

Original Research

Flaxseed in Lupus Nephritis: A Two-Year Nonplacebo-Controlled Crossover Study

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Objective: The objective of this study was to determine the renoprotective effects of ground flaxseed in patients with lupus nephritis.

Methods: Forty patients with lupus nephritis were asked to participate in a randomized crossover trial of flaxseed. Twenty-three agreed and were randomized to receive 30 grams of ground flaxseed daily or control (no placebo) for one year, followed by a twelve-week washout period and the reverse treatment for one year. At baseline and six month intervals, serum phospholipids, flaxseed sachet counts, serum creatinine, 12-hour urine albumin excretion and urine albumin to creatinine ratios, serum viscosity and plasma lipids were measured.

Results: There were eight drop-outs and of the 15 remaining subjects flaxseed sachet count and serum phospholipid levels indicated only nine were adherent to the flaxseed diet. Plasma lipids and serum viscosity were unaltered by the flaxseed supplementation whereas serum creatinine in the compliant patients during flaxseed administration declined from a mean of 0.97 ± 0.31 mg/dL to a mean of 0.94 ± 0.30 mg/dL and rose in the control phase to a mean of 1.03 ± 0.28 mg/dL [p value < 0.08]. Of the fifteen patients who completed the study, similar changes were noted [p value < 0.1]. The nine compliant patients had lower serum creatinines at the end of the two-year study than the 17 patients who refused to participate [$p < 0.05$]. Microalbumin at baseline declined in both control and flaxseed time periods, but there was a trend for a greater decline during flaxseed administration [$p < 0.2$].

Conclusions: Flaxseed appears to be renoprotective in lupus nephritis, but this interpretation is affected by under powering due to poor adherence and potential Hawthorne effects.

INTRODUCTION

Systemic lupus erythematosus [SLE] is an auto-immune disease in which patients, early in the disease, suffer inflammatory events and, late in the disease, significant morbidity and mortality occur due to kidney failure and accelerated vascular disease with heart attack, strokes and other atherogenic complications [1–9]. Throughout the entire disease process, patients suffer an increased risk for sepsis. This pattern attracted our interest in nutritional agents such as fish oil, rich in omega-3 fatty acids which exert anti-inflammatory and lipid lowering properties potentially able to reduce the accelerated renal and vascular disease, without increasing the risk of sepsis. Early work by Prickett and Robinson with fish oil in the NZB/NZW

mouse model of lupus nephritis demonstrated a renoprotective effect [10–12]. We observed some benefit in a short-term dosing study of fish oil in lupus nephritis patients but were able to show only a modest improvement in renal parameters in a two-year crossover study [13,14]. However, the concept of using a nutritional agent for adjunctive therapy has an attractive appeal, particularly in view of the accelerated vascular disease and septic risk that patients face with current therapy.

Flaxseed seemed to be a natural nutritional choice since it is composed of high concentrations of the omega-3 fatty acid precursor, α -linolenic acid, as well as a rich source of lignans [15]. The α -linolenic acid has a wide range of anti-inflammatory and anti-atherosclerotic actions that could potentially abrogate the progression of nephritis and accelerated vascular

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disease in patients with lupus [16,17]. The lignans produced specific reversible and competitive inhibition of platelet activating factor (PAF) [18,19]. PAF has been implicated in the immunopathogenesis of glomerular renal injury in lupus nephritis [20–24].

These potential actions prompted us to study the effects of flaxseed supplementation in the MRL/lpr mouse model of lupus nephritis [19]. We were able to conclude from these experiments that flaxseed ameliorated the immune renal disease and this effect was much greater than that demonstrated for fish oil [25]. These encouraging results prompted us to investigate the short-term effects of three different doses of flaxseed in patients with lupus nephritis [26]. This dosing study indicated that 30 grams of flaxseed was well tolerated and exerted significant effects on renal function. These preliminary findings led to this current two-year crossover study of the effects of 30 gram doses of flaxseed in patients with lupus nephritis.

METHODS

Patients

Forty patients with the diagnosis of SLE, who fulfilled four or more of the American Rheumatism Association criteria for the diagnosis of SLE, with a history of documented hematuria and proteinuria plus or minus renal biopsy, were asked to participate in the study. Twenty-three agreed to participate and signed an informed consent. Fifteen completed the two-year crossover study. The study was reviewed and approved for use in patients with lupus nephritis by the Human Ethics Committee of the University of Western Ontario.

Trial Design

The study was divided into three phases. In the first phase, subjects were randomized to receive one year of 30 grams daily of ground flaxseed or to receive no flaxseed. Phase II involved a three month washout followed by Phase III with a reversal of the flaxseed ingestion pattern in the second year. Ground flaxseed was sealed in 15 grams plastic sachets and refrigerated by patients prior to use to reduce the possibility of oxidation. We did not find a suitable (biologically inactive) placebo for the flaxseed; therefore, in view of our previous difficulties with crossover design and biologically active placebo effect in the fish oil trial, we opted for no placebo since we were observing objective serological and biochemical tests as end points [14]. All patients received daily or alternate-day low dose steroid therapy, and two patients received azathioprine. There were no major therapeutic changes during the study period. However, the physician involved in providing immuno-suppressive treatment to the patients was blinded to who was or was not receiving flaxseed. In Phase I and Phase III, the subjects who

were randomized to receive flaxseed ingested 15 grams of ground flaxseed twice daily with cereal, tomato or orange juice.

Dietary Intake Assessment. A three-day dietary intake record was obtained from each patient at each phase of the study and analysed using the Canadian Nutrient File data base [Nutrition Research Division, Health Protection Branch, Ottawa, Ontario, Canada]. Total calories, protein, fat, cholesterol, saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids were calculated.

Compliance. Sachets containing 15 grams of ground flaxseed were provided to each patient. Patients were given more sachets than required considering the daily dose and the time period. The number of extra sachets varied each time flaxseed was distributed. At the end of each phase, patients were required to return any leftover flaxseed sachets and report the days that they were unable to take the flaxseed. These data were combined with the relative changes of α -linolenic acid in the fatty acid analysis of serum phospholipids during the different phases of the flaxseed study.

Fatty Acid Contents of Serum Phospholipids

Serum phospholipids were extracted and assessed for fatty acids as previously described [19]. In brief, the lipid extracts were separated by thin layer chromatography. The phospholipid band was scraped from the plate, methylated and analysed for fatty acid composition by gas liquid chromatography [26].

Plasma Lipids. Fasting blood samples [12 to 14 hours] were collected in EDTA and put on ice. Plasma was assayed for total triglycerides and total cholesterol, HDL and the LDL cholesterol as previously described [19].

Rheology. The viscosity of heparinized whole blood relative to water was measured using a water pipette at room temperature according to the method of Wright and Jenkins [27].

Renal Function Tests. Throughout the study periods in three different phases urine microalbumin (mg/12 hrs) was measured in the 12-hour urine collections by an ELISA technique using reagents from Nordic Immunological Laboratories [Cedarlane Laboratories, Hornsby, Ontario, Canada] in two 12-hour [8 pm to 8 am] urine collections. Serum creatinine was measured by kinetic Jaffé chromogen reaction.

Statistical Analysis

Baseline comparisons between treatment groups and analysis subgroups were done using one-way analysis of variance and Chi-square tables as appropriate to the level of measurement of the outcome measures. The primary analysis involved the 15 patients who completed the two-year follow up. It utilized a repeated-measures analysis of variance to assess the effect of the time-dependent treatment sequence (baseline, flaxseed, washout, control), treatment group (start flaxseed vs. control) and the interaction of treatment by group, on lipid and renal function outcome measures and on α -linolenic acid levels. A number of *post hoc* analyses employing several methods

were undertaken subsequent to the primary analysis. Paired *t* tests were used to contrast selected outcome variables under the flaxseed and control conditions within subgroups (compliant, non-compliant, dropouts and refusals). Comparisons between specific subgroups were drawn via *t* tests for independent samples and one-way analysis of variance.

RESULTS

Twenty-three of the forty patients who were approached agreed to participate and entered into the study. Eight dropped out of the study with the most consistent complaint being difficulty ingesting the 30 grams of flaxseed daily. Of the fifteen who completed the two-year cross-over study, two indicated increased laxation when taking flaxseed supplementation.

Dietary Intake Assessment

Three-day dietary intake records showed no change in the intake of total calories, protein, fat, cholesterol and saturated, monounsaturated and polyunsaturated fatty acids during three different phases of the study.

Compliance or Adherence

Compliance was assessed by sachet count and by serum α -linolenic acid levels. In the fifteen patients who completed the study, only nine showed a rise in their α -linolenic acid level while consuming the 30 grams of flaxseed and a decline when the flaxseed supplementation was stopped (Fig. 1, Tables 1 and 2). The six patients who had a reversal in pattern also showed major inconsistencies in their sachet count. At the conclusion of

Table 1. Serum α -Linolenic Acid Concentrations (mmol/L) in Lupus Patients Consuming 30 g of Flaxseed Daily

	Start	Base Line	Control	Flaxseed	Wash Out
Control					
Mean		9.7	2.3	27.7	24.0
SEM		2.5	1.6	3.5	3.0
n		7	7	7	7
Flaxseed					
Mean		3.5	15.1	7.7	18.2
SEM		2.0	4.1	4.2	3.2
n		8	7	8	8
Total					
Mean		6.6	8.5	17.0	20.9
SEM		1.8	2.8	3.8	2.2
n		15	14	15	15

Table 2. Serum α -Linolenic Acid Concentrations (mmol/L) in Patients Designated as Compliant with Flaxseed Supplementation

	n	Mean	SEM
Baseline	9	8.1	2.2
Control	9	5.4	2.4
Flaxseed	9	27.5	2.6
Washout	9	23.2	2.7

* $p < 0.001$.

each phase of the flaxseed supplementation study, four patients while receiving flaxseed supplementation did not have an excess of sachets. Two of the patients had a large number of sachets in excess of the correct calculation and admitted at that time to variable adherence. A sub-analysis of the nine patients who demonstrated an α -linolenic acid rise while consuming

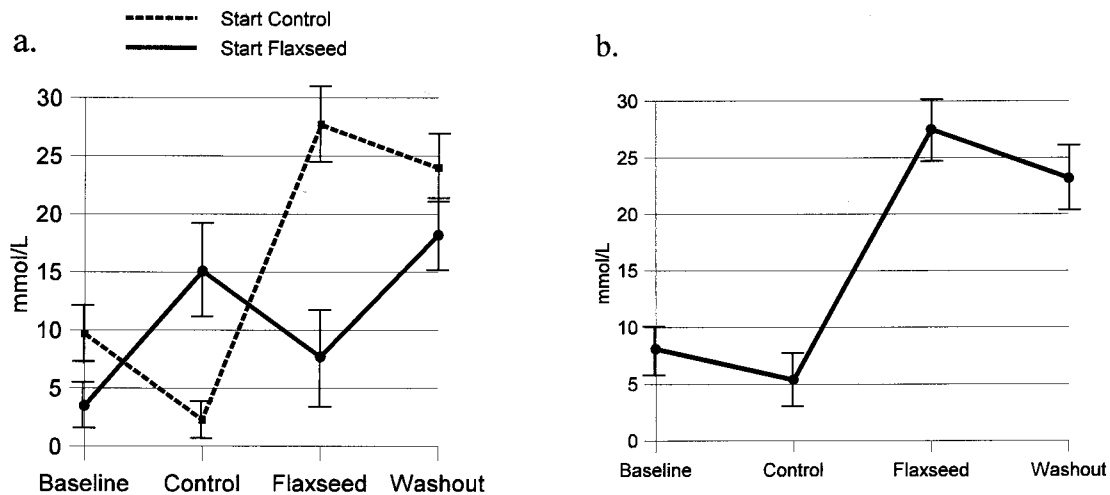


Fig. 1. Serum alpha-linolenic acid levels in lupus patients consuming 30g of flaxseed a day according to the level of patient compliance, noncompliance and/or nonparticipation. **a.** Values obtained in all groups of patients at the various phases of the study. It is impossible to explain the alpha-linolenic acid pattern of the start flaxseed group except on the basis of noncompliance since their levels are lower when taking flaxseed. This curve led us to isolate the nine patients who demonstrated the expected rise in alpha-linolenic acid when on flaxseed and a drop when off flaxseed. **b.** Values obtained in the compliant patients at the different phases of the study.

flaxseed and a drop while not consuming it, is shown in Fig. 1 b. and Table 2. This figure demonstrates very significant differences in different phases and is compatible with adherence ($p < 0.001$).

Plasma Lipids. The flaxseed did not exert a significant effect on any of the lipid parameters after ingestion for one year. The mean cholesterol concentration at baseline for the flaxseed group was 6.03 ± 0.61 mmol/L and this rose to 6.05 ± 1.05 mmol/L. As well, HDL cholesterol in the flaxseed-compliant patients rose from a baseline of 1.32 ± 0.45 to 1.36 ± 0.51 mmol/L. LDL cholesterol with a baseline of 3.95 mmol/L in the compliant patients consuming flaxseed underwent a slight but non-statistical decline to 3.86 ± 0.74 mmol/L ($p < 0.7$).

Rheology. Whole blood viscosity in the nine compliant patients was unaltered by ingestion of flaxseed. Subjects experienced a slight but insignificant increase from a baseline of 2.91 ± 0.26 to 2.95 ± 0.27 seconds. A similar non-statistical rise was noted for those patients who did not take flaxseed from a baseline of 2.95 ± 0.38 to 2.97 ± 0.40 seconds.

Renal Function Tests. Serum creatinine in the compliant flaxseed group declined from a mean of 0.97 ± 0.31 mg/dL to a mean of 0.94 ± 0.30 mg/dL and rose in the control phase to a mean of 1.03 ± 0.28 mg/dL and rose further in the washout to 1.08 ± 0.31 mg/dL. The difference between control *versus* flaxseed in the compliant subjects showed a trend toward significance with a p value of 0.081 in a paired t test [Table 3]. The fifteen patients who completed the study demonstrated a similar trend with a serum creatinine of 1.12 ± 0.51 mg/dL in those consuming no flaxseed for one year compared to a serum creatinine of 1.00 ± 0.36 mg/dL in those who took flaxseed [p value < 0.12]. The two-year serum creatinine determination [Table 4] demonstrated that there was a statistically significant difference with compliant patients having lower serum creatinine at the end of the study than those 17 patients who refused to participate in the study [$p < 0.05$]. As well, there was a trend toward statistical significance when the compliant patients at the end of two years were compared with those who refused to participate in the study plus those who dropped out with a p value of < 0.07 . The compliant patients did better than those who refused to enter the study. Mean 12-hour urine microalbumin was 220 ± 290 mg at baseline, in the control phase it

Table 4. Serum Creatinine Levels (mg/dL) at Completion of Study of All Groups of Patients

	n	Mean	SEM
Completed Study	15	1.00	0.14
Compliant*†	9	0.94	0.11
Refused†	17	1.20	0.21
Refused/Dropped Out*	21	1.40	0.23

* $p = 0.073$, † $p < 0.05$.

increased to 222 ± 170 mg and in the flaxseed phase decreased to 190 ± 170 mg. This trend was not statistically significant. A non-statistically significant trend for the microalbumin to urine creatinine ratio was demonstrated in the flaxseed *versus* the control phase where the ratio was 27.6 ± 42.3 *versus* 50.8 ± 74.1 [Table 3] [$p < 0.235$].

DISCUSSION

The immunologic mediation of inflammatory vascular injury and the concomitant accelerated rate of atherogenesis predisposes lupus patients to increased renal failure and vascular death late in the disease [1–9]. The pattern of vascular injury may be amenable to flaxseed dietary supplementation which can alter immune, inflammatory and atherosclerotic events [19–26]. The current study indicates that 30 grams of flaxseed, which were well tolerated in the 12 week dosing study, were not well tolerated over one year of the two-year crossover [16]. Twenty-three patients were enrolled, and eight dropped out of the study, and six of those who remained failed to demonstrate an α -linolenic acid profile compatible with the ingestion of the flaxseed. An adherence rate of 39% for a one-year study suggests that a 30-gram dose of flaxseed was not well tolerated for an extended time period. Adherence studies for asymptomatic disease often indicate a one-year self-reported compliance rate of approximately 50% [28,29]. The dietary enquiry did indicate that subjects were not changing their diet *vis-à-vis* whether they were consuming the flaxseed or not. Patients complying with flaxseed supplementation over the period of one year did not show any significant alteration in LDL or HDL levels. We had demonstrated a small

Table 3. Serum Creatinine Levels (mg/dL) and Microalbumin:Urine Creatinine Ratio in the Compliant Patients at Various Phases of the Study

	n	Serum Creatinine		Microalbumin:Urine Creatinine Ratio	
		Mean	SEM	Mean	SEM
Baseline	9	0.97	0.11	38.9	17.0
Control	9	1.03†	0.10	50.8‡	26.2
Flaxseed	9	0.94†	0.11	27.6‡	15.0
Washout	9	1.08	0.11	44.2	18.6

† $p = 0.081$, ‡ $p = 0.235$.

lipid-lowering effect of the LDL during our dosing study, but this effect was not apparent with the longer usage in this study [26]. Singer had noted in 15 male subjects with essential hypertension that supplementing their diet with approximately 4× the quantity of α -linolenic acid than our patients received would have produced a significant LDL cholesterol lowering of approximately 16% [30]. Cunnane had also noted in a short 4-week dosing study that 50 grams of flaxseed per day resulted in an 8% decrease in the LDL cholesterol [31]. We noted a non-significant decline of 4% in the LDL cholesterol using a reduced dose of flaxseed [30 *versus* 50 grams]. We had noted in our previous short-term dosing study that 45 grams of flaxseed produced an even greater lowering in LDL cholesterol [26]. Thus, our current findings are compatible with the observations of Singer and Cunnane.

Renal function as assessed by serum creatinine and microalbumin and microalbumin to creatinine ratio did reveal trends. The patients who complied with the flaxseed supplementation over the period of one year, as compared to the year without flaxseed supplementation, had a reduction in their serum creatinine and a similar trend in the reduction of their proteinuria with both 12-hour microalbumin levels and the microalbumin:creatinine ratio. The trend for the serum creatinine to decline in the nine flaxseed compliant patients and to rise when they were not taking flaxseed supplementation was similar in the fifteen lupus patients who completed the study.

When the serum creatinine from baseline to end of flaxseed is compared in patients who were compliant *versus* those who refused to enter the study, a statistically significant difference of <0.05 was noted [Table 4]. This result may be due to the action of the flaxseed. However, there are two other explanations for some of the changes in renal function noted in our study. It is possible that patients involved in the study demonstrated the Hawthorne effect in which subjects have better outcomes when they are under conditions of study. This Hawthorne effect could have explained the difference with study patients *versus* the non-entry and drop-out comparisons. This difference, as well, might have reflected the better outcome that occurred to compliant patients who are taking their other medications, i.e. immuno suppressives and antihypertensives, more faithfully and thus gain the known benefits of therapy with resultant better renal outcome [32]. However, when kidney function was compared for compliant subjects consuming and not consuming flaxseed, trends for improved renal function occurred while taking the flaxseed and declined when not taking the flaxseed. It is possible that a smaller dose of flaxseed such as the 15 grams per day flaxseed supplementation used in our previous short term dosing study might have been as effective in slowing the progression of the nephritis without the complications of increased laxation and indifferent patient cooperation noted with taking the 30 grams of flaxseed [26].

We can conclude that 30 grams of flaxseed per day was poorly tolerated by the majority of patients with SLE nephritis. However, in those who were adherent to the 30 grams of

ground flaxseed per day, there was an improvement in renal function as we had noted in our shorter dosing study [26]. The power of this crossover design to detect a $>10\%$ difference in serum creatinine was 0.62. However, the 39% adherence rate compromised the limited power of our study. Thus, the findings underscore the difficulties of adherence with a 30 gram ground flaxseed supplement over an extended time period and may serve to stimulate larger controlled studies to confirm or refute flaxseed's potential. It may also attract studies directed at specific subcomponents of flaxseed which may have better adherence patterns. We can conclude that our study was underpowered due to poor adherence and suffered from potential Hawthorne effects which may have been responsible for some, but not all, of the improved trends in renal outcome in patients taking flaxseed.

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REFERENCES

1. Dubois EL, Wierchowicki M, Cos MB, Weiner JM: Duration and death in systemic lupus erythematosus. An analysis of 249 cases. *JAMA* 227:1399–1402, 1974.
2. Albert DA, Hadler NM, Ropes MW: Does corticosteroid therapy affect the survival of patients with systemic lupus erythematosus? *Arthr Rheum* 22:945–953, 1979.
3. Ginzler EM, Diamond HS, Weiner M, Schlesinger M, Fries JF, Wasner C, Medsger Jr TA, Ziegler G, Klippel JH, Hadler NM, Albert DA, Hess EV, Spencer-Green G, Grayzel A, Worth D, Hahn BH, Barnett EV: A multi-center study of outcome in systemic lupus erythematosus. 1. Entry variables as predictors of prognosis. *Arthr Rheum* 25:601–611, 1982.
4. Balow JE, Austin III HA, Tsokos GC, Antonobych TT, Steinberg AD, Klippel JH: Lupus nephritis [NIH Conference]. *Ann Int Med* 106:79–94, 1987.
5. Ponticelli C, Zucchelli P, Moroni G, Cagnali L, Bonfi G, Pasquali S: Long-term prognosis of diffuse lupus nephritis. *Clin Nephrol* 28:263–271, 1987.
6. Urowitz MB, Bookman AAM, Koehler BE, Gordon DA, Smythe HA, Orgyzo MA: The bi-model mortality of systemic lupus erythematosus. *Am J Med* 60:221–225, 1976.
7. Karsh J, Klippel JH, Balow JE, Decker JL: Mortality in lupus nephritis. *Arthr Rheum* 22:764–769, 1979.
8. Correia P, Cameron JS, Lian JD, Hicks J, Ogg CS, Williams DG, Chantler C, Haycock DG: Why do patients with lupus nephritis die? *Brit Med J* 290:126–131, 1985.
9. Hosenpud JD, Mortanaro A, Hart MV, Haines JE, Specht HD, Bennett RM, Kloster FE: Myocardial perfusion abnormalities in asymptomatic patients with systemic lupus erythematosus. *Am J Med* 77:286–292, 1984.
10. Prickett JD, Robinson DR, Steinberg AD: Dietary enrichment with

- the polyunsaturated fatty acid eicosapentaenoic acid prevents proteinuria and prolongs survival in NZB × NZW/F₁ mice. *J Clin Invest* 68:556–559, 1981.
11. Prickett JD, Robinson DR, Steinberg AD: Effects of dietary enrichment with eicosapentaenoic acid upon auto-immune nephritis in female NZB × NZW/F₁ mice. *Arthr Rheum* 26:133–139, 1983.
 12. Robinson DR, Prickett JD, Makoul GT, Steinberg AD, Calvin RB: Dietary fish oil reduces progression of established renal disease in [NZB × NZW]F₁ mice and delays renal disease in BXSb, and MRL/1 strains. *Arthr Rheum* 29:539–546, 1986.
 13. Clark WF, Parbtani A, Huff MW, Reid B, Holub BJ, Falardeau P: Omega-3 fatty acid dietary supplementation in systemic lupus erythematosus. *Kidney Int* 36:653–660, 1989.
 14. Clark WF, Parbtani A, Naylor CD, Levinton CM, Muirhead N, Spanner E, Huff MW, Philbrick DJ, Holub BJ: Fish oil in lupus nephritis: Clinical findings and methodological implications. *Kidney Int* 44:75–86, 1993.
 15. Thompson LU, Robb P, Serraino M, Cheung F: Mammalian lignan production for various foods. *Nutr Cancer* 16:43–52, 1991.
 16. Kelley DS, Branch LB, Love JE, Taylor OC, Rivera YM, Iacono JM: Dietary alpha-linolenic acid and immunocompetence in humans. *Am J Clin Nutr* 53:40–46, 1991.
 17. Singer P, Jaeger W, Berger I, Barleben H, Wirth M, Richter-Heinrich E, Voigt S, Godicke W: Effects of dietary oleic, linolenic and alpha-linolenic acids on blood pressure, serum lipids, lipoproteins and the formation of eicosanoid precursors in patients with mild essential hypertension. *J Human Hypertens* 4:227–233, 1990.
 18. Shen TY, Hussaini IM: Kadsurenone and other related lignans as antagonists of platelet-activating factor receptor. *Meth Enzymol* 187:446–454, 1990.
 19. Hall AV, Parbtani A, Clark WF, Spanner E, Keeney M, Chin-Yee I, Philbrick DJ, Holub BJ: Abrogation of MRL/lpr lupus nephritis by dietary flaxseed. *Am J Kidney Dis* 2:326–332, 1993.
 20. Camussi G, Tetta C, Coda R, Segoloni GP, Vercellone A: Platelet-activating factor-induced loses of glomerular anionic charges. *Kidney Int* 25:73–81, 1984.
 21. Macconi D, Noris M, Benfenati E, Quaglia R, Pagliarino G, Remuzzi G: Increased urinary excretion of platelet activating factor in mice with lupus nephritis. *Life Sci* 48:1429–1437, 1991.
 22. Morigi M, MacConi D, Riccardi E, Baccardo P, Zilio P, Bertani T, Remuzzi G: Platelet-activating factor receptor blocking reduces proteinuria and improves survival in lupus auto-immune mice. *J Pharm Exp Ther* 258:601–606, 1991.
 23. Baldi E, Emancipator SN, Hassan MO, Dunn MJ: Platelet activating factor receptor blockade ameliorates murine systemic lupus erythematosus. *Kidney Int* 38:1030–1038, 1990.
 24. Tetta C, Bussolino F, Modena V, Montruccio G, Segoloni G, Pescarmona G, Camussi G: Release of platelet-activating factor in systemic lupus erythematosus. *Int Arch Allergy Appl Immunol* 91:244–256, 1990.
 25. Kelley VE, Ferretti A, Izui S, Strom TB: A fish oil diet rich in eicosapentaenoic acid reduces cyclooxygenase metabolites, and suppresses lupus in MRL-lpr mice. *J Immunol* 134:1914–1919, 1985.
 26. Clark WF, Parbtani A, Huff MW, Spanner E, de Salis H, Chin-Yee I, Philbrick DJ, Holub BJ: Flaxseed: A potential treatment for lupus nephritis. *Kidney Int* 48:475–480, 1995.
 27. Wright DJ, Jenkins DE: Simplified method for estimations of serum and plasma viscosity in multiple myeloma and related disorders. *Blood* 36:516–522, 1970.
 28. Eraker SA, Kirscht JP, Becker MH: Understanding and Improving Patient Compliance. *Ann Int Med* 100:258–268, 1984.
 29. Gibaldi Milo: Failure to Comply: A Therapeutic Dilemma and the Bane of Clinical Trials. *J Clin Pharmacol* 36:674–682, 1996.
 30. Singer P, Jaeger W, Berger I, Barleben H, Wirth M, Richter-Heinrich E, Voigt S, Gödicke W: Effects of dietary oleic, linolenic and α-linolenic acids on blood pressure, serum lipids, lipoproteins and the formation of eicosanoid precursors in patients with mild essential hypertension. *J Human Hypertension* 4:227–233, 1990.
 31. Cunnane SC, Hamadeh MJ, Liede AC, Thompson LU, Wolever TM, Jenkins DJ: Nutritional attributes of traditional flaxseed in healthy young adults. *Am J Clin Nutr* 61:62–68, 1995.
 32. Horwitz RI, Horwitz SM: Adherence to Treatment and Health Outcomes. *Arch Intern Med* 153:1863–1868, 1993.

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