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Antihypertensive Effects of Dietary Flaxseed

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Antihypertensive Effects of Dietary Flaxseed

Abstract

Background: Hypertension is one of the largest health burdens in the world, leading to stroke, coronary heart disease, myocardial infarct, peripheral artery disease (PAD) and renal failure. There are many pharmaceutical medications on the market for blood pressure management. Many of these medications have undesirable side effects or are expensive. Dietary intervention with omega-3 fatty acids has become a popular alternative to medication for blood pressure (BP) control. The cardiovascular benefits of omega-3 fatty acids consumed via fish oil have been well established. More research is being done to establish the mechanism and efficacy of other dietary sources containing fatty acids. It has been suggested that foods high in alpha-linolenic acid (ALA) may have cardio protective properties. Dietary flaxseed is one of the foods of interest being it contains the highest level of ALA. Although the mechanisms are not fully understood, dietary flaxseed may be an effective and safe alternative for BP management.

Methods: An exhaustive search was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: flax, flaxseed, linseed oil, blood pressure, and hypertension. Relevant articles were assessed for quality using GRADE. A search on the NIH clinical trials site reveals there is one trial currently registered relating to the antihypertensive effects of dietary flaxseed.

Results: Two studies met the search criteria and were included in this systematic review. The first study, FLAX-PAD, was a double blind, placebo-controlled, randomized controlled study (RCT) utilized to examine the effects of dietary flaxseed on systolic BP and diastolic BP in patients newly diagnosed with PAD. This study demonstrated the antihypertensive effects in patients consuming dietary flaxseed. Researchers also revealed the relationship between plasma ALA levels and blood pressure. The second study was a prospective, two-group, parallel-arm design RCT to examine the effects of dietary flaxseed on blood pressure in middle-aged dyslipidemic men. This study revealed a significant reduction in blood pressure in individuals receiving the intervention.

Conclusion: Daily consumption of 30g of milled flaxseed or 15mL of flax oil per day has shown an antihypertensive effect on select patient populations. The latest studies regarding flaxseed and its antihypertensive effects seem promising, but further randomized controlled trials are needed to clearly establish its efficacy.

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Antihypertensive Effects of Dietary Flaxseed

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A Clinical Graduate Project Submitted to the Faculty of the

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Biography

[Redacted for privacy]

Abstract

Background: Hypertension is one of the largest health burdens in the world, leading to stroke, coronary heart disease, myocardial infarct, peripheral artery disease (PAD) and renal failure. There are many pharmaceutical medications on the market for blood pressure management. Many of these medications have undesirable side effects or are expensive. Dietary intervention with omega-3 fatty acids has become a popular alternative to medication for blood pressure (BP) control. The cardiovascular benefits of omega-3 fatty acids consumed via fish oil have been well established. More research is being done to establish the mechanism and efficacy of other dietary sources containing fatty acids. It has been suggested that foods high in alpha-linolenic acid (ALA) may have cardio protective properties. Dietary flaxseed is one of the foods of interest being it contains the highest level of ALA. Although the mechanisms are not fully understood, dietary flaxseed may be an effective and safe alternative for BP management.

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Conclusion: Daily consumption of 30g of milled flaxseed or 15mL of flax oil per day has shown an antihypertensive effect on select patient populations. The latest studies regarding flaxseed and its antihypertensive effects seem promising, but further randomized controlled trials are needed to clearly establish its efficacy.

Keywords: Flaxseed, flax, linseed oil, hypertension, blood pressure.

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Table I: Nutritional Information of Flaxseed

Table II: Characteristics of Reviewed Studies

List of Abbreviations

AA.....	Arachodonic Acid
ABI.....	Ankle Brachial Index
ALA.....	Alpha Linolenic Acid
BMI.....	Body Mass Index
BP.....	Blood Pressure
CHD.....	Coronary Heart Disease
CHF.....	Congestive Heart Failure
COX.....	Cyclooxygenase
CV.....	Cardiovascular
CVD.....	Cardiovascular Disease
DBP.....	Diastolic Blood Pressure
DHA.....	Docosahexaenoic Acid
EPA.....	Eicosapentaenoic Acid
GRADE.....	Grade of Recommendations Assessment, Development and Evaluation
HDL.....	High Density Lipoprotein
LA.....	Linoleic Acid
MAP.....	Mean Arterial Pressure
NIH.....	National Institutes of Health
PAD.....	Peripheral Artery Disease
RCT.....	Randomized Controlled Trial
SBP.....	Systolic Blood Pressure
TXA2.....	Thromboxane A2
TXA3.....	Thromboxane A3

Antihypertensive Effects of Dietary Flaxseed

BACKGROUND

Hypertension is one of the leading causes of the global burden of disease.¹ Worldwide, 7.6 million premature deaths were attributed to high blood pressure.² It is estimated that as of 2008, approximately 68 million Americans over the age of 18 had hypertension and of those approximately 31 million had their disease under control.³ The prevalence of hypertension increases with advancing age to the point where more than half of people 60–69 years of age and approximately three-fourths of those 70 years of age and older are affected.⁴ Hypertension is an independent risk factor for coronary heart disease (CHD), congestive heart failure (CHF), stroke, renal failure and peripheral artery disease (PAD) and is defined as a blood pressure of $<140/90$. There have been numerous studies published on the importance of blood pressure control in reducing these risks. There are a variety of different antihypertensive medications on the market, and many are expensive or have side effects that may deter an individual from taking them.

Many people in the US and the world look to alternative therapy for treatment of various diseases as opposed to taking pharmaceutical medications. Dietary supplementation has become a popular alternate, providing people with numerous health benefits and reducing the risk of disease. Recent research has shown that increased levels of omega-3 fatty acid consumption appear to have a dose dependent hypotensive effect on patients who have hypertension and little to no effect on normotensive patients.⁵ Generally, we consume these fatty acids through marine oils found in fish, but recently various nuts and seeds have been identified as containing these essential fatty acids. One

such dietary supplement is flaxseed and may prove to be an important addition to the management of hypertension.

Flax is a blue flowered crop named *Linum usitatissimum* that is in the botanical family Linaceae. The terms flaxseed and linseed are used interchangeably in the US, although flaxseed is more commonly associated with the dietary supplement consumed by humans. Flax comes in a variety of forms ranging from whole seeds to oil. The seeds themselves have a chewy consistency and a nutty flavor. Flax is rich in fat, protein, and dietary fiber. It also contains modest amounts of amino acids, vitamins, and minerals (see Table I). In Canada, the most common form of flax is brown-seeded flax. It is rich in the omega-3 fatty acid alpha-linolenic acid (ALA), an essential fatty acid. The US has developed its own form of flax called Omega, which has the same high content of ALA. Flax is the richest source of ALA constituting fifty-seven percent of its total fatty acids. Both brown and Omega flax can be purchased at grocery stores or online.⁶

The mechanisms by which dietary flaxseed may help to lower blood pressure are not well established. The research to date suggests that ALA and other fatty acids may have the ability to interfere with pro-inflammatory and pro-aggregatory eicosanoids. For example, both ALA and linoleic acid (LA) are essential fatty acids that can be converted to different fatty acids, which yield different classes of the eicosanoids. Eicosanoids are signaling molecules that exert control over many bodily functions. LA can be converted to arachidonic acid (AA) via the COX pathway. By the same method, ALA can be converted to eicosapentaenoic acid (EPA) and, on a much smaller scale, docosahexaenoic acid (DHA). These are the fatty acids primarily found in cold-water marine fish.^{7,8} AA is a precursor for the powerful vasoconstrictor and platelet agonist thromboxane (TXA₂),

whereas, COX metabolism of EPA produces TXA₃, which is relatively inactive.⁹ The theory is that these two fatty acids are in competition because they utilize the same enzymatic pathways. Therefore, an excess of one can lead to the production of specific eicosanoids.^{7,8} Another possible mechanism in which flax may affect blood pressure is the presence of gamma-tocopherol, a form of Vitamin E. It is an antioxidant that promotes sodium excretion in the urine and therefore may help lower blood pressure. This has not been thoroughly researched.⁶

There have been many studies demonstrating the antihypertensive properties of ALA in animals,^{10,11,12} but not many specifically geared toward the antihypertensive effects of dietary flaxseed in humans. This review will focus on the antihypertensive effect of dietary flaxseed in humans.

METHODS

An exhaustive search was performed in OVID using the terms flax, linseed oil, or flaxseed and blood pressure or hypertension. Similar search strategy was utilized in CINAHL and Web of Knowledge. Eligibility criteria included articles written in the English-language, human studies, and randomized-controlled trials (RCT). Exclusion criteria were any articles written before the year 2005 and any studies that were not specific to dietary flaxseed. Grading of Recommendations, Assessment, Development and Evaluation (GRADE)¹³ was utilized to assess the quality of relevant articles. The National Institute of Health (NIH) clinical trials website was reviewed and found to have one registered trial¹⁴ assessing the efficacy of dietary flaxseed in reducing blood pressure in newly diagnosed hypertensive individuals. This study is still in developmental stages and is not yet recruiting any study participants.

RESULTS

The original search using the method described above generated 42 articles. After limitations were applied a total of 11 articles resulted. Of those 11 articles, two met the inclusion and exclusion criteria (See Table II).^{15,16}

The FLAX-PAD study¹⁵ was a double blind, placebo controlled RCT utilized to examine the effects of dietary flaxseed on systolic and diastolic blood pressure in patients newly diagnosed with PAD. Total length of the study was for 1 year, but the data analyzed was only up to 6 months. Inclusion criteria were patients over 40 years old who have had PAD for greater than 6 months with an Ankle Brachial Index (ABI) less than 0.9. Exclusion criteria included inability to walk, bowel disease, moderate to severe renal failure, life expectancy of less than 2 years with high baseline cardiac risk, allergies to any ingredient used in the study, patients who plan to undergo surgery during the trial, and no more than two meals of fish per week.¹⁵

A total of 110 patients were selected for this study. After randomization, patients were allocated to a treatment group and placebo. Patients in the treatment group (n=58) received 30g per day of milled flaxseed via several different foods. The patients in the placebo group (n=52) received the same foods with no flaxseed. The intervention lasted for 6 months. Care was taken to conceal the ingredients of the foods ingested. Overall, 13 patients from the flaxseed group and 11 patients from the placebo group were lost to follow-up.¹⁵

Baseline characteristics, such as, age, cardiovascular (CV) risk factors, treatments for various CV risk factors, serum lipid levels, body mass index (BMI), and BP were measured. Plasma levels of ALA were measured at baseline. Although there were no

significant differences between the treatment group and placebo in regards to baseline BMI, BP, and serum ALA, other baseline characteristics were prognostically worse in the treatment group. There were no significant differences between patients when examined as a function of the group to which they were allocated. Some patients in both groups were taking diabetic medications, lipid-lowering agents, antithrombotic, or antihypertensive medications through the course of this study.¹⁵

The primary end-point of this study was the ABI. Changes in SBP and DBP were designated as secondary end-points. Skilled nurses using a mercury sphygmomanometer in a controlled, quiet environment measured resting blood pressure. The average of three measurements was used. Plasma ALA, EPA, and DHA were measured as markers for dietary compliance. Body weight, waist circumference, and BMI were also measured.¹⁵

ABI did not change significantly in the treatment group or the placebo group at baseline (0.80 ± 0.24 versus 0.81 ± 0.22 ; $P=0.8$) or during the intervention period (0.77 ± 0.23 versus 0.78 ± 0.22 ; $P=0.8$). BMI and waist circumference did not differ significantly between the two groups at any time during the trial. Body weights also showed no significant difference between the treatment and placebo groups at baseline (81.0 ± 14.9 versus 82.4 ± 14.8 ; $P=0.6$) or after six months (83.8 ± 14.8 versus 81.4 ± 14.5 ; $P=0.4$).¹⁵

Plasma levels of ALA, EPA, and DHA were similar at baseline in both groups. There were no significant increases in any of the plasma levels of fatty acids in the placebo group at any point during the study. On the contrary, ALA plasma levels increased two-fold in the flaxseed fed groups when measured at 1 and 6 months ($P=0.003$ versus placebo). There was also a significant increase in EPA levels in the flaxseed

group compared with placebo. DHA levels in the flaxseed group did not change during the study, suggesting that subjects did not consume fish during meals. The study also assessed the relationship between plasma ALA levels and SBP ($P<0.04$) and DBP ($P<0.01$) to find there was a significant correlation.¹⁵

Both SBP and DBP decreased in the flaxseed group over the course of the study. SBP dropped to 136 ± 22 mmHg ($P=0.04$) at 6 months in the flaxseed group. DBP also fell in the flaxseed group at 6 months to 71 ± 11 mmHg ($P=0.004$). A subgroup analysis was completed with patients in the trial with a SBP of >140 . The study found patients who received flaxseed achieved a larger reduction in SBP (15mm Hg) and DBP (7mm Hg) after 6 months of intervention. The placebo group showed no significant difference in SBP or DBP during the same period.¹⁵

In summary, researchers found the most important finding in the FLAX-PAD study was the antihypertensive effect shown by patients who ingested dietary flaxseed. These effects were demonstrated even in patients already taking antihypertensive medications, therefore, representing an effective combination of pharmacologic and non-pharmacologic therapies on lowering blood pressure. The authors also imply that the results from the study suggest severely hypertensive patients benefit the most from dietary flaxseed. Further trials will be needed to clearly show the antihypertensive effect of flaxseed as an independent factor.¹⁵

Pachos et al¹⁶ was a prospective, two-group, parallel-arm design RCT to examine the effects of dietary flaxseed on blood pressure in middle-aged dyslipidemic men. Inclusion criteria were total cholesterol of higher than 200mg/dl and/or HDL cholesterol level lower than 40mg/dl. Exclusion criteria consisted of individuals with evidence of

infection or coexisting diabetes mellitus or renal, liver, or inflammatory disease. Subjects taking lipid-lowering or antihypertensive medications, consuming more than 30 U of alcohol per week, smoking more than two packs of cigarettes per day, or exercising more than 6 hours per week were also excluded. None of the participants were taking other forms of dietary supplements, such as fish oil, during the intervention period.¹⁶

A total of 87 patients were recruited from the Department of Cardiology of Laiko Hospital, Athens, Greece, after history and physical examination, ECG, and laboratory analysis. All of the participants were males aged 35 to 70, who were first diagnosed with dyslipidemia without evidence of CHD. The subjects were randomly assigned in to two groups using a 2:1 process. The treatment group (n=59) received 15mL of flaxseed oil per day containing 8g of ALA and the placebo group (n=28) received 15ml of safflower oil per day containing 11g of LA. The intervention period lasted for 12 weeks. Allocation concealment was not specified and there were no losses to follow-up during the study.¹⁶

Baseline characteristic, such as, age, height, weight, and BMI were not significantly different between groups. BMI did not change in either group over the course of the study ($P>0.05$). Baseline blood pressure was measured in the two groups and there were no significant differences found. There were no significant differences between the two groups in regards to diet and smoking habits (all $P>0.05$) at baseline or during the intervention period. Energy and macronutrient intake, as well as intake of individual *n*-3 polyunsaturated fatty acids (PUFA), were not significantly different between both groups.¹⁶

The primary end points used in this study were SBP, DBP, and mean arterial pressure (MAP). Blood pressure was measured using a manual sphygmomanometer by a

single physician who was blinded as to which group individuals were allocated. The patients were seated and resting for at least 15 minutes at the time of measurement. Appropriate blood pressure monitoring standards were enforced and an average of three measurements from the right-arm were recorded. Dietary habits, alcohol consumption, and physical activity of each subject were monitored by weekly phone calls and monthly hospital visits. Collecting one 3-day dietary record during each monthly visit assessed dietary compliance. Dietary assessment was performed at entry to confirm that all patients were eating the average Greek diet.¹⁶

After dietary supplementation was initiated, SBP, DBP, and MAP were all significantly lower (See Table III) in the flaxseed group when compared to the safflower group ($P < 0.001$). Group analysis revealed that dietary supplementation in the placebo group had no significant effect on blood pressure (all $P > 0.05$). In contrast, the flaxseed group exhibited a decrease in SBP, DBP, and MAP compared to baseline ($P < 0.001$).¹⁶

Researches in this study concluded that dietary supplementation with flaxseed oil containing 8g/day for a 12-week period lowers both SBP and DBP in dyslipidemic men. They suggest the magnitude of the hypotensive effect (5mm Hg or 3-6%) is clinically relevant and expected to reduce the overall cardiovascular disease risks in these patients. Future studies will be needed to determine the underlying mechanism through which dietary ALA might lower blood pressure.¹⁶

DISCUSSION

Up to 50g of ground, raw flaxseed per day has been shown to be safe and nutritionally beneficial in humans.²² These recent RCTs^{15,16} indicate the use of dietary flax supplementation may have a blood pressure lowering effect in selective patients, but

further research is still needed. In the FLAX-PAD trial,¹⁵ SBP and DBP were lower in the flax fed group when compared with placebo. Additionally, patients who entered the trial with a SBP >140 mm Hg obtained a significant reduction in both SBP and DBP from flaxseed consumption. The FLAX-PAD study¹⁵ further exhibited the correlation between circulating ALA levels and decreases in SBP and DBP, as well as enterolignan levels and decreases in DBP. In the Pachos et al¹⁶ article, another RCT, found that dietary supplementation with flax oil containing 8g/day of ALA for 12 weeks lowered both SBP and DBP in dyslipidemic men. These findings are clinically significant because they were both blinded, randomized, placebo controlled trials. In addition, the FLAX-PAD study¹⁵ monitored dietary compliance by measuring serum ALA, EPA, and DHA levels. Both the flax and placebo group maintained the proper diet, as no inconsistencies were found. Effort was made in both studies^{15,16} to control for confounding factors and minimize their influence. Each study carefully selected its study population and monitored throughout the study with respect to their diet, physical activity, and smoking habits.

However, encouraging as these results are, they are not conclusive when compared to other studies. In one study,¹⁷ the effects of three diets supplemented with fish oil, safflower oil, and linseed oil on plasma lipoprotein concentration and blood pressure were examined. This study included thirty-nine normotensive and slightly hypercholesterolemic men. Researchers found that SBP fell by approximately 4% in the fish oil group and no significant changes in blood pressure were measured in the other two groups. Another observational study¹⁸ found conflicting evidence as well. This study examined the effects of short-term supplementation with dietary flaxseed on blood pressure and various other serum markers in healthy humans. Results from this study

showed that 4 weeks use of dietary flaxseed did not demonstrate a decrease in blood pressure.¹⁸ In addition, previous studies^{19,20} (although not specific to dietary flaxseed) failed to show a blood pressure lowering effect of ALA. In contrast, the results from a double blind, RCT²¹ of the effects flaxseed had on metabolic syndrome composite score demonstrated that men and women supplementing their diets with flaxseed lignan complex for six months lowered DBP. It is likely that these studies^{17,18,19,20} conflict with the evidence from the RCTs^{15,16} included in this review due to several factors. First, the observational study,¹⁸ which found against the antihypertensive effect of dietary flaxseed, may have been due to the type of study utilized. Second, it is also possible that results differ because some of the studies^{19,20} were not specific to dietary flaxseed, which suggests that there may be some additional components to flaxseed that might contribute to its antihypertensive effect. Lastly, it may also be suggested that dietary flaxseed intervention is more effective at lowering BP in patients who are already hypertensive, where subjects from both studies,^{17,18} were normotensive at baseline.

While these studies^{15,16} demonstrated the antihypertensive effects of dietary flaxseed, they both have some limitations that need to be addressed (See Table II). In the FLAX-PAD trial,¹⁵ the presence of antihypertensive medications during the trial made it impossible to conclusively determine the effects of dietary flaxseed independently on blood pressure. This study also had a high attrition rate among both flaxseed and placebo groups. Although the losses were similar, this still may have affected the outcomes. In the Pachos et al study,¹⁶ several limitations were discussed. First, the parallel study design is not as strong as a crossover design. It was chosen because the washout period cannot be readily specified in a lipid intervention trial; thus avoiding any carryover effect that may

be caused by a crossover trial. Second, the dose of ALA is difficult to achieve by usual dietary intake. However, researchers suggested that certain food products might be infused with similar levels if not higher levels of ALA and are therefore attainable.¹⁶ Lastly, this study¹⁶ utilized an imprecise method to report results due to the use of medians with 25th and 75th percentiles.

CONCLUSION

Daily consumption of 30g of milled flaxseed or 15mL of flax oil per day has shown an antihypertensive effect on select patient populations. The latest studies regarding flaxseed and its antihypertensive effects seem promising, but further randomized controlled trials are needed to clearly establish its efficacy. Future studies should also be designed to identify the underlying mechanism by which ALA may reduce blood pressure, clearly identify the independent blood pressure lowering action of flax and show these effects on larger populations. Based on the GRADE criteria, the overall quality of the studies reviewed is moderate.

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Table I. Nutritional Information of Flaxseed

Flax	Weight	Energy kcal	Total Fat	ALA	Protein	Total Carbs	Total Dietary Fiber
Whole Seed	180g (1 cup)	810	74.0g	41.0g	36.0g	52.0g	50.0g
	11g (1 tbsp)	50	4.5g	2.5g	2.2g	3.0g	3.0g
Milled Seed	130g (1 cup)	585	53.0g	30.0g	26.0g	38.g	36.0g
	8g (1 tbsp)	36	3.3g	1.8g	1.6g	2.3g	2.2g
Flax Oil	100g	884	100.0g	57.0g	—	—	—
	14g (1tbsp)	124	14g	8.0g	—	—	—

Table II. Characteristics of Reviewed Studies, GRADE Profile

Quality Assessment							
Downgrade Criteria							
Studies	Design	Limitations	Indirectness	Imprecision	Inconsistency	Publication bias likely	Quality
Lowering Blood Pressure							
FLAXPAD Study	RCT	Loss to follow-up over %20 in both Flax and placebo groups	No serious limitations	No serious limitations	No serious limitations	No bias likely	Moderate
Pachos et al	RCT	No serious limitations	No serious limitations	Values are medians (25 th to 75 th percentile)	No serious limitations	No bias likely	Moderate

Table III. Blood Pressure Data Before and After Dietary Flaxseed Intervention

	LA group (n=28)			ALA group (n=59)			P
	Before	After	Change %	Before	After	Change %	
SBP (mmHg)	122.5 (120,140)	127.5 (118,132)	-1.7	120 (110,130)	110 (108,124)	-3.1	0.016
DBP (mmHg)	80 (75,85)	79 (75,85)	-2.5	80 (75,88)	72 (65,80)	-6.3	0.011
MAP (mmHg)	94.2 (90.2,104.6)	95 (88.7,100.8)	-1.4	93.3 (86.7,98.3)	85 (78.3,98.3)	-6.0	0.010

Values are medians (25th, 75th percentile)

P-value indicates differences between LA and ALA groups, and has been derived from the analysis of variance for repeated measures.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), linoleic acid (LA), alpha-linolenic acid (ALA).