UNIVERSITI PUTRA MALAYSIA

EFFECTS OF GROUND FLAXSEED SUPPLEMENTATION ON CARDIOVASCULAR DISEASE AMONG HEMODIALYSIS PATIENTS AT A GOVERNMENT HOSPITAL, IN TEHRAN, IRAN

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FPSK(M) 2013 5

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By

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Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

January 2013

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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January 2013

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The leading cause of death in patients with chronic kidney disease including dialysis patients is cardiovascular disease (CVD). Approximately 50% of deaths in these patients are related to CVD. Among patients undergoing hemodialysis (HD), one of the major risk factors for CVD is lipid abnormalities. Besides, low level of serum albumin and high concentration of serum systemic inflammation markers, especially C-reactive protein (CRP) are important risk factors for CVD among patients undergoing HD.

The present study was conducted to investigate the effects of flaxseed supplementation on cardiovascular risk factors among patients undergoing HD. This was a randomized interventional study involving 38 patients on maintenance HD (20

males, 18 females) with lipid abnormalities (Triglyceride > 2.26 mmol/L and/or high density lipoprotein-cholesterol < 1.1 mmol/L) in the age range of 23 to 77 years. Patients enrolled in the study did not have diabetes, inflammatory diseases, or infection disease, and none of them received omega-3 fatty acid supplement and lipid lowering drugs. They were randomly assigned to either a flaxseed or control group (n=19). Subjects in the flaxseed group received 40 g/d ground flaxseed for 8 weeks, whereas subjects in the control group consumed their usual diet, without any flaxseed supplementation. The outcomes of the study were evaluated at baseline, week 4 and 8. The primary outcomes were serum lipid profile, serum CRP and serum albumin levels. The secondary outcome measures were anthropometric measurements and dietary intake (assessed by 2- day record and one day food recall).

In this study, serum concentrations of triglyceride (TG; $p < 0.001$), total cholesterol (TC; $p < 0.01$), and low density lipoprotein-cholesterol (LDL-C; $p < 0.01$) decreased significantly within the flaxseed group over time by 30%, 14% and 17%, respectively. There were significant increases in serum concentrations of TG, TC, and LDL-C within the control group by 21%, 15% and 8%, respectively. The mean changes in serum TG, TC, and LDL-C were statistically significant from baseline to week 4 ($p < 0.05$) and 8 ($p < 0.001$) between the two groups.

Serum high density lipoprotein-cholesterol (HDL-C) and serum albumin increased significantly by 16% and 9%, respectively within the flaxseed group over time ($p < 0.01$). There was significant reduction in serum HDL-C and albumin level within the

control group over time by 10% and 5%, respectively. Serum CRP concentration reduced significantly by 31% within the flaxseed group over time ($p < 0.05$), whereas no significant change was observed in the control group. The mean changes in serum CRP was significant difference between the two groups ($p < 0.05$).

Baseline dietary intakes data were comparable with the exception of the control group having higher intake of dietary fiber than the flaxseed group ($p < 0.05$). At baseline, mean intakes of energy, protein, carbohydrate and dietary fiber in a large percentage of the subjects in both groups were lower than the recommended intakes. At week 8, subjects in the flaxseed group achieved the recommendation for energy (30.5 ± 9 kcal/ kg body weight/day), protein (1.2 ± 0.36 g/kg body weight/day) and dietary fiber (25 ± 4 g/d).

In conclusion, 40 g/d flaxseed supplementation for 8 weeks improved lipid profiles and serum albumin level and reduces systemic inflammation in patients on maintenance HD with lipid abnormalities in addition to an overall dietary improvement.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN SUPLEMENTASI BIJI FLAX TERHADAP PENYAKIT KARDIOVASKULAR DI KALANGAN PESAKIT YANG MENJALANI HEMODIALYSIS DI HOSPITAL KERAJAAN, TEHRAN, IRAN

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Penyebab utama kepada kematian pesakit buah pinggang kronik termasuk pesakit yang sedang menjalani dialisis adalah penyakit kardiovaskular (PKV). Hampir 50% daripada kematian pesakit-pesakit ini berkaitan dengan penyakit kardiovaskular. Dalam kalangan pesakit yang sedang menjalani rawatan hemodialisis, salah satu faktor risiko utama penyakit kardiovaskular adalah ketidaknormalan lemak dalam darah. Disamping itu, tahap kepekatan serum albumin yang rendah dan penanda serum keradangan sistemik, terutamanya protein C-reaktif (CRP) yang tinggi merupakan faktor risiko penting bagi penyakit kardiovaskular dalam kalangan pesakit yang sedang menjalani hemodialisis.

Kajian ini dijalankan untuk mengkaji kesan suplemen biji flax ke atas faktor risiko penyakit kardiovaskular dalam kalangan pesakit yang sedang menjalani hemodialisis. Ini adalah satu kajian intervensi rawak yang melibatkan 38 orang pesakit yang sedang menjalani rawatan hemodialisis (20 lelaki, 18 perempuan) yang mempunyai ketidaknormalan lemak dalam darah (Trigliserida > 2.26 mmol/L dan/atau kolesterol lipoprotein berketumpatan tinggi <1.1 mmol/L) dalam lingkungan umur 23 hingga 77 tahun. Pesakit yang mendaftar dalam kajian ini tidak mempunyai kencing manis, penyakit keradangan atau penyakit jangkitan, dan tidak seorang pun daripada mereka menerima suplemen asid lemak omega-3 dan dadah yang mengurangkan lemak. Mereka dibahagikan secara rawak kepada kumpulan intervensi (diberikan suplemen biji flax) atau kumpulan kawalan (n=19). Pesakit dalam kumpulan intervensi menerima 40 g/hari suplemen biji flax selama 8 minggu, manakala pesakit dalam kumpulan kawalan hanya mengambil diet biasa tanpa suplemen biji flax. Hasil kajian telah dinilai pada permulaan, minggu ke-4 dan ke-8. Hasil utama adalah serum untuk profil lemak, CRP dan paras albumin. Hasil kedua yang diukur adalah ukuran antropometri dan pengambilan diet (dinilai dengan rekod pengambilan makanan selama 2 hari dan satu hari dengan mengingat makanan).

Dalam kajian ini, kepekatan serum trigliserida (TG; $p < 0.001$), jumlah kolesterol (TC; $p < 0.01$), dan kolesterol lipoprotein berkepadatan rendah (LDL-C; $p < 0.01$) menurun dengan ketara dalam kumpulan intervensi dengan masa masing-masing sebanyak 30%, 14% dan 17%. Terdapat peningkatan yang signifikan dalam serum TG, TC, dan LDL-C dalam kumpulan kawalan dengan masing-masing sebanyak

21%, 15% dan 8%. Min perubahan dalam serum TG, TC, dan LDL-C adalah signifikan secara statistik dari permulaan ke minggu ke-4 ($p<0.05$) dan ke-8 ($p<0.001$) antara dua kumpulan tersebut.

Serum kolesterol lipoprotein berketumpatan tinggi (HDL-C) dan albumin meningkat dengan signifikan masing-masing sebanyak 16% dan 9% dalam kumpulan intervensi dengan masa ($p<0.01$). Terdapat penurunan yang signifikan dalam serum HDL-C dan albumin dalam kumpulan kawalan dengan masa masing-masing dengan 10% dan 5%. Kepekatan serum CRP berkurang dengan signifikan sebanyak 31% dalam kumpulan intervensi dengan masa ($p<0.05$) dimana tiada perubahan yang ketara dilihat dalam kumpulan kawalan. Min perubahan dalam serum CRP adalah berbeza secara signifikan antara dua kumpulan ($p<0.05$).

Data permulaan bagi pengambilan makanan dibandingkan dengan pengecualian dari kumpulan kawalan yang mempunyai lebih tinggi pengambilan serat daripada kumpulan intervensi ($p <0.05$). Pada permulaan, min pengambilan tenaga, protein, karbohidrat dan serat makanan dalam peratusan yang besar yang diambil oleh subjek dalam kedua-dua kumpulan adalah lebih rendah daripada pengambilan yang disyorkan. Pada minggu ke-8, subjek dalam kumpulan intervensi telah mencapai tahap pengambilan yang disyorkan untuk tenaga (30.5 ± 9 kkal/kg berat badan/hari), protein (1.2 ± 0.36 g/kg berat badan/hari) dan serat (25 ± 4 g/hari).

Kesimpulannya, suplemen biji flax sebanyak 40 g/hari selama 8 minggu boleh

memperbaiki profil lemak dalam darah dan paras serum albumin serta mengurangkan keradangan sistemik dalam kalangan pesakit yang sedang menjalani hemodialisis yang mempunyai ketidaknormalan lemak dalam darah di samping memperbaiki keseluruhan pengambilan makanan.

ACKNOWLEDGEMENT

I would like to express my deep and sincere gratitude to all those who provided me the support and encouragement necessary to complete this journey. I would like to thank my supervisor, Dr. Rosita Jamaluddin for her supervision and enormous support from the very beginning. Her detailed comments have made this thesis possible. I would like to express my gratitude to my three co-supervisors, Dr. Barekatun Nisak Mohd Yusof, Dr. Hadi Tabibi and Dr. Su Peng Loh, all of whom advised me and offered me their support throughout these times.

My sincere thanks to Dr. Shahnaz Atabak, from Modarres Hospital, Tehran, Iran. Her expertise in clinical and research of patients undergoing hemodialysis was invaluable. I thank all the staff of the Hemodialysis Unit in Modarres Hospital for their assistance and cooperation throughout the study. Special thanks to all the patients who consented to join the study. Their cooperation and patience are highly appreciated.

I acknowledge the faculty of Medicine and health Science of Universiti Putra Malaysia members and the head of the department of Nutrition and Dietetics for their assistance to run this experiment.

My loving thanks to my beloved parents and sisters for their love and fortitude. This work would not have been possible without the endless support of my family. I would like to thank all the precious friends for their encouragement during the research. To them I dedicate this thesis.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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ALA	α-linolenic acid
BMI	Body mass index
CKD	Chronic kidney disease
CRP	C-reactive protein
CVD	Cardiovascular disease
DHA	Docosahexanoic acid
EPA	Eicosapentanoic acid
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HD	Hemodialysis
HDL-C	High-density lipoprotein cholesterol
K/DOQI	Kidney Disease Outcomes Quality Initiative
LDL-C	Low-density lipoprotein cholesterol
MUFA	Mono unsaturated fatty acid
PEM	Protein-energy malnutrition
PUFA	Polyunsaturated fatty acids
RRT	Renal replacement therapy
SFA	Saturated fatty acid
TC	Total cholesterol
TG	Triglyceride

WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Introduction

Chronic kidney disease (CKD), a worldwide public health problem is associated with a high mortality rate. End stage renal disease (ESRD) is a costly and disabling stage of CKD. Prevalence of ESRD globally continues to grow at an unexpected rate (Sarnak et al., 2003). Renal replacement therapy (RRT) has a vital role to ensure the survival and maintenance of the health status in ESRD patients (Noshad et al., 2009).

Cardiovascular disease (CVD) is the main cause of death in patients with ESRD. Cardiovascular mortality among ESRD patients is 10 to 30 folds higher than the general population (Suliman et al., 2005). Every year, between 10% and 20% of all dialysis patients died throughout the world, with approximately 45% of the deaths attributed to cardiovascular causes (Foley et al., 1998; Herselman et al., 2010). Lipid abnormalities, inflammation and hypoalbuminemia are estimated to be the leading cause of cardiovascular mortality among patients undergoing HD (Rosamond et al., 2008).

Kidney disease can adversely alter plasma lipid profiles. Typically, patients who were undergoing HD had increased level triglyceride (TG) and decreased level of high density lipoprotein cholesterol (HDL-C) (Reddy et al., 2009).

Protein–energy malnutrition (PEM) is extremely widespread among HD patients and is linked with high mortality in CKD patients. Several studies had reported that hypoalbuminaemia as one of the major signs of malnutrition among patients on maintenance HD (Lowrie et al., 1995; Owen et al., 1993; Shah & Dumler, 2008). The evaluation of nutritional status is mainly based on serum albumin and anthropometric measurements among patients undergoing HD (Qureshi et al., 2002). Low protein and energy intakes and low body weight have also been shown to be predictors of PEM. An inverse relationship between mortality rate and BMI is highly significant for patients within lower 50^{th} percentile of BMI. Moreover, both PEM and inflammation are associated with increased mortality, including risk of cardiovascular death (Qureshi et al., 2002; Kalantar-Zadeh et al., 2001).

Inflammation is common among patients on maintenance HD. C-reactive protein (CRP) is the marker of inflammation (Peterson et al., 2010). CRP which is a positive acute-phase reactant is a well-known indicator of inflammation. Inflammation has been linked to cardiovascular risk and mortality among patients undergoing HD (Wang et al., 2003).

Serum albumin, a negative acute-phase reactant and marker for underlying inflammation and/or malnutrition, is an independent predictor of CVD and mortality in patients undergoing HD (Yilmaz et al., 2007). Hypoalbuminaemia was associated with decreased albumin synthesis among patients on maintenance HD (Louden et al., 2001).

A primary action for reducing risk factors of CVD among patients on maintenance HD is diet therapy (Qureshi et al., 2002). Diet with low saturated fatty acids (SFA), high in unsaturated fatty acids especially omega-3 fatty acids, which is abundant in fish and some oily seeds, as well as high consumption of dietary fiber, are proposed to reduce the risk factors of CVD, specifically by improving blood lipid profile (National Kidney Foundation, 2000).

In terms of oily seeds, flaxseed has gained increased attention. Flaxseed or linseed (*Linum usitatissimum L*.) is a member of the *Linacea* family which is an annual herb. It is a blue flowering crop that produces small, flat petals and range in color from golden yellow to brown (Pradhan et al., 2010). Flaxseed is a generally available seed, which is cultivated in over 50 countries throughout the world. Due to its beneficial dietary nutrient and vast area of cultivation, it has become a nutrient food for direct usage or for developing some cereal products, especially breads, cookies, muffins, and salad dressing among others (Muir & Westcott, 2003).

Flaxseed is a rich source of plant-based omega-3 (n-3) fatty acid, α-linolenic acid (ALA, C18:3, n-3), which has been linked to reduce CVD risk factors, especially hypertriglyceridemia and inflammatory markers (Kaul et al., 2008; Zhao et al., 2004). Flaxseed contains about 35-45% oil, which ALA accounts for about half of the total fatty acids present (53.3%) and it also contains 12.7% of linoleic acid (LN, C18:2, n-6), yielding the highest n-3/n-6 fatty acid ratio among plant sources (Barcelo-Coblijin & Murphy, 2009).

Flaxseed is also the richest source of dietary lignans, where secoisolariciresinol diglucoside is the principal one and approved as a lipid-lowering agent (Patade et al., 2008). Lignans is one of the major groups of phytoestrogens that has antioxidant properties (Thompson et al., 2005). Moreover, flaxseed also contains 28% of dietary fiber by weight which is linked to decrease cholesterol and reduced risk of CVD (Tarpila et al., 2005).

Therefore, investigating the effects of flaxseed supplementation on CVD risk factors which regards in improving blood lipid profiles and markers of inflammation could be helpful for patients on maintenance HD.

1.2 Problem statement

Despite many years of efforts and improvement in HD technique and patient's care, the mortality rate among patients undergoing HD remain to be high with most deaths resulting from CVD (Reddy et al., 2009). Lipid abnormalities, chronic inflammation and hypoalbuminemia are three important leading cause of high cardiovascular mortality rate among patients on maintenance HD (Rosamond et al., 2008). Efforts regarding introducing diet which can improve CVD risk factors resulted to numerous studies on plants and herbs. Among all plants, flaxseed found to have a great concern due to its health benefits. A number of studies in non-uremic individuals and laboratory animals have shown that flaxseed supplementation could improve cardiovascular risk factors according to its high contents of ALA, lignans and fiber

which have been well established as lipid-lowering agents (Bloedon et al., 2008; Dodin et al., 2005; Pan et al., 2009; Rodriguez-Leyva et al., 2010). ALA which is the main component of flaxseed has been shown to have an anti- inflammatory effect (Zhao et al., 2004). Besides, flaxseed compared to other rich source of omega-3 (oily fishes) has lower price and higher availability. Moreover, due to high prevalence of PEM among patients on maintenance HD, adequate nutrient intakes play an important role. One of the most important parameter for assessing malnutrition is hypoalbuminemia, which could be due to both chronic inflammation and lower dietary protein and energy intakes compare to the recommendation levels, thus nutritional support is necessary for these patients (Qureshi et al., 2002). Flaxseed high content of PUFA especially ALA and high biological value protein which comprise of albumin and globulins may resulted in an overall dietary improvement among patients undergoing HD (Madhusudhan, 2009).

In Iran, research in the area of flaxseed consumption is still at its infancy. However, no research has been carried out in determining the effects of flaxseed supplementation in CVD management of patients on maintenance HD. This study was conducted to determine the effects of flaxseed supplementation on reduction of CVD risk factors among patients undergoing HD.

1. 3 Significance of study

Dietary management plays an important role in the maintenance of CVD health. The uses of dietary supplements that are safe and feasible would serve as an alternative to medications in lowering the risk of CVD. Nowadays, flaxseed is increasingly incorporated into the diet, and commonly consumed as a component of breads, muffins and cereals. Indeed, flaxseed has gained recent attention as a potential functional food. In the last 10 years, a significant number of products containing flaxseed have been developed for the health food market (Tarpila et al., 2005). However, there is no interventional study on flaxseed supplementation among patients undergoing HD, in addition to shortage of information on the health benefits of flaxseed among Iranian.

The outcomes of this study should provide useful information about the consumption of flaxseed and its effects on lipid profile, inflammatory response (CRP) and hypoalbuminemia among patients on maintenance HD. Besides, this study may also recommend flaxseed to the patients undergoing HD as a dietary supplement.

The following are the research questions addressed in this study:

1. Does flaxseed supplementation have significant effects on CVD risk factors (lipid profile, serum CRP and albumin levels) among patients on maintenance HD after 8-week period?

2. Does flaxseed supplementation have significant effects on anthropometric measurements among patients on maintenance HD after 8-week period?

3. Does flaxseed supplementation have significant effects on dietary intakes after 8-week period?

1.4 Objectives of study

1.4.1 General objective

The general objective of this study was to investigate the effects of flaxseed supplementation on cardiovascular risk factors among individuals on maintenance hemodialysis, at Modarres Hospital, in Tehran, Iran.

1.4.2 Specific objectives

1. To compare the effects of 8 weeks flaxseed supplementation on CVD risk factors (lipid profile, serum C-reactive protein and albumin concentration) between the flaxseed and control groups.

2. To compare the effects of 8 weeks flaxseed supplementation on anthropometric measurements between the flaxseed and control groups.

3. To compare the effects of 8 weeks flaxseed supplementation on dietary intake (Energy, protein, total carbohydrate, fat, PUFA, ALA, cholesterol, fiber, potassium and phosphate) between the flaxseed and control groups.

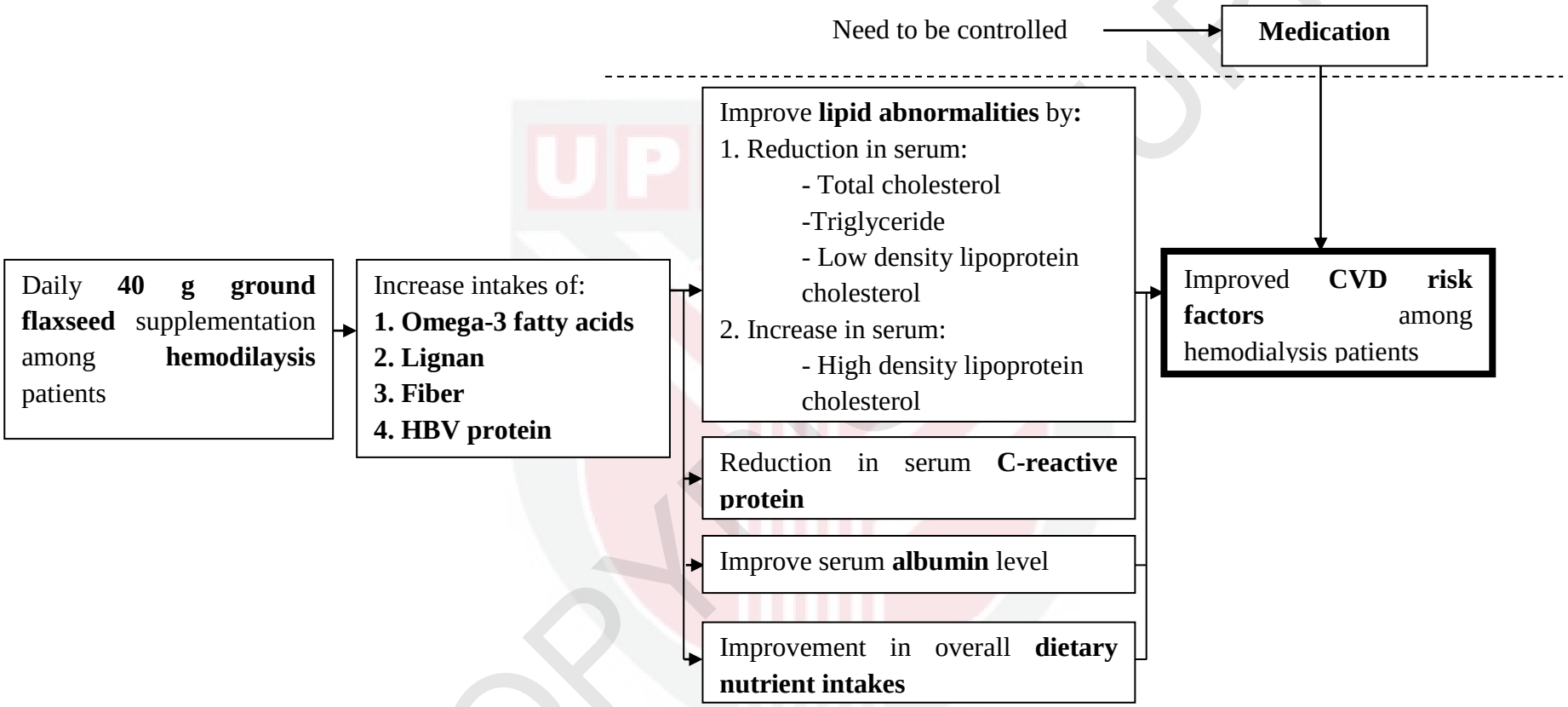
1.5 Study hypotheses

Subjects on maintenance hemodilaysis who received flaxseed supplementation for 8 weeks would have improved cardiovascular disease risk factors as assessed by improvement in lipid profiles, serum CRP and albumin levels as compared to the control group.

1.6 Conceptual framework

The conceptual framework of this study adopted from various researches which include the three most important CVD risk factors among HD patients (Figure 1.1). The three major CVD risk factors among HD patients are lipid abnormalities, elevated serum CRP and hypoalbuminemia (Foley et al., 1998; Herselman et al., 2010; Kalantar-Zadeh et al., 2005; Majumdar & Wheeler, 2000; Owen et al., 1993; Wanner, 2000). In addition, the role of medications and dietary intake has been fairly established as a component of CVD management among HD patients (Foley et al., 1998; Moreira et al., 2007; Wanner et al., 2000).

In brief , incorporating of flaxseed in the daily diet can reduce risk factors of CVD especially lipid abnormalities and serum CRP level, due to its high content of omega-3 fatty acids, lignan, dietary fiber and protein (Arjmandi et al., 1998; Bassett et al., 2009; Bloedon et al., 2008; Herselman et al., 2010; Yeun et al., 2000). Thus, the conceptual framework of this study is divided into two aspects, investigating the effects of flaxseed supplementation on CVD risk factors and dietary intake among patients on maintenance HD.



HBV, High biological value; CVD, cardiovascular disease

Figure 1.1 Conceptual framework of potential effect of flaxseed supplementation on cardiovascular risk factors among patients undergoing HD

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