pretreatment and in Vitro Batch Fermentation System Model. *Nutrients,* 5**,** 1500-1510.
Nunes, F., Nunes, C., Levis, E., Dantas, F., Varella, R., Rubens, M. & Geller, M. 2005. A double-blind, placebo controlled clinical evaluation of Psyllium husk and microencapsulated paraffin in the treatment of constipation. *REVISTA BRASILEIRA DE MEDICINA,* 62**,** 352.
Pasman, W., Wils, D., Saniez, M. & Kardinaal, A. 2006. Long-term gastrointestinal tolerance of NUTRIOSE® FB in healthy men. *European journal of clinical nutrition,* 60**,** 1024-1034.
Passmore, A., Davies, K., Flanagan, P., Stoker, C. & Scott, M. 1993. A comparison of Agiolax and lactulose in elderly patients with chronic constipation. *Pharmacology,* 47**,** 249-252.
Peppas, G., Alexiou, V. G., Mourtzoukou, E. & Falagas, M. E. 2008. Epidemiology of constipation in Europe and Oceania: a systematic review. *BMC gastroenterology,* 8**,** 5.
Polymeros, D., Beintaris, I., Gaglia, A., Karamanolis, G., Papanikolaou, I. S., Dimitriadis, G. & Triantafyllou, K. 2014. Partially hydrolyzed guar gum accelerates colonic transit time and improves symptoms in adults with chronic constipation. *Digestive diseases and sciences,* 59**,** 2207-2214.
Putcha, N. & Allon, M. Management of hyperkalemia in dialysis patients. Seminars in dialysis, 2007. Wiley Online Library, 431-439.
Quigley, E., Talley, N. J. & Schoenfeld, P. 2005. An evidence-based approach to the management of chronic constipation in North America. *American Journal of Gastroenterology,* 100.
Ramos, C. I., De Lima, A. F. A., Grilli, D. G. & Cuppari, L. 2015. The Short-Term Effects of Olive Oil and Flaxseed Oil for the Treatment of Constipation in Hemodialysis Patients. *Journal of Renal Nutrition,* 25**,** 50-56.
Rao, S., Yu, S. & Fedewa, A. 2015. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. *Alimentary pharmacology & therapeutics*.
Rossi, M., Johnson, D. W. & Campbell, K. L. 2015. The Kidney–Gut Axis: Implications for Nutrition Care. *Journal of Renal Nutrition*.
Rouse, M., Chapman, N., Mahapatra, M., Grillage, M., Atkinson, S. & Prescott, P. 1990. An open, randomised, parallel group study of lactulose versus ispaghula in the treatment of chronic constipation in adults. *The British journal of clinical practice,* 45**,** 28-30.
Rush, E. C., Patel, M., Plank, L. D. & Ferguson, L. R. 2002. Kiwifruit promotes laxation in the elderly. *Asia Pacific Journal of Clinical Nutrition,* 11**,** 164-168.
Ruston, T., Hunter, K., Cummings, G. & Lazarescu, A. 2013. Efficacy and side-effect profiles of lactulose, docusate sodium, and sennosides compared to PEG in opioid-induced constipation: A systematic review. *Canadian Oncology Nursing Journal/Revue canadienne de soins infirmiers en oncologie,* 23**,** 236-240.
Sairanen, U., Piirainen, L., Nevala, R. & Korpela, R. 2007. Yoghurt containing galacto-oligosaccharides, prunes and linseed reduces the severity of mild constipation in elderly subjects. *European journal of clinical nutrition*.
Salmean, Y. A., Segal, M. S., Palii, S. P. & Dahl, W. J. 2015. Fiber Supplementation Lowers Plasma p-Cresol in Chronic Kidney Disease Patients. *Journal of Renal Nutrition,* 25**,** 316-320.
Saran, R., Li, Y., Robinson, B., Ayanian, J., Balkrishnan, R., Bragg-Gresham, J., Chen, J., Cope, E., Gipson, D. & He, K. 2015. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. *American journal of kidney diseases: the official journal of the National Kidney Foundation,* 66**,** S139-S144.
Shinaberger, C. S., Greenland, S., Kopple, J. D., Van Wyck, D., Mehrotra, R., Kovesdy, C. P. & Kalantar-Zadeh, K. 2008. Is controlling phosphorus by decreasing dietary protein

intake beneficial or harmful in persons with chronic kidney disease? *The American journal of clinical nutrition,* 88**,** 1511-1518.
Slinin, Y., Foley, R. N. & Collins, A. J. 2005. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: The USRDS waves 1, 3, and 4 study. *Journal of the American Society of Nephrology,* 16**,** 1788-1793. Available: DOI 10.1681/asn.2004040275.
Soret, R., Chevalier, J., De Coppet, P., Poupeau, G., Derkinderen, P., Segain, J. P. & Neunlist, M. 2010. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. *Gastroenterology,* 138**,** 1772-1782. e4.
Statistics New Zealand 2013. 2013 Census QuickStats about Maori. Wellington, New Zealand.
Stewart, M. L., Savarino, V. & Slavin, J. L. 2009. Assessment of dietary fiber fermentation: Effect of Lactobacillus reuteri and reproducibility of short-chain fatty acid concentrations. *Molecular nutrition & food research,* 53**,** S114-S120.
Strid, H., Simrén, M., Johansson, A. C., Svedlund, J., Samuelsson, O. & Björnsson, E. S. 2002. The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological general well-being. *Nephrology Dialysis Transplantation,* 17**,** 1434-1439.
Sturtzel, B., Dietrich, A., Wagner, K.-H., Gisinger, C. & Elmadfa, I. 2010. The status of vitamins B6, B12, folate, and of homocysteine in geriatric home residents receiving laxatives or dietary fiber. *The journal of nutrition, health & aging,* 14**,** 219-223.
Su, C.-Y., Pei, J., Lu, X.-H., Tang, W. & Wang, T. 2012. Gastrointestinal symptoms predict peritonitis rates in CAPD patients. *Clinical nephrology,* 77**,** 267.
Suares, N. & Ford, A. 2011a. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *The American journal of gastroenterology,* 106**,** 1582-1591.
Suares, N. & Ford, A. 2011b. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. *Alimentary pharmacology & therapeutics,* 33**,** 895-901.
Sutton, D., Dumbleton, S. & Allaway, C. 2007a. Can increased dietary fibre reduce laxative requirement in peritoneal dialysis patients? *Journal of renal care,* 33**,** 174-178.
Sutton, D., Higgins, B. & Stevens, J. M. 2007b. Continuous ambulatory peritoneal dialysis patients are unable to increase dietary intake to recommended levels. *Journal of Renal Nutrition,* 17**,** 329-335.
Sutton, D., Ovington, S. & Engel, B. 2014. A multi-centre, randomised trial to assess whether increased dietary fibre intake (using a fibre supplement or high-fibre foods) produces healthy bowel performance and reduces laxative requirement in free living patients on peritoneal dialysis. *Journal of renal care,* 40**,** 157-163.
Sutton, D., Talbot, S. T. & Stevens, J. M. 2001. Is there a relationship between diet and nutrition status in continuous ambulatory peritoneal dialysis patients? *Peritoneal dialysis international,* 21**,** S168-S173.
Takahashi, H., Wako, N., Okubo, T., Ishihara, N., Yamanaka, J. & Yamamoto, T. 1994. Influence of partially hydrolyzed guar gum on constipation in women. *Journal of nutritional science and vitaminology,* 40**,** 251-259.
Talley, N. J., Howell, S. & Poulton, R. 2004. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. *The American journal of gastroenterology,* 99**,** 1807-1814.
Tarumi, Y., Wilson, M. P., Szafran, O. & Spooner, G. R. 2013. Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. *Journal of pain and symptom management,* 45**,** 2-13.
Therrien, M., Byham-Gray, L., Denmark, R. & Beto, J. 2014. Comparison of Dietary Intake Among Women on Maintenance Dialysis to a Women's Health Initiative Cohort: Results From the NKF-CRN Second National Research Question Collaborative

Study. *Journal of Renal Nutrition,* 24**,** 72-80. Available: DOI http://dx.doi.org/10.1053/j.jrn.2013.09.005.
Tomas-Ridocci, M., Anon, R., Minguez, M., Zaragoza, A., Ballester, J. & Benages, A. 1992. [The efficacy of Plantago ovata as a regulator of intestinal transit. A double-blind study compared to placebo]. *Revista española de enfermedades digestivas: organo oficial de la Sociedad Española de Patología Digestiva,* 82**,** 17-22.
United States Renal Data System 2014. USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, Maryland.
Uribarri, J. 2007. PHOSPHORUS METABOLISM AND MANAGEMENT IN CHRONIC KIDNEY DISEASE: Phosphorus Homeostasis in Normal Health and in Chronic Kidney Disease Patients with Special Emphasis on Dietary Phosphorus Intake. *Seminars in Dialysis,* 20**,** 295-301. Available: DOI 10.1111/j.1525-139X.2007.00309.x.
Van Den Heuvel, E., Wils, D., Pasman, W., Bakker, M., Saniez, M. & Kardinaal, A. 2004. Short-term digestive tolerance of different doses of NUTRIOSE® FB, a food dextrin, in adult men. *European journal of clinical nutrition,* 58**,** 1046-1055.
Van Den Heuvel, E., Wils, D., Pasman, W. J., Saniez, M.-H. & Kardinaal, A. F. 2005. Dietary supplementation of different doses of NUTRIOSE® FB, a fermentable dextrin, alters the activity of faecal enzymes in healthy men. *European journal of nutrition,* 44**,** 445-451.
Wang, H.-F., Lim, P.-S., Kao, M.-D., Chan, E.-C., Lin, L.-C. & Wang, N.-P. 2001. Use of isomalto-oligosaccharide in the treatment of lipid profiles and constipation in hemodialysis patients. *Journal of Renal Nutrition,* 11**,** 73-79.
Wexner, S. D., Bartolo, D. C. & Duthie, G. S. 2007. *Constipation: etiology, evaluation and management*, Springer Science & Business Media.
Woolery, M., Bisanz, A., Lyons, H. F., Gaido, L., Yenulevich, M., Fulton, S. & Mcmillan, S. C. 2008. Putting evidence into Practice (R): Evidence-based interventions for the prevention and management of constipation in patients with cancer. *Clinical Journal of Oncology Nursing,* 12**,** 317-337. Available: DOI 10.1188/08.cjon.317-337.
Wu, M.-J., Chang, C.-S., Cheng, C.-H., Chen, C.-H., Lee, W.-C., Hsu, Y.-H., Shu, K.-H. & Tang, M.-J. 2004. Colonic transit time in long-term dialysis patients. *American journal of kidney diseases,* 44**,** 322-327.
Yasuda, G., Shibata, K., Takizawa, T., Ikeda, Y., Tokita, Y., Umemura, S. & Tochikubo, O. 2002. Prevalence of constipation in continuous ambulatory peritoneal dialysis patients and comparison with hemodialysis patients. *American journal of kidney diseases,* 39**,** 1292-1299.
Yasuda, G., Takeshita, Y., Kimura, T., Tochikubo, O., Ikeda, Y., Tokita, Y., Takeda, K. & Ishii, M. 1995. Constipation occurs less frequently in CAPD patients than in HD patients. *Peritoneal Dialysis International,* 15**,** 283-283.
Yen, C.-H., Tseng, Y.-H., Kuo, Y.-W., Lee, M.-C. & Chen, H.-L. 2011. Long-term supplementation of isomalto-oligosaccharides improved colonic microflora profile, bowel function, and blood cholesterol levels in constipated elderly people—A placebo-controlled, diet-controlled trial. *Nutrition,* 27**,** 445-450.
Zhang, J., Huang, C., Li, Y., Chen, J., Shen, F., Yao, Q., Qian, J., Bao, B. & Yao, X. 2013. Health-related quality of life in dialysis patients with constipation: a cross-sectional study. *Patient preference and adherence,* 7**,** 589.

Appendices

Appendix A: Instructions how to consume both powder supplements and how to adjust laxative use based on stool form

MASSEY UNIVERSITY
COLLEGE OF HEALTH
TE KURA HAUORA TANGATA

Instructions to take supplements for fibre study

We want to find out if one of the fibre supplements (black or red) can replace your bowel medications and keep your bowel movements soft.

The study needs accurate information to allow us to check this so please record each day on the forms provided.

For the study please eat your normal diet.

Mixing your supplement with the following foods and drinks should not alter the taste, colour or texture of your foods.

- Tea
- Coffee
- Casseroles
- Water
- Renilon
- Nepro
- Sauces
- On cereal with your milk allowance
- Stews
- Stewed fruit

NOTE: To help remember, use in the drink you use to take your medications

How much fibre supplement (black or red) to add to your food or drink?

Your supplement for the four week period can be found in the white tub. There is a measuring scoop inside.

Week 1	
Day 1 to 2	1 scoop in the morning and 1 scoop in the evening
Day 3 to 5	2 scoops in the morning and 2 scoop in the evening
Day 6 to 7	3 scoops in the morning and 2 scoop in the evening
Week 2	
Every day	3 scoops in the morning and 2 scoops in the evening
Week 3	
Every day	3 scoops in the morning and 2 scoops in the evening

NOTE: Please make them all level scoops

<u>If bowel motions become too loose (Bristol Stool scale 5, 6 or 7) you should:</u>

1. Cut back lactulose
    - If prescribed dose is 15 ml (3 teaspoons) per day, stop altogether
    - If prescribed dose is 30 ml, cut back to 15 ml for 3 days. If still loose then stop lactulose altogether.
2. If not on lactulose and you are taking laxsol
    - If prescribed 1 tablet laxsol – stop taking altogether
    - If prescribed 2 tablets, stop 1 tablet for 3 days, if still loose then stop the second tablet.
    - If prescribed 3 tablets or more, cut 1 tablet out every 3 days until stool consistency has improved (Bristol Stool Scale 3 or 4).

If you have a stool of 5, 6 or 7 and you are not taking laxatives, please reduce the supplement use by half a scoop every 3 days until your stool form drops to 4 or below.

REMINDER: PLEASE RECORD ON THE PROVIDED CHART ALL DAILY USE OF LACTULOSE AND/OR LAXSOL AND THE AMOUNT OF SUPPLEMENT TAKEN EVERY DAY

Appendix B: Written consent form

MASSEY UNIVERSITY
COLLEGE OF HEALTH
TE KURA HAUORA TANGATA

Wheat Dextrin Fibre Supplement Study Patient Consent Form

If you need an INTERPRETER, please tell us.

Please tick to indicate you consent to the following

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.	Yes ☐	
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	Yes ☐	No ☐
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	Yes ☐	
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.	Yes ☐	No ☐
I agree to an approved auditor appointed by the New Zealand	Yes ☐	

Health and Disability Ethic Committee\Northern B, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.		
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	Yes ☐	
I understand the compensation provisions in case of injury during the study.	Yes ☐	
I know who to contact if I have any questions about the study in general.	Yes ☐	
I understand my responsibilities as a study participant.	Yes ☐	
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name:

Signature:	Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature:	Date:

Appendix C: Information sheet sent in the post to potential subjects

MASSEY UNIVERSITY
COLLEGE OF HEALTH
TE KURA HAUORA TANGATA

Wheat Dextrin Fibre Supplement Study Information Sheet

Dear Renal Dialysis Patient

Do you take any laxatives? If so, you are likely to be eligible to take part in a study being run in the Northland District Health Board area.

My name is Chester Edwards. I'm running a research project in Northland for my Masters Thesis titled 'Does the use of a wheat dextrin fibre supplement reduce constipation in renal dialysis patients?

Currently there is no fibre supplement which is funded for dialysis patients. Constipation in those on dialysis is very common and has serious side effects. Laxatives can have side effects and the safety of their use long term is unknown. This research will work towards finding evidence that a fibre supplement using wheat dextrin can help reduce constipation in those on dialysis. We can then have a case to put forward to the authorative body to get the supplement funded to patients for no cost.

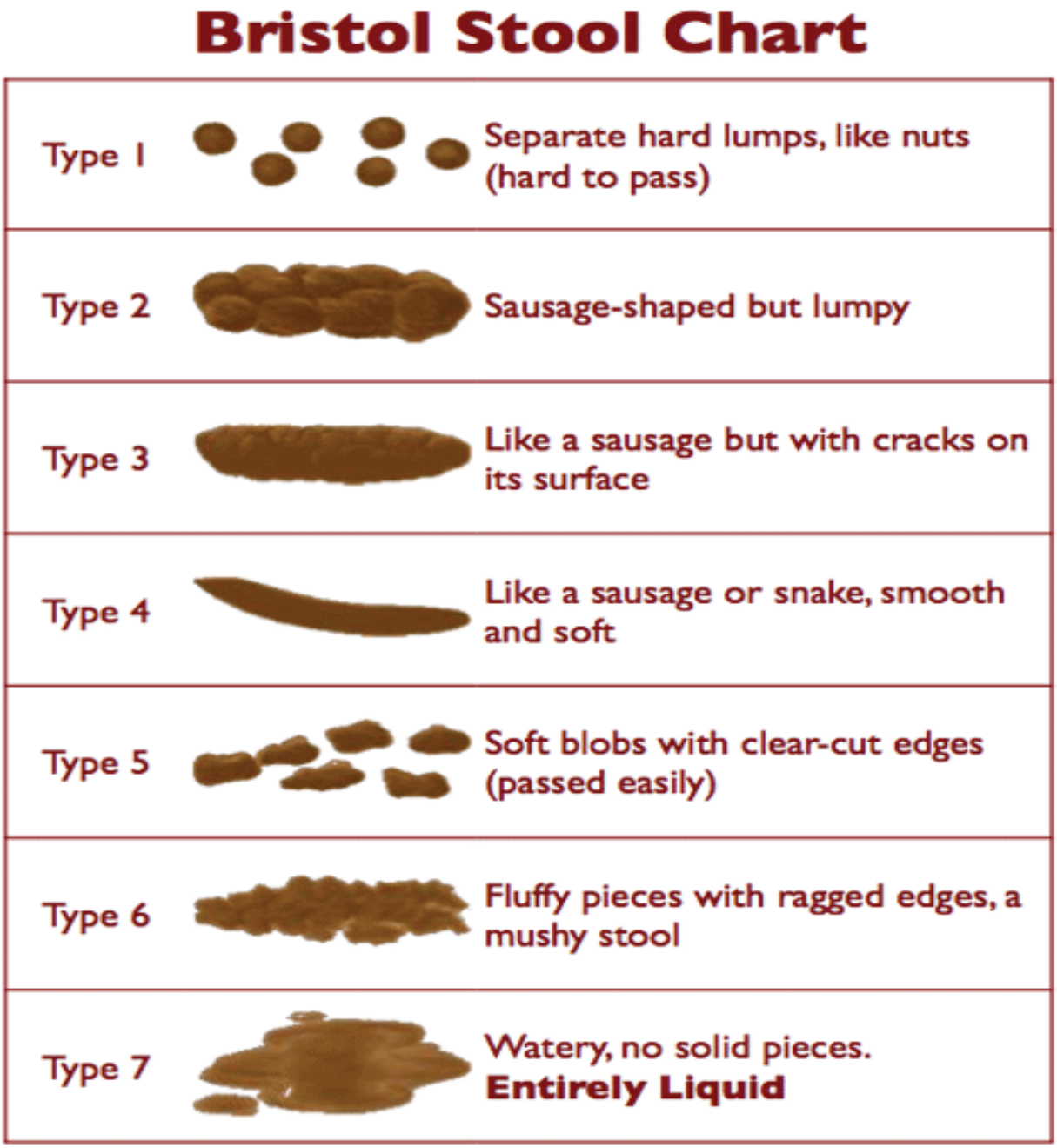
Wheat dextrin is a 100% natural product derived from wheat. It is a soluble fibre and prebiotic which feeds the good bacteria in your gut. It is completely safe to use and has little side effects at the doses recommended in the study. It's odourless, tasteless and completely dissolves in water or food.

This study is being encouraged by the Doctors and Nurses within the Northland District Board. It's your chance to take part in some research that could change the health and quality of life for dialysis patients within Northland.

In this envelope is more information about the study and what is involved. I will follow up this letter with a phone call to see if you have any questions or if you would like to take part. If you would like to take part, we can arrange to deliver the supplement packs to you or you can pick up if coming into Whangarei Hospital for an appointment.

Thank you
I hope you consider taking part in this research
Chester Edwards

Appendix D: The Bristol Stool Form Scale



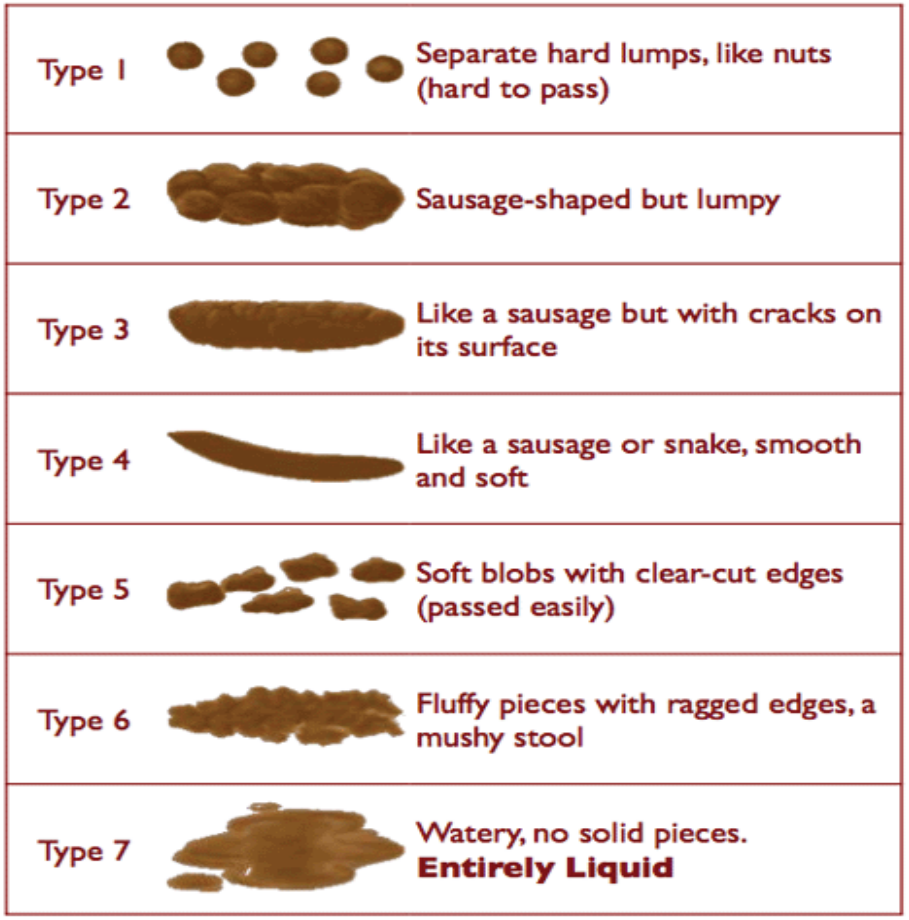
Appendix E: Patient held record kept in all three study stages

Date	Time	Dose of lactulose taken	Dose of Laxsol taken	Scoops of powder taken	Bowels open? (Tick if yes)	Stool Score
	am					
	pm					
	am					
	pm					
	am					
	pm					
	am					
	pm					
	am					
	pm					
	am					
	am					
	pm					
	am					

MASSEY UNIVERSITY
COLLEGE OF HEALTH
TE KURA HAUORA TANGATA

Participant number: **Red** **Black**

Bristol Stool Chart



Don't rush!

Record before you flush

Please try fill in the information as fully as you can. It is important that we have as complete a record as possible for everyone taking part.

Your will see that there is an illustrated chart on the front that we would like you to use to describe the consistency of your stools.

If you have any queries please do not hesitate to phone the research team who are able to help.

Chester Edwards 027 490 5770

Date	Dose of lactulose	Dose Laxsol	Dose Fibre Supplement	Bowels open Y	N	Stool Score

Date	Dose of lactulose	Dose Laxsol	Dose Fibre Supplement	Bowels open Y	N	Stool Score

Appendix F: Patient Assessment of Constipation Quality of Life Quality Questionnaire (PAC-QOL)

PAC-QOL ©

PATIENT ASSESSMENT OF CONSTIPATION ©

The following questions are designed to measure the impact constipation has had on your daily life **during the past 2 weeks**. For each question, please tick one box.

The following questions ask you about the intensity of your symptoms. To what extent, during the past 2 weeks...	**Not at all** **0**	**A little bit** **1**	**Moderately** **2**	**Quite a bit** **3**	**Extremely** **4**
1. have you felt bloated to the point of bursting?	☐	☐	☐	☐	☐
2. have you felt heavy because of your constipation?	☐	☐	☐	☐	☐

The next few questions ask you about the effects of constipation on your daily life. How much of the time, during the past 2 weeks...	**None of the time** **0**	**A little of the time** **1**	**Some of the time** **2**	**Most of the time** **3**	**All of the time** **4**
3. have you felt any physical discomfort?	☐	☐	☐	☐	☐
4. have you felt the need to open your bowel but not been able to?	☐	☐	☐	☐	☐
5. have you been embarrassed to be with other people?	☐	☐	☐	☐	☐
6. have you been eating less and less because of not being able to have bowel movements?	☐	☐	☐	☐	☐

The next few questions ask you about the effects of constipation on your daily life. To what extent, during the past 2 weeks…	**Not at all** **0**	**A little bit** **1**	**Moderately** **2**	**Quite a bit** **3**	**Extremely** **4**
7. have you had to be careful about what you eat?	☐	☐	☐	☐	☐
8. have you had a decreased appetite?	☐	☐	☐	☐	☐
9. have you been worried about not being able to choose what you eat (for example, at friend's)?	☐	☐	☐	☐	☐
10. have you been embarrassed about staying in the toilet for so long when you were away from home?	☐	☐	☐	☐	☐
11. have you been embarrassed about having to go to the toilet so often when you were away from home?	☐	☐	☐	☐	☐
12. have you been worried about having to change your daily routine (for example, travelling, being away from home)?	☐	☐	☐	☐	☐

The next few questions ask you about your feelings. How much of the time, during the past 2 weeks…	**None of the time** **0**	**A little of the time** **1**	**Some of the time** **2**	**Most of the time** **3**	**All of the time** **4**
13. have you felt irritable because of your condition?	☐	☐	☐	☐	☐
14. have you been upset by your condition?	☐	☐	☐	☐	☐
15. have you felt obsessed by your condition?	☐	☐	☐	☐	☐
16. have you felt stressed by your condition?	☐	☐	☐	☐	☐
17. have you been less self-confident because of your condition?	☐	☐	☐	☐	☐
18. have you felt in control of your situation?	☐	☐	☐	☐	☐

The next questions ask you about your feelings. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
19. have you been worried about not knowing when you are going to be able to open your bowels?	☐	☐	☐	☐	☐
20. have you been worried about not being able to open your bowels when you needed to?	☐	☐	☐	☐	☐
21. have you been more and more bothered by not being able to open your bowels?	☐	☐	☐	☐	☐

The next questions ask about your life with constipation. How much of the time, during the past 2 weeks...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
22. have you been afraid that your condition will get worse?	☐	☐	☐	☐	☐
23. have you felt that your body was not working properly?	☐	☐	☐	☐	☐
24. have you had fewer bowel movements than you would like?	☐	☐	☐	☐	☐

The next questions ask you about how satisfied you are. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
25. have you been satisfied with how often you open your bowels?	☐	☐	☐	☐	☐
26. have you been satisfied with the regularity with which you open your bowels?	☐	☐	☐	☐	☐
27. have you been satisfied with your bowel function?	☐	☐	☐	☐	☐
28. have you been satisfied with your treatment?	☐	☐	☐	☐	☐

Appendix G: Full information sheet sent or given to potential subjects

MASSEY UNIVERSITY
COLLEGE OF HEALTH
TE KURA HAUORA TANGATA

Wheat Dextrin Fibre Supplement Study Information Sheet

You are invited to take part in a study on using a wheat dextrin fibre supplement to reduce constipation in those who undergo haemodialysis or peritoneal dialysis. Whether or not you take part is your choice. If you don't wish to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 5 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

- The purpose of this study is to see if a wheat dextrin fibre supplement helps to reduce constipation in those patients who undergo peritoneal or haemodialysis.
- The study has been designed by senior research members of Massey University and a renal dietitian from Whangarei Hospital to find out whether a wheat dextrin fibre supplement can reduce constipation in those of renal dialysis.
- The Study is part of a masters project for the investigators from Massey University.
- Funding is from Massey University and the investigators are from either Massey University or Northland District Health Board. To make contact with these investigators see the contact details on the following page.
- The study has been approved by The NZ Health & Disability Ethics Committee.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

- You have been asked to participate as you meet the criteria for involvement which is undergoing dialysis, being over 18, having the mental capacity to participate, being free of coeliac disease and not using opiods or Benefiber as well as not having surgery scheduled in the next few months.
- The study will involve an initial observation period of 2 weeks where you will record your daily bowel habits with the help of the Bristol Stool Chart. The name and amount of any laxatives taken will also be recorded. Both bowel habits and laxative use will be recorded in a hand held booklet. During this period you will also be completing a 28 question quality of life questionnaire.
- After this observation period those who have constipation or those who do not have constipation but who take laxatives will be invited into the 2nd phase of the study.
- The 2nd phase involves taking a wheat dextrin fibre supplement or a non-wheat dextrin product daily at a recommended dosage for 4 weeks.
- A two week period of taking no product will then follow.
- Another 4 week period will then follow as with the 1st four weeks but you will receive the opposite product as to what you received in the 1st 4 weeks. You will not be told whether you are receiving the wheat dextrin or non-wheast dextrin product in either of the four week periods.
- During the two four week periods while taking the product, you will record your daily bowel habits with the help of the Bristol Stool Chart. The name and amount of any laxatives taken will also be recorded. Both bowel habits and laxative use will be recorded in a hand held booklet. At the end of each four week period you will also complete a 28 question quality of life questionnaire.
- Information will be collected in hard copy by a research team member when you visit the hospital or a meeting will be arranged to collect the information from you.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

- The benefits of this study are likely to be the reduction in constipation due to the consumption of the fibre supplement.
- The fibre supplement may also help to reduce laxative use.
- The combination of the reduction in constipation and laxative use may give an increased in quality of life.

There is a low risk of bloating and discomfort which has occurred in patients taking high doses of fibre supplements. However this study uses relatively low doses of fibre and the risk is minimised by increasing the dose slowly over the first week.

WHO PAYS FOR THE STUDY?

- All costs will be paid for by Massey University. This includes the Benefiber and non-Benefiber product as well as all printing of materials needed throughout the study period.
- There will be NO COSTS for patients.
- After the study period, the fibre supplement will need to be paid for in full by the patient if they wish to continue taking the supplement.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you may be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

- After the study is complete, participants will be sent a copy of the study results via either email or in hard copy.
- Study data will be stored in a secure location for 10 years.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Chester Edwards – Masters student, Massey University

027 490 5770

Chester.edwards@yahoo.co.nz

Olwyn Talbot-Titley – Renal Dietitian NDHB

021 463 353

Olwyn.TalbotTitley@northlanddhb.org.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

For Maori Heath support please contact :

Kim Tito – General Manager of Maori Health Service

09 430 4101 ext. 3239

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS Email: hdecs@moh.govt.nz

Appendix H: Health and Disability Ethics Committee approval letter

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
Freyberg Building
20 Aitken Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@moh.govt.nz

23 March 2015

Mr Chester Edwards
21 Clarence St
Ponsonby
Auckland 1011

Dear Mr Edwards

Re:	Ethics ref:	15/NTB/46
	Study title:	Does the use of a wheat dextrin fibre supplement improve bowel performance in patients on dialysis?

I am pleased to advise that this application has been *approved* by the Northern B Health and Disability Ethics Committee. This decision was made through the HDEC-Expedited Review pathway.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Northern B Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.
2. Before the study commences at *any* locality in New Zealand, it must be registered in a WHO-approved clinical trials registry (such as the Australia New Zealand Clinical Trials Registry, www.anzctr.org.au).
3. Before the study commences at *a given* locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

After HDEC review

Please refer to the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.

Your next progress report is due by 22 March 2016.

Participant access to ACC

The Northern B Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or