Canadian Journal of Physiology and Pharmacology

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Journal:	<i>Canadian Journal of Physiology and Pharmacology</i>
Manuscript ID	cjpp-2018-0280.R1
Manuscript Type:	Article
Date Submitted by the Author:	20-Jun-2018
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Is the invited manuscript for consideration in a Special Issue:	2018 IACS Cuba
Keyword:	peripheral arterial disease, flaxseed, heart disease, arrhythmia, claudication

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The Effects of Dietary Flaxseed on Cardiac Arrhythmias and Claudication in Patients with Peripheral Arterial Disease

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Running Title: Arrhythmias, claudication and flaxseed

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Key words: diet; cardiovascular disease; peripheral arterial disease; claudication; atherosclerosis; heart disease; arrhythmia; exercise;

Abstract

Patients with peripheral artery disease (PAD) are at increased risk for cardiovascular events and higher susceptibility for cardiac arrhythmias may be involved. The objectives of this double blinded, randomized controlled FLAX-PAD trial were to determine whether daily consumption of a diet supplemented with 30g of milled flaxseed (or placebo) over one year by PAD patients has effects on the prevalence of cardiac arrhythmias and exercise capacity. Cardiac arrhythmias were assessed on a cardiac stress test and at rest. At baseline, the PAD patients had a high incidence of cardiac arrhythmias (48% in the flaxseed group and 32% in the placebo group). After 1 year, the presence of cardiac arrhythmias in the flaxseed group decreased by 2% and increased by 12% in the placebo group ($P>0.05$). Electrocardiographic variables (P, PR, QRS, QT, QTc) did not change in either group during the trial. Patients from both groups improved initial and absolute claudication distances but the intergroup difference was also not statistically significant. In summary, the prevalence of cardiac arrhythmias and physical capacity trended in a positive direction for patients ingesting flaxseed but either a larger sample size or a longer intervention with flaxseed may be required to show statistically significant differences.

Introduction

Peripheral arterial disease (PAD) is a disease of limited circulation in the peripheral regions of the body, primarily the legs. PAD symptoms include painful cramping of the leg or hip muscles during walking, cooling of the skin in specific areas of the legs or feet, color changes in the skin, particularly in the arms or legs, impaired healing in toe and foot, burning or aching in the feet and toes while at rest and particularly while lying flat (this is a sign of more severe PAD). However, PAD can also be asymptomatic (Stevens et al, 2006). Clinically, PAD is defined by the presence of an ankle-brachial index (ABI) of $< .90$ (Mahoney et al, 2008; Stevens et al, 2006). Some of the apparent inconsistencies regarding data on the prevalence of symptomatic PAD may be due to methodology, but it can be generally concluded that for every patient with symptomatic PAD, there are another three to four subjects with PAD who do not meet the clinical criteria for intermittent claudication (Norgren et al, 2007).

The overall disease prevalence of PAD is in the range of 3%-10%, which increases to 15%-20% in individuals older than 70 years of age (Dua and Lee, 2016). Eight to ten million Americans suffer from PAD with an overall prevalence of 12% in the adult population (Norgren et al, 2007). In Canada, around 800,000 persons present with PAD (Hirsch et al, 2007). This prevalence has economic implications. Symptomatic PAD patients have significantly higher medical resource use and costs when compared with a matched control population (Chase et al, 2016). All-cause inpatient costs \$8,494 vs. \$3,778 when a patient with PAD is compared to one without it, respectively (Chase et al, 2016). Outpatient costs are \$8,459 vs. \$5,692; and total costs are \$20,880 vs. \$12,501 per year in patients with PAD and without PAD (Chase et al, 2016). Based on these results, the annual cost in 2008 for vascular-related hospitalizations for symptomatic PAD in the United States was estimated to be $> \$21$ billion (Mahoney et al, 2008).

PAD has been associated with diabetes mellitus, high blood pressure and dyslipidemia (Lane et al, 2006). It is an important manifestation of atherosclerosis (Fowkes et al, 2013) and an important marker of cardiovascular risk (Criqui et al, 2010; Araki et al, 2012). It is associated with increased all-cause and cardiovascular mortality (Resnick et al, 2004; Heald et al, 2006; Luo et al, 2007). There is a prevalence of 40% - 60% for coronary artery disease (CAD) and cerebral artery disease in this population (Lane et al, 2006). In patients with CAD, cardiac arrhythmias contribute to an increase in cardiac event rates and mortality risk (Engstrom et al, 2006). Because of the overlap between CAD and PAD (Hirsch et al, 2001), it is reasonable to propose that cardiac arrhythmias may also be prevalent in patients with PAD. Indeed, PAD and atrial fibrillation (AF) share several common risk factors, including diabetes and smoking (Chang et al, 2016). However, a direct study of arrhythmias in patients with PAD has not been reported.

In the management of patients with PAD it is important to include modifications of traditional risk factors such as smoking, hypercholesterolemia, hypertension and diabetes mellitus through smoking cessation, low fat / low salt diet, exercise, weight reduction and dietary changes (Lane et al, 2008). Results from the National Health and Nutritional Examination Survey (Lane et al, 2008) found that nutrition has a significant impact on the prevalence of PAD. High consumption of fibre containing foods such as whole grain cereals, fruits and vegetables are associated with a lower risk of CVD, hypertension, obesity and type-2 diabetes (Bazzano et al, 2003, Liese et al, 2003). Higher cereal fibre intake may lead to a lowering of blood pressure, triacylglycerols and higher HDL cholesterol by improved glucose metabolism, thereby improving the risk profile for PAD (Hunninghake et al, 1994). In addition, higher consumption of foods rich in antioxidants (vitamin A, C, and E), folate, vitamins B6, fibre and ω -3 fatty acids have

significant protective effects with decreased prevalence of PAD (Lane et al, 2008). Flaxseed, an important source of the ω -3 fatty acid, alpha linolenic acid (ALA) (Rodriguez-Leyva et al, 2011), is also high in dietary fiber, and contains lignans which are potent antioxidants (Rodriguez-Leyva et al, 2013). In animal trials, flaxseed has shown anti-atherogenic effects (Dupasquier et al, 2006; Dupasquier et al, 2007; Francis et al, 2013), anti-inflammatory properties (Dupasquier et al, 2007) and a potent anti-arrhythmic action during ischemic challenge (Ander et al, 2004). Therefore, it is possible that the prevalence of cardiac arrhythmias and claudication in patients with PAD could be improved with a diet supplemented with flaxseed. The objectives of this study, therefore, were to determine whether consumption of a diet rich in flaxseed has any effect in the prevalence of cardiac arrhythmias as well as claudication in patients with PAD.

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Methods

In this study, we included patients from the FlaxPAD trial, (NCT00781950 at clinicaltrials.gov), that was conducted at St. Boniface Hospital (Winnipeg, Canada). This was a single center, double blinded, controlled clinical trial that examined the effects of 30g of milled flaxseed (or placebo) per day in PAD individuals (Rodriguez-Leyva et al, 2011;2013). Prevalence of arrhythmias was considered a secondary endpoint. The study conformed to the principles delineated in the Declaration of Helsinki. Written approval from Health Canada and the Research Ethics Boards at the University of Manitoba and St Boniface Hospital was obtained.

Study Procedures

A total of 110 patients were enrolled in the FlaxPAD study. After randomization, 58 were allocated to the flaxseed group and 52 to the placebo group. A total of 84 patients completed the 12 months intervention. Comorbidities and treatment of these patients has been published previously (Rodriguez-Leyva et al, 2013). Eighty three patients completed the 12 month dietary intervention, forty two in the flaxseed group and forty one in the placebo group. Each subject was administered a standard 12 lead EKG at rest (recorded at 25mm/s and 1mV/cm standardization) by trained staff with a Welch Allyn's electrocardiograph. Subjects were also administered a supervised walking exercise test on a treadmill to evaluate performance and cardiac electrical activity. A Welch Allyn's Stress Test System including a Track Master Treadmill was used for the stress tests and for the resting EKGs. The speed of the treadmill testing was 3.2 km/h at a grade of 12%. The treadmill speed was increased every 15 seconds. This was done at baseline, 1 month, 6 months and 12 months. Cardiac electrical activity was continuously monitored for 15 minutes at rest before exercise, during the exercise test and then

followed for 10 minutes after the exercise was terminated while the patient was sitting. Premature supraventricular or ventricular contractions were considered if they were more than 5 per minute (Norgren et al, 2007). Bigeminy, trigeminy, couplets, multifocal PVCs or ventricular tachycardia as well as atrial fibrillation were also considered as arrhythmias in this study.

A continuous wave, hand held Doppler machine (Bidop ES- 100V3 by Koven) was used with a blood pressure cuff and a conventional sphygmomanometer to measure the systolic pressure in the posterior tibial and dorsalis pedis arteries. If neither arterial signals were found, the anterior tibial and/or peroneal artery pressures were recorded. The ankle and brachial systolic blood pressures were calculated as ankle systolic pressure/brachial systolic pressure (ABI).

The initial claudication distance (ICD) was recorded when the patient first reported the onset of pain. The ICD represents the pain-free walking distance. For the absolute claudication distance (ACD), the patient was asked to continue walking until the pain did not allow them to walk any farther. The ACD represents the maximal walking distance. These tests were performed at baseline, 1 month, 6 months and 12 months.

Statistical methods

Continuous variables were expressed as a mean $\pm$ SD. Categorical variables were expressed as proportions. A Z test was used to compare the proportions of 2 groups found within a single category. Statistical significance was determined with one-way ANOVA analysis. Differences were considered significant when $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics 20.

Results

Baseline Characteristics

Stress test data from eighty-three patients, 42 from the flaxseed group and 41 from the placebo group, was available for this investigation. Baseline characteristics are shown in Table 1. The average age in both groups was similar and males represented ~ 2/3 of the sample.

Cardiac Electrical Activity

Patients from both groups exhibited a high prevalence of cardiac arrhythmias. At baseline, 48% of the individuals from the flaxseed group and 32% of those from the placebo group showed electrocardiographic evidence of rhythm abnormalities as shown in Table 2. After 1 year of dietary intervention, the prevalence of cardiac arrhythmias in the flaxseed group decreased by 2%. Cardiac arrhythmias increased by 12% in the individuals from the placebo group but this intra-group difference did not achieve statistical significance ($P>0.05$).

Table 3 shows the type of arrhythmias distributed by groups and duration of intervention. Patients that presented arrhythmias in the flaxseed group demonstrated at baseline at least one of the following cardiac rhythm disturbances: premature ventricular contractions (PVC) (50%), premature supraventricular contractions (PSVC) (25%), atrial fibrillation (AF) (10%), couplets (10%) and triplets (7.69%). Patients from the placebo group showed at least one of the following arrhythmias: PVC (92.3%), PSVC (23.07%), AF (7.69%) and couplets (7.69%). There were no trends to observe in the incidence of the different arrhythmias over time in either group nor were there any significant differences in the incidences of any of the specific arrhythmias between the two groups over the duration of the study ($P>0.05$).

The data were also examined from the perspective of including only that data from patients who exhibited an arrhythmia (Table 4). At 12 months, patients with arrhythmias from

the flaxseed group presented with at least one of the following cardiac rhythm disturbances: PVC (68.4%), PSVC (26.3%), AF (10.5%), couplets (10.5%) and bigeminy (21.05%). Patients from the placebo group exhibited at least one of the following arrhythmias: PVC (61.1%), PSVC (27.7%), AF (11.1%), couplets (10.5%), bigeminy (10.5%). There were no trends to observe in the incidence of the different arrhythmias over time in either group nor were there any significant differences in the incidences of any of the specific arrhythmias between the two groups over the duration of the study ($P > 0.05$).

Prior to the standardized treadmill walking test, average heart rate in both groups was in a normal range (Table 1). Electrocardiographic variables (P, PR, QRS, QT, QTc) did not change significantly in either group during the trial and remained within a normal range (Table 5).

Claudication

At baseline, ABI measurements from both the right and left legs suggested moderate but clinically significant obstruction of peripheral arteries. This obstruction was severe enough to induce ischemic episodes in the legs that resulted in a significant impairment of physical activity as shown in Figure 1. At baseline there were no significant differences in initial claudication distance (ICD) when comparing flaxseed and placebo groups (85.3 ± 47.2 vs. 84.4 ± 52.9 , respectively; $P = 0.9$). The same trend was observed with respect to absolute claudication distance (ACD) (146 ± 93.3 vs. 126.1 ± 68 for flaxseed and placebo, respectively; $P = 0.2$).

After 12 months, patients from flaxseed group were able to walk farther before reporting leg pain (ICD) (Figure 1A). They also walked farther before pain did not allow them to walk any more (ACD) (Figure 1B). In patients from the placebo group, the ICD and ACD values were greater than basal values as well at 12 months (Figure 1). Therefore, there was a trend to improve both ICD and ACD over the duration of the study but this trend was observed in both groups and

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it was not statistically significant. The differences between both groups were also not statistically significant at any time point measured.

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Discussion

This study was part of a larger trial investigating the effects of dietary flaxseed on a variety of primary and secondary cardiovascular parameters in PAD patients (Rodriguez-Leyva et al, 2011). The prevalence of cardiac arrhythmias was assessed in this series of tests using a conventional cardiac stress test at rest and during exercise. Because the participants in this study suffered from PAD, their capacity to exercise was extremely limited but did allow for the collection of cardiac electrical activity during exercise. The baseline incidence of arrhythmias at rest for the PAD patients appears to be relatively high but with the concomitant morbidities of diabetes, coronary heart disease and hyperlipidemia in this population (Rodriguez-Leyva et al, 2011; 2013), it is difficult at the present time to isolate the independent effects of PAD. The primary focus of this study was to determine the effect of the dietary flaxseed intervention on the type and incidence of arrhythmias. After a year of supplementing the diet with flaxseed, the presence of cardiac arrhythmias in the flaxseed group decreased by 2%. Although this contrasts sharply with the increase in arrhythmias in the placebo group (an increase of 12%), these differences were not statistically significant. The absence of any statistically significant change over the course of the dietary intervention with any of the electrocardiographic variables (P, PR, QRS, QT, QTc) would support this negative finding in arrhythmias. These findings contrast with isolated animal hearts in an ischemia-reperfusion challenge (Ander et al, 2004). Dietary flaxseed decreased the incidence of ventricular tachycardia and shortened the QT interval in ischemic rabbit hearts (Ander et al, 2004). The effect was attributed to the rich omega-3 fatty acid content of alpha linolenic acid in the flaxseed diet. Others have shown marine omega-3 fatty acids can decrease the incidence of cardiac arrhythmias (Billman et al, 1999; Leaf et al, 1999). The present data does not support this action in PAD patients. It is possible that a longer dietary

intervention is required or the pathology in these PAD patients is too severe to be susceptible to changes in cardiac electrical activity.

Flaxseed also did not induce significant changes in claudication values when compared to the control PAD group. Patients from both groups improved initial and absolute claudication distances over the course of this trial. The intergroup difference was not statistically significant. This finding may appear to be at odds with the significant antihypertensive action of the flaxseed diet in these same PAD patients (Rodriguez-Leyva et al, 2013). It may also appear to be in conflict with the capacity of dietary flaxseed to reverse atherogenesis in animal models (Francis et al, 2013). However, once again, it is likely that the clinically significant peripheral atherosclerotic plaques that were decades in the making in these PAD patients were too advanced to be affected by a one year dietary intervention. The vascular and metabolic changes needed to alter hypertension (Caligiuri et al, 2014; 2016) may be far more amenable to shorter term dietary modifications than claudication.

The absence of some changes in biologic activity may have been the result of an inadequate dose of flaxseed or an insufficient time to induce effects. With respect to the former parameter, a dose dependency study of the effects of milled flaxseed on cardiovascular parameters has never been carried out and needs to be done. However, a 30g/day dosage is relatively high (the equivalent of three heaping tablespoons of flaxseed) and has produced significant changes in other cardiovascular parameters (i.e. blood pressure (Rodriguez et al, 2013)). Further increases in flaxseed dosage (up to 50 g/day (Dodin et al, 2005)) have been successfully carried out but only for shorter time periods. The one year study duration used in this study is beyond the 6 months currently recommended for dietary interventions to induce significant biologic effects (Sacks and Campos, 2010.).

In summary, the prevalence of cardiac arrhythmias trended in a positive direction but it was not statistically significant for patients ingesting flaxseed. Either a larger sample size or a longer intervention with flaxseed may be required to show changes in cardiac electrical activity compared to placebo. A similar conclusion with regard to claudication and altering exercise tolerance and capacity may also be valid.

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Acknowledgements

This work was supported by operating grants to DRL from the Manitoba Medical Service Foundation and to GNP from a CIHR Foundation grant, and grants from the Western Grains Research Foundation, ARDI, SaskFlax and St Boniface Hospital Foundation.

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Table 1. Baseline characteristics of the study population (Mean±SD).

Baseline	Group 1	Group 2	p
n	42	41	
Age (years)	66.8 ± 7.7	66.1 ± 9.3	0.7
Males (%)	79	71	0.8
Females (%)	21	29	0.8
HR (beats/minute)	67 ± 11	69 ± 12	0.4
Systolic BP (mmHg)	145 ± 22	144 ± 17	0.7
Diastolic BP (mmHg)	78 ± 8	80 ± 17	0.3

Table 2. Prevalence of cardiac arrhythmias in patients from both groups at baseline, 1 month, 6 months and 12 months.

Prevalence of arrhythmias (%)	Flaxseed Group	Placebo Group	P value
Baseline	47.6	31.7	0.13
1 Month	54.8	39	0.14
6 Months	51.2	53.65	0.8
12 Months	45.2	43.9	0.9

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Table 3. Type of arrhythmias presented by patients from both groups.

		Baseline	1 month	6 months	12 months
		% prevalence	% prevalence	% prevalence	% prevalence
PVC	<i>Flaxseed</i>	23.8	50	42.8	30.9
	<i>Placebo</i>	29.2	21.9	43.9	26.8
PSVC	<i>Flaxseed</i>	11.9	14.2	7.3	11.9
	<i>Placebo</i>	7.3	14.6	9.7	12.1
AF	<i>Flaxseed</i>	4.7	4.7	4.7	4.7
	<i>Placebo</i>	2.4	2.4	2.4	4.8
Couplets	<i>Flaxseed</i>	4.7	9.5	4.7	4.7
	<i>Placebo</i>	2.4	4.8	9.7	4.8
Bigeminy	<i>Flaxseed</i>	0	2.3	9.5	9.5
	<i>Placebo</i>	0	0	2.4	4.8
Triplets	<i>Flaxseed</i>	4.7	0	0	0
	<i>Placebo</i>	0	0	0	0
VT	<i>Flaxseed</i>	0	0	0	0
	<i>Placebo</i>	0	0	0	0

PVC: Premature ventricular contractions, PSVC: Premature supraventricular contractions, AF: Atrial fibrillation; VT: Ventricular tachycardia.

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Table 4. Characterization of arrhythmias from both groups including only patients with cardiac arrhythmias.

		Baseline	1 month	6 months	12 months
		% prevalence	% prevalence	% prevalence	% prevalence
PVC	<i>Flaxseed</i>	50	91.3	85.7	68.4
	<i>Placebo</i>	92.3	56.25	81.8	61.1
PSVC	<i>Flaxseed</i>	25	26.1	14.2	26.31
	<i>Placebo</i>	23.1	37.5	18	27.7
AF	<i>Flaxseed</i>	10	8.69	9.52	10.52
	<i>Placebo</i>	7.69	6.25	4.54	11.11
Couplets	<i>Flaxseed</i>	10	17.39	9.52	10.52
	<i>Placebo</i>	7.69	12.5	18.18	10.52
Bigeminy	<i>Flaxseed</i>	0	6.25	18.18	21.05
	<i>Placebo</i>	0	0	4.54	10.52
Triplets	<i>Flaxseed</i>	7.69	0	0	0
	<i>Placebo</i>	0	0	0	0
VT	<i>Flaxseed</i>	0	0	0	0
	<i>Placebo</i>	0	0	0	0

<hr/>	<i>Placebo</i>	0	0	0	0
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PVC: Premature ventricular contractions, PSVC: Premature supraventricular contractions, AF: Atrial fibrillation. VT: Ventricular tachycardia.

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Table 5. Electrocardiography (EKG) variables presented by patients from flaxseed and placebo groups (Mean±SD).

EKG variables		Baseline	1 month	6 months	12 months
P wave (ms)	<i>Flaxseed</i>	114.5 ± 13.4	116.0 ± 15.3	114.6 ± 15.7	113.4 ± 15.3
	<i>Placebo</i>	114.5 ± 13.4	118.6 ± 10.7	116.0 ± 10.8	118.7 ± 15.9
PR segment (ms)	<i>Flaxseed</i>	172.6 ± 29.4	173.4 ± 35.3	174.0 ± 33.4	175.2 ± 35.8
	<i>Placebo</i>	164 ± 23.2	164.1 ± 23.8	164.3 ± 24.2	168.3 ± 27.5
QRS complex (ms)	<i>Flaxseed</i>	100.2 ± 18.5	100.1 ± 17.6	101.1 ± 19.5	106.5 ± 28.3
	<i>Placebo</i>	98.5 ± 19.5	97.7 ± 18.6	101.1 ± 24.4	103.1 ± 27.6
QT interval (ms)	<i>Flaxseed</i>	411 ± 33.0	406.9 ± 37.6	411.1 ± 38.3	416.8 ± 44.3

	<i>Placebo</i>	401.2 ± 33.9	396.6 ± 36.9	404.5 ± 42.7	405.9 ± 39.1
QTc interval (ms)	<i>Flaxseed</i>	422.5 ± 24.5	423.8 ± 27.6	421.4 ± 26.4	426.6± 32.1
	<i>Placebo</i>	419.1 ± 24.6	420.2 ± 20.6	421.3 ± 28.8	424.9 ± 31.2

All values were not statistically different within and between groups (P>0.05).

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Figure Legends

Figure 1. Initial claudication (A) and absolute claudication (B) distances for patients in both groups at baseline, 1 month, 6 months and 12 months. The initial claudication distance was the distance walked on the treadmill before the subject first reported the onset of pain. Thus, the initial claudication distance represents the distance walked without muscle pain in the legs. The subject then continued to walk until the leg muscle pain did not allow him/her to walk any farther. This was the absolute claudication distance. Thus, the absolute claudication distance represents the maximal walking distance.

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Figure 1

289x414mm (300 x 300 DPI)