Potent Antihypertensive Action of Dietary Flaxseed in Hypertensive Patients

Delfin Rodriguez-Leyva, Wendy Weighell, Andrea L. Edel, Renee LaVallee, Elena Dibrov, Reinhold Pinneker, Thane G. Maddaford, Bram Ramjiawan, Michel Aliani, Randolph Guzman, Grant N. Pierce

Abstract—Flaxseed contains ω-3 fatty acids, lignans, and fiber that together may provide benefits to patients with cardiovascular disease. Animal work identified that patients with peripheral artery disease may particularly benefit from dietary supplementation with flaxseed. Hypertension is commonly associated with peripheral artery disease. The purpose of the study was to examine the effects of daily ingestion of flaxseed on systolic (SBP) and diastolic blood pressure (DBP) in peripheral artery disease patients. In this prospective, double-blinded, placebo-controlled, randomized trial, patients (110 in total) ingested a variety of foods that contained 30 g of milled flaxseed or placebo each day over 6 months. Plasma levels of the ω-3 fatty acid α-linolenic acid and enterolignans increased 2- to 50-fold in the flaxseed-fed group but did not increase significantly in the placebo group. Patient body weights were not significantly different between the 2 groups at any time. SBP was ≈10 mm Hg lower, and DBP was ≈7 mm Hg lower in the flaxseed group compared with placebo after 6 months. Patients who entered the trial with a SBP ≥140 mm Hg at baseline obtained a significant reduction of 15 mm Hg in SBP and 7 mm Hg in DBP from flaxseed ingestion. The antihypertensive effect was achieved selectively in hypertensive patients. Circulating α-linolenic acid levels correlated with SBP and DBP, and lignan levels correlated with changes in DBP. In summary, flaxseed induced one of the most potent antihypertensive effects achieved by a dietary intervention. (Hypertension. 2013;62:00-00.)

Key Words: alpha linolenic acid ▪ flax ▪ hypertension ▪ myocardial infarction ▪ peripheral arterial disease ▪ polyunsaturated fatty acid ▪ stroke

Hypertension is one of the most important risk factors associated with both cardiovascular and cerebrovascular disease.1,2 Hypertension is defined as a systolic blood pressure (SBP) of ≥140 mm Hg or a diastolic blood pressure (DBP) of ≥90 mm Hg.3 A SBP of >115 mm Hg has been suggested to be the single most important determinant for death in the world today.4 The direct and indirect economic cost of hypertension was >$76 billion 2 years ago.5 Understanding how to reduce BP has become, therefore, a critical challenge.

Improper nutrition has been implicated in hypertensive cardiovascular disease (CVD). At the same time that BP was increasing in the United States in the 1990s, healthy eating patterns and the intake of fresh fruits and vegetables were decreasing and the incidence of obesity was increasing.6 People who were eating more vegetables (ie, vegetarians) or who had low sodium intake do not exhibit any change in BP with advancing age.6 It has been estimated that nutritional factors may be responsible for ≈40% of all CVD,7 including hypertension. The dietary factors that influence BP have traditionally included Na+, K+, caloric content, caffeine, and alcohol.8

The purpose of this research was to study another nutritional intervention—flaxseed. The seed has a pleasant nutty flavor that can be eaten as is or incorporated into a number of food products. In animal trials, flaxseed has shown an unusually strong capacity to regulate CVD through its antiatherogenic effects,9-12 anti-inflammatory properties,11 improvements in vascular contractile function,10 and a potent antiarrhythmic action during ischemic challenge.13 Flaxseed may achieve these cardiovascular actions through its composition. It is high in dietary fiber, one of the richest sources of the short-chain ω-3 fatty acid α-linolenic acid (ALA), and it also contains lignans, which are potent antioxidants.9-13 Although these data provide compelling evidence to justify the use of flaxseed in CVD, few studies have investigated its efficacy in a patient population.

Received July 22, 2013; first decision August 12, 2013; revision accepted September 6, 2013.

From the Cardiovascular Research Division, V.I. Lenin University Hospital, Holguin, Cuba (D.R.-L.); and Department of Surgery, St Boniface Hospital and the Asper Clinical Research Institute (W.W., R.G.), Canadian Centre for Agri-food Research in Health and Medicine, St Boniface Hospital Research Centre, Department of Physiology, Faculties of Medicine and Pharmacy (A.L.E., R.L., E.D., R.P., T.G.M., B.R., G.N.P.), and Department of Human Nutritional Sciences, Faculty of Human Ecology (M.A.), University of Manitoba, Winnipeg, Manitoba, Canada.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.orglookup/suppl/doi:10.1161/HYPERTENSIONAHA.113.02094/-/DC1.

Correspondence to Grant N. Pierce, St Boniface Hospital Research Centre, 351 Tache Ave, Winnipeg, Manitoba, Canada R2H 2A6. E-mail gpierce@sbc.ca

© 2013 American Heart Association, Inc.

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.113.02094
Hypertension is strongly associated with patients who have peripheral artery disease (PAD). Ninety-two percent of PAD patients in the PARTNER trials had high BP. BP is a strong predictor of PAD. BP is a major risk factor for both symptomatic and noninvasively determined PAD. It is not surprising, therefore, that the majority of deaths in patients with PAD are the result of cardiovascular events. Approximately 20% of people >70 years of age have PAD. PAD patients also have a prevalence of heavy smoking habits, diabetes mellitus, hypercholesterolemia, and coronary atherosclerosis. Because of the vascular effects of flaxseed in animal studies, it was thought that a patient population with PAD may be ideal to respond to dietary flaxseed. This double-blinded, placebo-controlled, randomized FLAX-PAD (FLAX effects in Peripheral Arterial Disease) trial has focussed on the effects of dietary flaxseed on SBP and DBP over a 6-month ingestion period.

### Methods

The study design has been described previously. This clinical trial was registered (NCT00781950) at ClinicalTrials.gov. Briefly, 110 PAD patients were recruited into this double-blinded, placebo-controlled, randomized trial. Inclusion criteria were patients must be >40 years and have had PAD for >6 months with an ankle brachial index <0.9. Exclusion criteria included inability to walk, bowel disease, moderate to severe renal failure, life expectancy <2 years with high baseline cardiac risk, allergies to any ingredient in the study product, patients who plan to undergo surgery during the course of the trial, and no more than 2 fish meals per week. In this trial, changes in SBP and DBP were defined as secondary end points. During the baseline visit, a questionnaire related to past and present medical history as well as medications was administered by the attending nurses. As depicted previously, the baseline characteristics of the FLAX-PAD patients are shown in the Table. Briefly, these patients had an average age of 67 years, 90% were current or ex-smokers, 75% were hypertensive, 32% diabetic, and 79% hyperlipidemic. Some of these patients were on blood sugar–lowering, lipid-lowering, antihypertensive, or antithrombotic medication. The patients were fed a variety of foods (bagels, muffins, bars, buns, and Table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (N=110)</th>
<th>Flaxseed (n=58)</th>
<th>Placebo (n=52)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>67.3±8.5</td>
<td>67.4±8.06</td>
<td>65.3±9.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smokers, %</td>
<td>66.4</td>
<td>68.4</td>
<td>65.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>26.3</td>
<td>19.2</td>
<td>34.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>75.4</td>
<td>81.0</td>
<td>69.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus, %†</td>
<td>31.8</td>
<td>36.2</td>
<td>26.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Hyperlipidemia, %‡</td>
<td>79.1</td>
<td>81.0</td>
<td>76.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Known CAD, %</td>
<td>39.1</td>
<td>44.8</td>
<td>32.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin therapy or BSLD, %</td>
<td>25.4§</td>
<td>29.3</td>
<td>19.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Lipid-lowering drugs, %</td>
<td>73.6</td>
<td>77.5</td>
<td>71.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Antihypertensive drugs, %</td>
<td>79.1</td>
<td>84.4</td>
<td>73.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Antithrombotic drugs, %</td>
<td>90.0</td>
<td></td>
<td></td>
<td>89.6</td>
</tr>
<tr>
<td>Baseline lipids, mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total-C, mmol/L</td>
<td>4.5±1.2</td>
<td>4.4±1.1</td>
<td>4.5±1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.6±0.7</td>
<td>1.6±0.7</td>
<td>1.7±0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
<td>1</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.5±1.0</td>
<td>2.5±1.0</td>
<td>2.6±1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>3.9±1.2</td>
<td>3.9±1.1</td>
<td>3.9±1.2</td>
<td>1</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>2.2±1.0</td>
<td>2.2±1.1</td>
<td>2.3±0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Other measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8±4.5</td>
<td>27.4±4.4</td>
<td>28.1±4.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Baseline systolic BP, mm Hg</td>
<td>142.9±20.1</td>
<td>143.3±22.2</td>
<td>142.4±17.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Baseline diastolic BP, mm Hg</td>
<td>77.5±12.8</td>
<td>77.0±9.5</td>
<td>79.0±15.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Baseline right ABI</td>
<td>0.78±0.2</td>
<td>0.77±0.23</td>
<td>0.78±0.22</td>
<td>0.8</td>
</tr>
<tr>
<td>Baseline left ABI</td>
<td>0.77±0.2</td>
<td>0.78±0.21</td>
<td>0.76±0.22</td>
<td>0.6</td>
</tr>
</tbody>
</table>

ABI indicates ankle brachial index; BP, blood pressure; BSLD, blood sugar–lowering drugs; CAD, coronary artery disease; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; and total-C, total cholesterol. Part of this table (the All Patients column) is reproduced from Leyva et al with permission.

*Hypertension is classified according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).
†Previous personal history of diabetes mellitus or insulin therapy/oral blood glucose–lowering drugs.
‡Total-C ≥5.2 mmol/L, LDL-C ≥3.4 mmol/L, triglycerides ≥1.7 mmol/L, HDL-C ≤1.0 mmol/L, or on lipid-lowering drugs.
§80% of diabetic patients were under insulin therapy or blood sugar–lowering drugs.
||At least 1 antithrombotic drug.
pasta, tea biscuits) that contained 30 g of milled flaxseed or a placebo. Each product contained 30 g of milled flaxseed, and 1 product was ingested per day over the 6-month period of the study. Some of the foods had different flavorings to give the foods sufficient variety to ensure compliancy over the time of the study. The placebo product contained the same flavorings but did not contain flaxseed. Milled wheat replaced the flaxseed. In some products, wheat was mixed with a very small amount of bran, and molasses was used so that the color and texture resembled that of a product that contained flaxseed. Details concerning the ingredients have been described previously. \(^{18–20}\) In preliminary tests, subjects could not easily identify if the food contained the flaxseed or not. Furthermore, at the end of the study, 44% of subjects failed to correctly identify the group in which they participated. Food composition is described in detail elsewhere. \(^{18–20}\) BP measurements were done according to previously published recommendations. \(^21\) Briefly, resting BP was measured in the seated position in a quiet room by well-trained nurses using a mercury sphygmomanometer. The average of a total of 3 readings was used as the final measurement. The measurement was performed under controlled conditions in a quiet room and using the same protocol at both the baseline and follow-up examinations. Plasma fatty acids were quantified as described. \(^{10–13,18}\) Enterolignans were deconjugated as previously described \(^{22}\) followed by supported liquid extraction to isolate the liberated compounds. Analysis was by gas chromatography/mass spectrometry in microselected ion storage mode using a target ion of 180 for quantitation of both enterolignans. The study was conducted in accordance with the Declaration of Helsinki. Written approval from Health Canada and its Natural Health Products Directorate, the University of Manitoba Research Ethics Board, and St Boniface Hospital was obtained. Each FLAX-PAD participant provided written consent. The procedures followed were in accordance with institutional guidelines. A Safety Monitoring Committee met during the study to ensure patient safety was monitored.

### Statistical Analysis

Continuous variables were expressed as a mean±SD. Categorical variables were expressed as proportions. A Z test was used to compare the proportions of 2 groups found within a single category. Categorical variables were compared with \(\chi^2\) test. Continuous variables were compared with a 2-tailed Student t test. When smaller than expected frequencies were found, a Fisher exact test was used. Pearson correlation coefficients were used to explore the bivariate associations between SBP, DBP, plasma lipids, and enterolignans. Differences were considered significant when probability values were <0.05.

### Results

A total of 110 patients were enrolled in the FLAX-PAD study. After randomization, 58 were allocated to the flaxseed group and 52 to the placebo group (Figure 1). Their baseline characteristics are found in the Table. \(^18\) There were no significant differences in any of the characteristics of the patients when they were examined as a function of the group in which they were enrolled (Table). After 6 months, 13 patients from the flaxseed group and 11 from placebo group withdrew from the study (Figure 1). Overall, the dropout rate was 22.4% and 21.2% for the flaxseed and the placebo groups, respectively (\(P>0.05\)).

Body weights of the patients were not significantly different between flaxseed versus placebo groups at baseline (81.0±14.9 versus 82.4±14.8; \(P=0.6\)) or after 6-month intervention (83.8±14.8 versus 81.4±14.5; \(P=0.4\)). Body mass index (Table) and waist circumference values (data not shown) were not significantly different between the 2 groups at any time point.

Plasma levels of enterolignans and the \(\omega-3\) fatty acid ALA were used as markers of dietary compliancy. Both ALA and lignans are enriched in flaxseed, and both are not commonly found in most food products. Therefore, the identification of 1 or both of these bioactives in the blood of the patients represents a clear indication of dietary compliancy. Levels of ALA, eicosapentaenoic acid, and docosahexaenoic acid at baseline, 1 month, and 6 months are shown in Figure 2A–C. Plasma levels of all of the \(\omega-3\) fatty acids were similar at baseline.

![Figure 1](http://hyper.ahajournals.org/DownloadedFrom/10.1161/HYPAHA.117.139444.Figure1.png)
in the placebo and flaxseed-fed groups. A significant 2-fold increase in plasma ALA levels was detected in the flaxseed group (P=0.003 versus placebo group) at 1 and 6 months. A significant increase in plasma eicosapentaenoic acid levels was also observed in the flaxseed group versus placebo. Docosahexaenoic acid levels in the flaxseed group did not change over the course of the study. No significant changes in any of the plasma ω-3 fatty acid levels of the placebo group were detected.

Plasma levels of the enterolignans were all similar at baseline in the placebo and flaxseed-fed groups. However, plasma levels of enterolactone increased about 10-fold in the flaxseed group, whereas enterodiol levels increased by ≈50-fold after 1 and 6 months of intervention (P<0.001 versus placebo; Figure 2D and 2E). Levels of total enterolignans also increased significantly (≈10-fold) in the flaxseed group (P<0.001 versus placebo) after 1 and 6 months (Figure 2F). No statistically significant changes were found in any enterolignans in the placebo group at any time point.

BP measurements at baseline did not differ significantly between the 2 experimental groups (Figure 3). SBP and DBP consistently decreased in the flaxseed group over the course of the study. After 6 months, SBP in the flaxseed group dropped significantly to 136±22 mm Hg (P=0.04). On the contrary, in the placebo group, SBP rose slightly to 146±21 mm Hg. After 6 months of intervention, DBP in the flaxseed group fell to 72±11 mm Hg (P=0.004), whereas DBP in the placebo group remained the same (79±10 mm Hg). In summary, the flaxseed intervention maintained SBP at 10 mm Hg lower than placebo (−6.5% reduction) and DBP at 7 mm Hg lower (−9.8% reduction). Although the present article has focussed on a report of data up to 6 months of intervention, this study continued to 1 year in duration. At 1 year, SBP had increased slightly to 138.2±20.4 mm Hg from 136.2 mm Hg at 6 months in the flaxseed group. SBP in the placebo group remained virtually unchanged from 145.6 at 6 months to 144.6±16.1 mm Hg at 1 year. DBP was also relatively unchanged in the flaxseed group from its 6-month value of 71.8 to 71.3±10.8 mm Hg at 1 year. DBP in the placebo group was 78.5 at 6 months and 75.4±9.1 mm Hg at 1 year.

Changes in SBP and DBP were examined in a subgroup of patients that entered the trial with a SBP ≥140 mm Hg (Figure 4). The patients who received flaxseed obtained a sustained and larger reduction in SBP (15 mm Hg) and DBP...
Rodriguez-Leyva  Flaxseed and Hypertension  5

...(7 mm Hg) after 6 months of intervention, whereas the BP did not change significantly in the placebo group.

Forty-nine patients from the flaxseed group (84.4%) and 38 from the placebo group (73.0%) were under treatment with 23 different combinations of antihypertensive drugs based on 5 pharmacological groups (diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers). Angiotensin-converting enzyme inhibitors and diuretics were present in 85% and 65% of the treatment regimes for the flaxseed and placebo groups, respectively (P>0.05).

Ankle brachial index did not change significantly during the intervention period (0.77±0.23 versus 0.78±0.22; P=0.8) at baseline for flaxseed and placebo groups, respectively (0.80±0.24 versus 0.81±0.22; P=0.8) at the end of the study.

Markers of renal function were examined. Plasma creatinine, uric acid, and blood urea nitrogen (Table S1 in the online-only Data Supplement) did not show any significant changes (P>0.05) in either group at any time point. Furthermore, subgroup analysis of these variables in patients with BP ≥140/90 mmHg did not demonstrate any variation over time (data not shown).

The relationship of plasma lipids and enterolignan levels to BP was studied. Circulating levels of ALA were significantly correlated with SBP (P<0.04) and DBP (P<0.01; Figure 5). Circulating levels of total enterolignans (Figure 6), enterodiol (Figure 7), and enterolactone (Figure 8) also...

Figure 3. Mean systolic and diastolic blood pressure at baseline, 1 month, and 6 months for placebo (PL) and flaxseed (FX) groups.*P=0.04, flaxseed vs placebo for systolic blood pressure at 6 months; †P=0.004, flaxseed vs placebo for diastolic blood pressure at 6 months.

Figure 4. Mean systolic and diastolic blood pressure among hypertensive patients (BP ≥140/90 mm Hg) on flaxseed (FX) at baseline, 1 month, and 6 months; *P=0.04 baseline vs 1 month; †P=0.002 baseline vs 6 months; ‡P=0.01 baseline vs 1 month; §P=0.003 baseline vs 6 months. PL indicates placebo.

Figure 5. Correlation of mean systolic blood pressure with mean plasma α-linolenic acid (ALA) levels (top) or diastolic blood pressure (bottom) in patients fed flaxseed at baseline (a), for 1 month (b) and 6 months (c) and in the placebo group at baseline (d), for 1 month (e) and 6 months (f). The Pearson correlative r values were statistically significant for ALA and both systolic (P=0.037) and diastolic (P=0.007) blood pressures.
Hypertension

December 2013

correlated with DBP \((P<0.05)\). Circulating levels of enterodiol (Figure 7) correlated with SBP \((P<0.05)\). Total enterolignans levels also trended toward a significant correlation with SBP (Figure 6) but did not reach statistical significance \((P=0.056)\). No other significant correlations of different lipids with BP were detected (Table S2).

The use of flaxseed in PAD patients was relatively safe. Two patients in the placebo group and 1 in the flaxseed group suffered strokes during the trial. Four patients in the placebo group and 2 patients in the flaxseed group suffered a myocardial infarction. One additional patient in the flaxseed group died from a myocardial infarction, but this occurred <3 weeks of enrolling in the study. There were no statistically significant differences between the groups in any of these parameters.

**Discussion**

SBP was elevated in many of the patients entering this study despite the presence of a variety of antihypertensive medications. This is not unusual in a PAD patient population where the physician is commonly trying to control a myriad of cardiovascular risk factors. The most important finding from the FLAX-PAD study was the potent antihypertensive effect shown by patients who ingested flaxseed. This represents a major advance in the treatment of hypertension from a number of perspectives. First, it is the first demonstration of the effects of dietary flaxseed on a hypertensive population. It is noteworthy that the present study was done in a placebo controlled, double-blinded, randomized manner. In contrast to the flaxseed-fed group, patients who fed the placebo food had BP values that were stable or slightly elevated over the course of the study. Compliance was carefully monitored through plasma ALA and enterolignan levels. The absence of a rise in these parameters for a patient in flaxseed group would strongly argue that the patient was noncompliant with the diet. Conversely, unexpected increases in both of these parameters in the blood from a patient in placebo group would strongly suggest dietary noncompliance as well. We did not detect either of these scenarios in patients enrolled in this study. Furthermore, the lack of a rise in plasma docosahexaenoic acid in both groups suggests all patients were compliant with restrictions in the intake of fish during this trial, and, therefore, marine \(\omega-3\) fats were not a confounding factor. It has been
shown previously that ALA can be converted in a limited manner to the longer-chain polyunsaturated fatty acid, eicosapentaenoic acid.\textsuperscript{24} In addition, the BP effects were gradual. After 1 month of dietary intervention (when the dose of flaxseed was still being phased in and gradually increased each week), SBP and DBP were reduced modestly but significantly. Second, the effects were demonstrated even in the presence of the administration of antihypertensive medication to these patients. Thus, flaxseed represents an effective combination of nonpharmacological and pharmacological therapies.\textsuperscript{3} Approximately 80% of those patients who ingested flaxseed decreased their dose of antihypertensive medications versus 3.5% in the placebo group. The presence of antihypertensive medication during the trial makes it impossible to conclusively determine if the effects of dietary flaxseed on BP were an independent antihypertensive action of flaxseed or because of a boosting of the effects of the medication. Further trials will be needed to clearly identify the independent BP-lowering action of flaxseed. Third, the magnitude of the effect on BP would be expected to result in a significant decrease in the incidence of cardiovascular events over time. A reduction of 7 mmHg in DBP would be expected to result in a 46% and 29% decrease in the incidence of stroke and coronary heart disease, respectively.\textsuperscript{25,26} A 10 mmHg decrease in SBP would result in a 36% and 27% decrease in the incidence of stroke and myocardial infarctions, respectively.\textsuperscript{25,26} Our results show a trend for a beneficial effect of flaxseed in decreasing the incidence of these events (2 patients and 1 patient suffered strokes in the placebo and flaxseed groups, respectively; and 4 patients and 2 patients suffered a myocardial infarction in the placebo and flaxseed groups, respectively), but a larger, comprehensive, multicentered trial is likely necessary to unequivocally show this. Fourth, severely hypertensive patients will benefit the most from dietary flaxseed. Hypertensive patients with an initial SBP >140 mm Hg responded to dietary flaxseed with an average decrease of 15 mm Hg. The magnitude of this decrease in BP demonstrated by dietary flaxseed, therefore, is as good or better than other nutritional intervention and comparable to many drugs.\textsuperscript{27} DBP did not react as strongly to the flaxseed intervention in the present trial (Figure 1), although this may be because it is not as highly elevated at the start of the study as was SBP. Finally, the use of flaxseed as an antihypertensive therapy appears to be relatively safe. There were no significant differences between the groups in any of the major cardiovascular complications. Furthermore, higher doses (up to 50 g/day) have been delivered without evidence of complications.\textsuperscript{28} In addition, patients with BP values in the normal range did not appear to respond to flaxseed with a decrease in BP, which may be dangerous. This is consistent with previous reports of modest (if any) effects of dietary flaxseed on BP in healthy populations.\textsuperscript{28–30} This lack of effect on BP in previous studies may have been because of the use of normotensive populations to examine the effects of flaxseed, or because of the relatively short study period (ie, 3 weeks).\textsuperscript{30}

Four components within flaxseed may be responsible for the changes in BP: ALA, lignans, fiber, peptides, or a synergistic action of all 4 components together. The correlation of plasma ALA with both DBP and SBP (Figure 5) is consistent with epidemiological associations of dietary ALA with a lower prevalence of hypertension and lower SBP.\textsuperscript{31–33} The anti-inflammatory action of ALA\textsuperscript{11} may explain its antihypertensive action. Inflammation has been implicated in the genesis of high BP.\textsuperscript{34} Alternatively, the rich lignan content within flaxseed may provide an antihypertensive effect through its antioxidant action.\textsuperscript{8–13} Free radicals have been suggested to play a role in hypertension.\textsuperscript{14} In a randomized controlled trial of older adults ingesting a lignan complex isolated from flaxseed, a modest but significant decrease in DBP (but not SBP) was observed at 6 months.\textsuperscript{35} The present data extend this to now show that both enterolactone and enterodiol are likely responsible for this effect on DBP, and the latter is associated with SBP. The high fiber content within flaxseed may also be important in regulating BP,\textsuperscript{36} but this could not be evaluated directly in our trial. Finally, peptides isolated from flaxseed have an inhibitory action on angiotensin-converting enzyme,\textsuperscript{37} and this may provide an antihypertensive action. However, no changes in renal biomarkers were identified. Ultimately,
the antihypertensive action of dietary flaxseed may represent a culmination of the synergistic effects of all of these components.

**Perspectives**

The antihypertensive effects of dietary flaxseed are potent, selective to hypertensive patients, and longlasting. The ALA and lignan content of flaxseed provides this antihypertensive effect. Hypertension has been recently identified as the number 1 burden of death today. It is a growing health risk in the United States and most other countries. The prevalence of hypertension increases dramatically with age, and with the percentage of elderly people growing rapidly, the threat of hypertension has become larger than before. The direct and indirect economic cost in the United States alone was >$76 billion. This presents an important challenge for countries where the financial capacity to purchase antihypertensive medication is limited. A nutritional strategy like flaxseed, which compliments antihypertensive medication and can be delivered in a relatively inexpensive manner, should be particularly appealing in economically disadvantaged populations.

**Acknowledgments**

We gratefully acknowledge the continued encouragement of Kelley Fitzpatrick and the Flax Council of Canada. We thank Canada Bread, the Canadian International Grain Institute (Winnipeg, Canada), and the Food Development Centre (Portage La Prairie, Canada) in preparing the foods for this trial. The flaxseed or wheat was provided by Glanbia Nutritional Inc. We also thank J. Alejandro Austria for distributing food to patients during this trial, and the Office for Clinical Research at St Boniface Hospital for their help in the conduct of this trial.

**Sources of Funding**

The work was supported through grants from Flax2015, the Canola Council of Canada, the Agri-food Research and Development Initiative, and the Canadian Institutes for Health Research. Indirect research support was obtained from St Boniface Hospital Foundation.

**Disclosures**

None.

**References**


What is New?

This is the first demonstration of the cardiovascular effects of dietary flaxseed in a hypertensive population.

What is Relevant?

Hypertensive patients with an initial systolic blood pressure of >140 mm Hg responded to dietary flaxseed with an average decrease of 15 mm Hg in systolic and 7 mm Hg in diastolic blood pressure. These decreases in BP are among the most potent dietary interventions observed and comparable to current medications.

Summary

In a double-blinded, placebo-controlled, randomized trial conducted >6 months, supplementation of the diet with foods that contained 30 g of milled flaxseed resulted in a potent antihypertensive effect, selectively in patients who were hypertensive.
Potent Antihypertensive Action of Dietary Flaxseed in Hypertensive Patients
Delfin Rodriguez-Leyva, Wendy Weighell, Andrea L. Edel, Renee LaVallee, Elena Dibrov, Reinhold Pinneker, Thane G. Maddaford, Bram Ramjiawan, Michel Aliani, Randolph Guzman and Grant N. Pierce

Hypertension. published online October 14, 2013;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2013/10/14/HYPERTENSIONAHA.113.02094

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2013/10/14/HYPERTENSIONAHA.113.02094.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
POTENT ANTI-HYPERTENSIVE ACTION OF DIETARY FLAXSEED IN HYPERTENSIVE PATIENTS

Delfin Rodriguez-Leyva1 MD, PhD, Wendy Weighell2 RN, Andrea L. Edel MSc3, Renee LaVallee3, Elena Dibrov3 PhD, Reinhold Pinneker3, Thane G. Maddaford3 BSc, Bram Ramjiawan PhD3, Michel Aliani4 PhD, Randolph Guzman2 MD and Grant N. Pierce3 PhD

Cardiovascular Research Division, V.I.Lenin Universitary Hospital, Holguin, Cuba1, Department of Surgery, St Boniface Hospital and the Asper Clinical Research Institute, University of Manitoba2, and Canadian Centre for Agri-food Research in Health and Medicine, St Boniface Hospital Research Centre, Department of Physiology, Faculties of Medicine and Pharmacy, University of Manitoba3, and Department of Human Nutritional Sciences, Faculty of Human Ecology, University of Manitoba, Winnipeg, Manitoba, Canada4

Running head: Flaxseed and hypertension

Word count: 5919; Abstract word count: 249

Total number of Figures: 8
Total number of Tables: 1
Total number of Supplementary Tables: 2

Address for correspondence:

Dr Grant N. Pierce, St Boniface Hospital Research Centre, 351 Tache Avenue, Winnipeg, MB Canada R2H 2A6; Tel: 204-235-3206; Fax: 204-235-3206; E-mail: gpierce@sbrc.ca
## Supplementary Tables

S1. Creatinine, uric acid and blood urea nitrogen at baseline, 1 month and 6 months in flaxseed and placebo group.

<table>
<thead>
<tr>
<th>Blood Parameter</th>
<th>Baseline</th>
<th>1 month</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flaxseed</td>
<td>123.7 ± 31.8</td>
<td>123.7 ± 27.4</td>
<td>123.7 ± 31.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>114.9 ± 32.7</td>
<td>106.0 ± 23.8</td>
<td>114.9 ± 34.4</td>
</tr>
<tr>
<td>Uric acid (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flaxseed</td>
<td>517.4 ± 93.9</td>
<td>541.2 ± 117.2</td>
<td>523.4 ± 117.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>487.7 ± 93.3</td>
<td>499.6 ± 101.1</td>
<td>511.5 ± 111.8</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flaxseed</td>
<td>8.4 ± 2.5</td>
<td>8.3 ± 2.6</td>
<td>8.4 ± 3.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.0 ± 2.9</td>
<td>7.5 ± 2.6</td>
<td>8.1 ± 3.1</td>
</tr>
</tbody>
</table>

P = NS between groups at all different point times.

Baseline: Flaxseed n=58, Placebo=52; 1 Month: Flaxseed n=52, Placebo n=47; 6 Months: Flaxseed n=45, Placebo=41.
S2. Correlation between the change in selected circulating lipids and the change in systolic and diastolic blood pressure in patients over the 6 months.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPA</strong></td>
<td>r = 0.20; P = 0.1</td>
<td>r = 0.009; P = 0.9</td>
</tr>
<tr>
<td><strong>DHA</strong></td>
<td>r = 0.10; P = 0.4</td>
<td>r = 0.002; P = 0.9</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td>r = 0.11; P = 0.5</td>
<td>r = 0.12; P = 0.4</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td>r = 0.08; P = 0.6</td>
<td>r = 0.11; P = 0.55</td>
</tr>
<tr>
<td><strong>Total Cholesterol</strong></td>
<td>r = 0.17; P = 0.3</td>
<td>r = 0.22; P = 0.17</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>r = 0.11; P = 0.5</td>
<td>r = 0.01; P = 0.97</td>
</tr>
</tbody>
</table>