Int J Diabetes & Metab (2010) 18:99-113

Gender differential in apo E genotypes' correlative tendency to dyslipidaemia responsiveness upon flaxseed oil administration in adult type 2 diabetic patients not meeting the 2008 Canadian Practice Guidelines

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Abstract
Fasting blood serum lipid concentrations, low density lipoprotein (LDL) oxidation, hypertension, and various anthropometric measures such as waist circumference are important measures of coronary atherosclerosis risk in type 2 diabetics. Apo E genotypes, leptin and adiponectin, modify fasting blood serum lipid levels and thus the degree of atherosclerosis as assessed in part by c-reactive protein (CRP). Hypertension, LDL oxidation and increased waist circumference promote atherosclerosis and hence the risk of myocardial infarction. It was hypothesised that there would be apo E, adiponectin, leptin and gender driven differences in myocardial infarction risk including hypertension, various anthropometric measures, CRP levels and at least some of the lipid levels including their modulating levels of leptin and adiponectin as the result of the administration of flaxseed oil (60 mg/kg bodyweight/day of alpha-linolenic acid for 90 days) and that apo E genotype would play a role in lipid responsiveness to such flaxseed oil administration. The purpose of this study was to assess this hypothesis. The only significant change seen was a statistically significant drop in cholesterol only in females consuming flaxseed oil with correlative evidence of apo E genotypic influence on other lipid parameter responsiveness in males and females. The absence of change in leptin and adiponectin levels suggests that this change did not occur due to these, lipid modulating, adipocytokines. Dietary intakes of calories, oleic acid and alpha-linolenic acid were consistent for each gender/treatment group and therefore consistent with no change in waist circumference. It is concluded that flaxseed oil consumption at an alpha-linolenic acid level of 60 mg/kg body weight/day for three months has no impact on the cardiovascular disease risk factors studied in the overall population herein except for cholesterol in female type 2 diabetics consuming flaxseed oil. However, in certain apo E genotypes there was a greater sensitivity to change in lipid parameters.

Keywords: *apo E genotype, leptin, adiponectin, dyslipidaemia, low density lipoprotein oxidation, blood pressure, waist circumference, flaxseed oil, type 2 diabetes*

Introduction

Cape Breton Island in the province of Nova Scotia, Canada suffers from among the highest rates of type 2 diabetes in Canada, the consequence of which are seen in the overall economy and in the competition for healthcare dollars with other health issues. Consequently, it is important to control this disease as much as possible so as to reduce its economic and social impact. There are no reports to date regarding the apo E genotype, leptin, adiponectin, and gender driven equity of flaxseed oil management of the features of dyslipidaemia, c-reactive protein (CRP), blood pressure and anthropometric measures, such information being of clear importance for the medical, economic and social impacts of this disease.

Dyslipidaemia is a feature of type 2 diabetes that contributes significantly to the major cause of death in these patients, atherosclerosis-induced myocardial infarction.[1,2] All references to dyslipidaemia herein refer to blood plasma or serum concentrations in fasted patients. Dyslipidaemia features elevated triglyceride concentrations, small dense low density lipoprotein cholesterol (sd LDL-c), and in some patients elevated total cholesterol and low density lipoprotein-cholesterol (LDL-c).[2-6] Elevated high density lipoprotein$_3$-cholesterol (HDL_3-c) concentrations may also feature. As well there are decreased fasting blood plasma concentrations of high density lipoprotein-cholesterol (HDL-c), and high density lipoprotein$_2$ - cholesterol (HDL_2-c). As triglycerides rise, HDL-c and HDL_2-c fall while small dense LDL-c and non-HDL-c also rise. This profile is pro-atherogenic and thus a promoter of plaque formation.[3] Free fatty acid concentrations also rise in type 2 diabetes contributing to increased blood plasma glucose concentrations[7] further exacerbating the dyslipidemia. As non-HDL-c, sd-LDL-c and LDL-c rise there is a greater influx of cholesterol into the arterial wall.[3] Low blood serum fasting levels of adiponectin and elevated leptin also contribute to dyslipidemia.[8-19] However, such relationships are in dispute.[20] CRP is a measure of the extent of atherosclerosis and therefore to some degree the risk of myocardial infarction.[21-22]

Received on: 30/9/2010
Accepted on 30/11/2010

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The opportunity for cholesterol efflux via HDL-c and more specifically HDL_2-c is lessened with the decrease in concentration of HDL-c and HDL_2-c.[3] Lipoprotein (a) has been suggested to contribute to the atherosclerotic process[23] in type 2 diabetics; one could suggest this in terms of atheromatous plaque formation. The increase in non-HDL-c, LDL-c and in particular the very aggressive pro-atheromatous sd-LDL-c give rise to increased cholesterol influx into the arterial wall.[3] Thus the atheromatous plaque grows resulting in partial or complete occlusion of artery and if the plaque ruptures the opportunity for thrombus or embolus formation is increased.[24] Thrombus or embolus formation can also result in arterial occlusion. Sufficient occlusion will cause myocardial infarction.

The susceptibility of LDL to oxidation is believed by some to play a role in atherosclerotic-induced occlusion and hence myocardial infarction[25-28] though this controversial. Fuller and associates[29] have reported that polymorphonuclear cells can oxidize LDL. As LDL becomes progressively more oxidized it putatively is more readily taken into both macrophages and arterial wall cells thus increasing the rate of cholesterol influx into the arterial wall.[30-36] Some authors have suggested that in type 2 diabetics compared to healthy controls, LDL is more susceptible to oxidation and such persons have higher levels of oxidation which may contribute to the more aggressive atherosclerosis found in type 2 diabetics compared to non-diabetics. [37-51] In contrast, Makimattila and associates [52] observed that LDL oxidation lag time (susceptibility to oxidation) did not contribute to reduced endothelial vasodilation nor did LDL oxidation levels.[53] Reduced endothelial vasodilation is a contributor to the atherosclerotic process. Further, Hayashi and associates[54] have indicated that no relation exists between oxidised LDL and carotid artery thickness a measure of coronary atherosclerotic progression. Leinonen and associates[55] found no relation between susceptibility of LDL to oxidation and coronary heart disease. After adjustment for lipids and lipoproteins hypertension, body mass index (BMI) and waist to hip ratios, differences in lag time between type 2 diabetics and healthy controls were eliminated.[56]

Hypertension increases platelet aggregation, in part via damage to the arterial endothelium,[57] which exposes platelets to vascular wall collagen.[58,59] Increased platelet aggregation enhances the risk of myocardial infarction.[60] Hypertension features in many type 2 diabetics[61] along with an increase in platelet aggregability. [62]

Increased waist, waist to height and waist to hip ratios, as well as BMI enhance the risk of complications associated with type 2 diabetes in men and women [63-68] The waist to height ratio is particularly good discriminator.[65,69]

Flaxseed oil is rich in alpha-linolenic acid (ALA, 18:3 n-3). ALA is converted to EPA and DHA in humans.[70] It is not clear whether ALA by itself has a cardioprotective effect.[70] There appears to have been only one paper published to date on flaxseed oil administration in human type 2 diabetics in terms of lipid management.[71] However, there are apparently no publications in type 2 diabetics using an ALA dose of higher than 35mg/kg body weight/day[71] and none whatsoever examining apo E, CRP, leptin and adiponectin and male female differences in lipid responsiveness to flaxseed oil in type 2 diabetics. Goh and associates[71] providing 35 mg of ALA/kg body weight/day in the form of flaxseed oil showed a drop only in LDL-c but not cholesterol or triglycerides in patients consuming a high polyunsaturated to saturated fatty acid diet. Paschos and associates,[72] in dyslipidemic individuals consuming flaxseed oil**,** observed an decrease in HDL-c but no change in other lipids (total cholesterol, LDL-c, LDL density and triglycerides) and a decrease in CRP. Rallidis and associates[73] observed a decrease in CRP also in dyslipidemic individuals consuming flaxseed oil. In normolipidemic individuals, Pang and associates[74] observed no changes in the lipid profile of young males consuming increased amounts of dietary ALA while Schwab and associates[75] observed a decrease in triglycerides due to flaxseed oil consumption and Kaul and associates[76] observed no impact of flaxseed oil on lipid levels. Harper and associates[70] found a decrease in HDL-c and no change in lipoprotein size or other lipid parameters as the result of flaxseed oil administration. Paschos and associates[77] and Nelson and associates[78] observed a decrease in adiponectin in dyslipidemic males and healthy adults, respectively as a result of the consumption of flaxseed oil. No one has published apparently on the impact, if any, of flaxseed oil on leptin levels.

Apolipoprotein E plays an important role in serum lipid levels and their distribution among lipoproteins.[79-81] Yet, despite a suggested links with diet and drug therapies' lipid responsiveness,[82] no one has previously published on apolipoprotein E genotype associated responsiveness of lipids to flaxseed oil administration in human type 2 diabetics.

Only two studies have been done on the impact of flaxseed oil on LDL oxidation and neither done in type 2 diabetics. In healthy humans, Kaul and associates[76] found that flaxseed oil consumption had no impact on LDL oxidation susceptibility. In persons overweight but otherwise free of metabolic disorders, Nestel and associates[83] found that copper-induced oxidation of LDL produced no difference in rate of formation of or maximal conjugated diene formation as the result of flaxseed oil consumption. However, in type 2 diabetics oxidation is higher as antioxidant levels are lower. Flaxseed oil is rich in polyunsaturated fatty acids which are subject to *in vivo* oxidation.

There have never been any studies done in human type 2 diabetics on the impact of flaxseed oil consumption on blood pressure. However, one study[84] with dyslipidaemic men indicated a drop in blood pressure as the result of flaxseed oil consumption while another study[83] indicated no drop in mean arterial pressure despite a flaxseed oil induced increase in arterial compliance which is a feature of lowered blood pressure. Flaxseed oil is rich in ALA (18:3 n-3). ALA is converted to eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexanenoic acid (DHA, 22:6 n-3). EPA produces

various vasodilatory eicosanoids (eg PGI_3) and both EPA and DHA reduce the availability of arachidonic acid (AA, 20:4 n-6) esterified to phospholipids thus reducing the production of AA- dervived vasoconstrictory eicosanoids (eg TxA_2). On this basis it was hypothesised that flaxseed oil would reduce blood pressure in type 2 diabetics.

Clearly dietary caloric intake plays a role in obesity and the manifestations of obesity in the various anthropometric parameters detailed in this paper. Further it has been suggested that increased consumption of oleic acid (OA, 18:1n-9) may stem appetite,[85] and hence contribute to improved anthropometric features resulting in improved pre- and post-onset management of type 2 diabetes. Further, various studies have suggested a role for long chain omega 3 fatty acids such as EPA, and docosahexanenoic acid (DHA, 22:6 n-3) in satiety and hence weight control in diabetes.[86-91] However, ALA, a metabolic precursor of EPA and DHA in humans, has never been examined in human type 2 diabetics in terms of anthropometric features representative of obesity. Thus, it was of interest to look at flaxseed oil which contains both OA and ALA and compare it to safflower oil which contains slightly less OA and negligible ALA. There appear to be no reports regarding gender and the anthropometric measures mentioned in this paper, in terms of their responsiveness to total OA and ALA consumption inclusive of the combination of diet and nutra ceutical intake of these fatty acids, in type 2 diabetes. Such information may be of clear importance for the medical, economic and social impacts and management of this disease.

It was hypothesised that there would be apo E, adiponectin, leptin and gender driven differences in myocardial infarction risk including hypertension, various anthropometric measures, CRP levels and at least some of the lipid levels including their modulating levels of leptin and adiponectin as the result of the administration of flaxseed oil (60 mg/kg bodyweight/day of alpha-linolenic acid for 90 days) and that apo E genotype would play a role in lipid responsiveness to such flaxseed oil administration. This hypothesis is based on gender differences in some lipid parameters in type 2 diabetics. The purpose of this study was to assess this hypothesis.

Methods

Subjects (n =18 males, 14 females) completed this study. This study received approval from the Cape Breton University Human Ethics Review Committee. Subjects came for visit 1 and 3 months later for visit 2 and 3 months later for visit 3. On all visits, body weight and height, waist and hip circumferences were determined and blood was drawn from the antecubital vein. There was no intervention between visits one and two. At visit 2, subjects were randomly assigned to consume flaxseed oil at a level of 60 mg ALA/kg/body weight/day (105 milligrams flaxseed oil/kg body weight/day) or safflower oil (103 milligrams/kg body weight/day) for 90 days. At visit 3, all subjects returned for final data collection. Analysis of dietary records kept by the patients on three days between visit 1 and 2 and then again from between visit 2 and 3 was performed using the Food Processor Software. Compliance was measured by returned capsule counts and blood fatty acid analysis using 1.3 M KOH in 95 % methanol hydrolysis and the HPLC method of Mehta and associates.[92]

Parameters were measured by following the kit manufacturer's instructions or published method (published method or kit and company in brackets) - triglycerides, (L-Type-TG H, Wako, Richmond, Virginia), total cholesterol (Cholesterol E method, Wako, Richmond VA, USA), HDL and HDL_3 isolated by precipitation (Quantolip, Technoclone, Vienna, Austria) and their respective cholesterols (Cholesterol E method, Wako, Richmond VA, USA), HDL_2-c (calculated as the difference between HDL-c and HDL_3-c), non-HDL-c calculated as TC-HDL-c, LDL-c (LDL-direct, Cholesterol E method, Wako, Richmond VA, USA), sdLDL-c,[93] Lp(a) by ELISA (Trinity Biotech, Jamestown, NY,USA), free fatty acids (half micro enzymatic method, Roche, Mannheim, Germany), leptin by ELISA (Linco, St. Charles, MO, USA), adiponectin by ELISA (Linco, St. Charles, MO, USA), and CRP by ELISA (Alpha Diagnostic, San Antonio, Texas, USA). LDL (density of 1.019-1.063) was isolated ultracentrifugation using potassium bromide.[94] Apo E genotyping was performed in accordance with Hixson and associates.[95]

As per Fuller and associates[96], the isolated LDL was dialysed for 24 hours at 4^{o}C against 10 L of saline/EDTA (150 mmol NaCl/L, 1 mmol/L EDTA/L). LDL was then filtered and stored at 4^{o}C until protein was measured via the Lowry method using bovine serum albumin for construction of a standard curve. LDL oxidation studies were performed within 48 hours of LDL isolation. LDL oxidation was done after an overnight dialysis of the LDL against 1 L phosphate buffered saline (PBS) pH 7.4 at 4^{o}C. LDL (200 mg protein/L) was oxidized over an 8 hour period at 37 ^{o} C in a cell free system using 5µmol $CuSO_4$/L in PBS pH 7.4. The time points were 0, 0.5, 1 1.5, 2, 3, 4, 5 and 8 hours. The level of oxidation was measured as conjugated dienes at 234 nm using a Spectromax 190 plate reader (Molecular Devices, Sunnyvale, CA). The lag phase was measured by determining the intersection point between the tangent to the slope of the propagation curve and the horizontal axis. The difference between zero time and that intersection time is the lag phase. The maximal slope (i.e rate of conjugated diene formation) is the steepest part of the slope of the propagation phase. The maximal oxidation conjugated diene formation was the difference in ΔA234 nm between the maximal absorbance measured and absorbance at 0 hours.

Waist and hip circumference measures were performed as per Lemieux and associates.[97]

Statistical analyses

The data in tables 3-8 was assessed by paired *t*-test for visit 1 versus visit 2 for males and again for females and then again for the average of visits 1 and 2. Furthermore, the data in tables 3-8 was assessed by unpaired t- test comparing the average of visits 1 and 2 for females versus the same for males. The data in tables 3-8 was assessed by unpaired t-test comparing the difference in a given parameter for the

difference between visit 3 and the average of visits 1 and 2 for a given gender for flaxseed oil versus safflower oil. The data in table 9 was performed by a two way ANOVA for days 1-3 and then separately for days 4- 6 as well as days 1-6.

Results

The fatty acid composition of the flaxseed and safflower oils is presented in table 1. The levels of oil and alpha-linolenic acid consumption are found in table 2. There were no significant differences in age or BMI between visits 1 and 2 for males or females nor was there any difference between males and females in age or BMI for the means of visit 1 and 2. Subject characteristics are contained in table 3. Measures of good treatment compliance via total plasma individual fatty acid levels are found in table 4. EPA and DHA both rose in the flaxseed oil group as expected by the increased consumption of their metabolic precursor, alpha-linolenic acid, such changes not occurring in the safflower oil group. Levels of fasting blood serum lipids, leptin, adiponectin and CRP are found in tables 5. There were no significant differences for a given gender in any lipid parameter going from visit 1 to visit 2. When the averages of visits 1 and 2 were compared, females had significantly higher levels, compared to males, of high density lipoprotein cholesterol (HDL-c) and its atherogenic subfraction HDL_2-c while at the same time having higher levels of HDL_3-c. Serum free fatty acids levels were significantly higher in females as was the leptin level. There were no gender differences in total cholesterol (TC), low density lipoprotein-cholesterol (LDL-c), small dense (sd) LDL-c, triglycerides, lipoprotein(a), non-HDL-c, adiponectin and CRP levels and the ratios of HDL-c: TC and HDL-c: LDL-c. The only significant group change was a decrease a decrease in total serum cholesterol in females consuming flaxseed oil. However, certain apo E genotypes did offer differing sensitivity to changes in lipid profiles as the result of flaxseed oil administration (table 5) (apo E 3/4 for the drop in triglycerides in females, apo E 4/4 for the greatest increase in HDLc and apo E 2/3 for the greatest drop in sd-LDL-c in females and apo E3 homozygotes for the resistance to drops in cholesterol in males). There were no changes in measures of LDL oxidation as the result of flaxseed oil administration (table 6). Flaxseed oil consumption was without impact on blood pressure (table 7)

Table 1: Fatty acid composition (weight percent i.e. mg of an individual fatty acid per 100 mg of fatty acids) in flaxseed oil (treatment) and safflower oil (placebo).

Fatty acid	Flaxseed oil	Safflower Oil
14:0	-	0.2
16:0	5.6	6.3
18:0	-	2.2
18:1 n-9	15.1	14.1
18:2 n-6	14.6	74.2
18:3 n-3	57.2	< 0.1
20:4 n-3	-	-
20:5 n-3	-	-
22:6n-3	-	-

Table 2: Oil and alpha-linolenic acid consumption[a] in human type 2 diabetic patients. Data (n= 32) is reported as mean (standard error of the mean) for subjects who completed the trial.

	Flaxseed oil	Safflower oil
Total oil consumption in g/d	9.6 ± 0.3	9.5 ± 0.3
Total oil consumption in mg per kg body weight per day	105.3 ± 0.8	103.2 ±1.2
Alpha-linolenic acid consumption in g/d	5.4 ± 0.2	< 0.01
Alpha-linolenic acid consumption in mg/kg body weight/day	60.0 ±0.5	< 0.01

Table 3: Pre-treatment characteristics of subjects (all Caucasian). Data (n = 32) is reported as mean ±standard error of the mean (S.E.M.). Values are means of visits 1 and 2.

	Flaxseed males	Safflower males	Flaxseed females	Safflower females
N	10	8	8	6
Age (years)	57.9 ±4.4	64.6 ± 3.0	56.6 ±2.6	60.8 ±1.1
Body mass index (BMI) (kg/m^2)	30.6± 1.2	29.8 ± 0.8	36.6± 2.0	31.1± 2.6

or anthropometric measures (table 8). There was consistent consumption of calories, OA and ALA from dietary sampling days 1-3 and from days 4-6 (table 9) within a given gender and treatment. ALA consumption increased days 4-6 relative to days 1-3 only in those consuming flaxseed oil.

Discussion

The parameters measured were all stable (showed no statistically significant difference) for visits one and two for each gender. Thus, data showing either a gender difference or similarity for the means of visits one and two is validated and gives credence to the influence of flaxseed oil on the parameters assessed. The patients presented a strongly pro-atherosclerotic fasting blood serum lipid profile despite the higher levels of anti-atherosclerotic HDL-c and HDL_2-c in females compared to males. Still, these levels were low and as well HDL_3-c was higher in the females than males. The role of HDL_3-c in atheroma formation and hence atherosclerotic risk is not clear. [3] However, despite these differences it would appear that there is an absence of gender difference in the level of risk is manifested in the gender statistically identical and low levels of HDL-c : TC and HDL-c : LDL-c ratios between males and females

Table 4: Compliance with flaxseed and safflower oil administration. Data (n = 32) is reported as mean ± standard error of the mean (S.E.M.). Compliance is noted by * ($p < 0.05$, v = visit).

Parameter	Male Flaxseed oil N=10	Male Safflower oil N=8	Female Flaxseed oil N=8	Female Safflower oil N = 6
12:0 v1,2	0.7 ±0.3	0.5 ±0.1	0.5 ± 0.1	0.4 ± 0.2
12:0 v3	0.5 ± 0.2	0.3 ± 0.1	1.4 ± 1.1	0.6 ±0.3
14:0 v1,2	2.8 ± 0.4	3.3 ± 0.6	4.4 ±0.6	2.5 ±0.6
14:1 v3	1.1 ± 0.5	2.7 ± 1.1	2.3 ± 1.2	1.9 ±1.3
16:0 v1,2	31.1 ± 0.9	36.5 ±5.4	31.3 ± 1.2	30.5 ± 1.4
16:0 v3	32.7 ± 2.8	30.3 ± 1.4	29.6 ± 3.6	31.4 ± 0.9
16:1 v1,2	1.8 ±0.7	0.4 ± 0.4	0.9 ± 0.6	1.7 ± 0.9
16:1 v3	2.0 ± 1.2	0.01 ± 0.01	0.5 ± 0.4	1.4 ±1.3
18:0 v1,2	4.9 ±0.6	4.5 ± 0.4	4.3 ± 0.3	5.5 ± 0.7
18:0 v3	7.0 ± 1.5	5.6 ± 0.9	8.8 ±3.6	4.5 ±1.3
18:1 v1,2	24.3 ±1.3	22.1 ±2.1	26.1 ± 0.9	23.4 ± 0.8
18:1 v3	22.3 ± 2.2	25.1 ± 1.1	22.4 ± 3.1	22.0 ± 0.5
18:2 v1,2	24.1 ±1.5	24.0 + 2.6	24.2 ± 0.9	24.1 ±2.3
18:2 v3	22.9 ± 3.6	26.2 ± 2.3*	21.6 ± 2.0	27.3 ±1.1*
18:3 v1,2	1.0 ± 0.1	1.0 ± 0.2	1.2 ± 0.2	1.0 ±0.2
18:3 v3	1.7 ± 0.5*	1.1 ± 0.2	2.0 ±0.7*	1.1 ± 0.4
20:4 v1,2	3.7 ± 0.4	3.2 ± 0.4	4.2 ± 0.5	3.1 ± 0.6
20:4 v3	3.1 ± 0.6	3.8 ± 0.3	3.4 ±0.6	4.3 ± 0.7
20:5 v1,2	0.2±0.1	0.2 ± 0.04	0.3 ± 0.1	0.5 ± 0.2
20:5 v3	1.8 ± 0.5*	0.1 ± 0.02	1.9 ± 5.1*	0.1 ± 0.07
22:6 v1,2	0.7 ± 0.1	0.5 ± 0.1	0.8 ± 0.2	0.3 ±0.2
22:6 v3	2.5 ± 0.6*	0.3 ±0.1	2.6 ± 0.5*	0.3 ± 0.1

coupled with statistically identical and elevated levels of the pro-atherogenic total cholesterol, triglycerides, non-HDL-c, LDL-c, sd-LDL-c that were observed. These ratios are a measure of arterial wall cholesterol influx versus efflux and it is apparent that these low ratios reflect the possibility of enhanced plaque formation derived from such greater influx. Elevated total cholesterol manifests in increased levels of LDL-c[98] while elevated triglycerides result in increased levels of the very highly pro-atherogenic sd-LDL-c.[99] sd-LDL-c represents a very high risk of atheroma formation via aggressive cholesterol influx into the arterial wall and hence atheroma formation.[3] Non-HDL-c (cholesterol associated with the pro-atherogenic LDL and very low density lipoprotein (VLDL) also contributes to increased cholesterol influx).[3] Further females presented a statistically higher level of FFA, which contributes to the pro-atherosclerotic impact of elevated blood serum glucose,[6,101] however, this was not manifested in the extent and severity of atherosclerosis as measured by the marker, CRP, which was identically (statistically) elevated between males and females. Lp(a) mean levels are not in the pro-atherosclerotic range (above 20-30 mg %) [23] and thus are not in need of address. Elevated Lp(a) may result in increased arterial wall cholesterol influx and hence atheroma formation. Lp(a) has variously been reported to enhance thrombus and embolus residence time or to decrease platelet aggregration resulting in thrombus formation (for review see Barre).[101]

Elevated leptin and decreased adiponectin is associated with higher triglycerides, cholesterol and LDL-c and lower levels of HDL-c [8-19]. Leptin is inversely correlated with HDL-c[11,17] but this is in dispute [102-105] Regardless, the higher levels of HDL-c in females was also associated with a higher level of leptin. Buyukbese and associates[105] has noted a positive significant correlation between leptin and HDL-c in female type 2 diabetics. The absence of gender difference in adiponectin was apparently without gender impact on the various lipid levels.

The lag phase, propagation rate (slope) and maximal conjugated diene production are consistent with the literature[106] and in going from visits one and two combined to visit 3. The metabolic stability in anthropometric measures going from combined visits one and two to visit 3 is consistent with the consistency in diet and self-reported absence of change in exercise patterns. Diets similar in terms of fatty acid composition contributed to the gender similarity of lag time, slope (propagation rate) and total conjugated diene formation. The tendency toward increased dietary saturated fatty acid consumption in males did not produce a difference in oxidation as it is increased polyunsaturated fatty acids that increase oxidation levels in type 2 diabetics [107] In this study, Caucasian males and females who are type 2 diabetics do not differ in lag time, slope (propagation rate) and total conjugated diene formation. It is clear that the combination of factors (antioxidants, diet, anthropometric measures) dictating LDL oxidation susceptibility, maximal rate and maximal production do not differ significantly by gender in this study. Thus it appears that the putative risk presented by LDL oxidation to the aggressive atherosclerosis experienced

Table 5: Comparison of the effect of flaxseed oil (mean 60 mg ALA/kg body weight/day) and safflower oil consumption for three months on fasting blood serum lipids, leptin, adiponectin and CRP concentrations in type 2 diabetics including apo E genotype trends and significant correlates of change in brackets[a] . Data (n= 32) is reported as mean (standard error of the mean) for subjects who completed the trial. (v = visit).

Parameter	Male Flaxseed oil N=10	Male Safflower oil N=8	Female Flaxseed oil N=8	Female Safflower oil N = 6
Triglycerides (mg/dl) v12	333.1 ± 154.9	134.1 ±17.2	200.3 + 21.9	150.9 ± 19.4
Triglycerides (mg/dl) v3	356.7 ± 184.4	141.6 ± 21.0	176.1 ± 17.9 (0.653 p = 0.079) Apo E 3/4 greatest decrease	132.4 ± 19.4
Total cholesterol (mg/dl) v12	222.1 ± 31.8	183.6 ± 10.5	200.4 ±11.7	193.5 ± 8.2
Total cholesterol v3	201.0 ± 28.2 (-0.579 p = 0.079) Total apo E3 least decrease	162.4 ± 28.2	181.5 ±15.7 p= 0.048 for v3 versus v12 compared to fema placebo	200.1 ± 10.2
HDL-c (mg/dl) v12	38.8 ± 3.0	36.8 ± 2.0	45.3 ± 4.0	38.6 ± 6.3
HDL-c (mg/dl) v3	40.0 ±2.8 (-0.683 p = 0.029) Apo E 4/4 greatest increase	64.8 ± 25.3	43.8 ± 3.3	48.5 ± 5.8
HDL_2-c (mg/dl) v12	9.4 ±1.8	8.2 ± 1.4	10.3 ± 1.2	5.8 ± 1.4
HDL_2-c (mg/dl) v3	9.8 ±1.6	26.2 ± 14.0	8.8 ± 0.8	9.5 ± 1.6
HDL_3-c (mg/dl) v12	29.4 ± 2.0	38.6 ± 1.6	35.0 ± 3.0	32.8 ± 1.4
HDL_3-c (mg/dl) v3	30.2 ± 2.0	51.2 ±20.4	34.0 ± 2.6	39.0 ± 5.4
LDL-c (mg/dl) v12	159.9 ± 22.9	131.5 ± 18.8	138.7 ± 12.3	146.3 ± 16.7
LDL-c (mg/dl) v3	166.4 ± 25.4	147.3 ± 38.3	155.8 ± 16.2	158.5 ± 21.7
Sd-LDL-c (mg/dl) v12	23.9 ± 3.4	21.6 ± 4.9	31.9 ± 5.4	25.7 ± 4.5
sd-LDL-c (mg/dl) v3	38.6 ± 8.1	33.2 ± 9.8	35.7 ± 5.9 (0.745 p = 0.089) Apo E 2/4 greatest decrease	31.6 ± 7.5
TC:HDL-c ratio v12	11.1 ± 2.5	11.1 ± 1.2	10.0 ± 1.0	7.7 ± 2.9
TC:HDL-c ratio v3	10.0 ± 2.0	7.2 ± 2.1	10.0 ± 1.0	10.0 ± 1.0
LDL-c:HDL-c ratio v12	8.3 ± 1.4	8.3 ±1.4	7.7 ± 1.2	9.1 ± 1.4
LDL-c:HDL-c ratio v3	9.1 ± 1.7	3.2 ± 2.0	9.1 ±1.6	7.1 ± 1.5
Non-HDL-c v12	209.3 ± 32.3	173.9 ± 12.2	186.2 ± 11.9	184.5 ±7.9
Non-HDL-c v3	187.1 ± 29.3	112.3 ± 15.8	166.7 ± 14.9	184.0 ±10.4
FFA (µmol/L) v12	329.7 ± 63.7	421.4 ± 50.1	431.0 ± 57.0	233.1 ±24.2
FFA (µmol/L) v3	376.0 ± 65.6	433.2 ± 89.4	370.0 ± 110.0	220.7 ± 36.2
Leptin (ng/ml) v12	18.0 ± 4.3	14.8 ± 4.0	95.0 ± 35.9	59.7 ± 19.4
Leptin (ng/ml) v3	20.5 ± 4.6	12.2 ± 3.4	110.5 ± 47.9	81.1 ± 20.6
Adiponectin (µg/ml) v12	17.9 ± 3.8	14.8 ± 0.8	15.6 ± 1.8	19.2 ± 3.2
Adiponectin (µg/ml) v3	17.1 ± 3.8	13.4 ± 0.4	14.0 ± 2.6	14.5 ± 2.0
c-reactive protein (mg/L) v12	7.57 ±1.15	7.28 ± 2.38	9.58 ± 2.46	8.10 ± 2.85
c-reactive protein (mg/L) v3	8.43 ± 1.43	6.29 ± 3.04	9.17 ± 2.53	11.55 ± 3.41

by type 2 diabetics[37-51] does not differ between males and females Caucasian type 2 diabetics consuming flaxseed oil or safflower oil in this study.

Platelet function and activation[58-59] are reflected in blood pressure. The reduction of blood pressure results in lower platelet activation[108] and risk of other cardiovascular

Table 6: Lag times, slopes and maximal oxidation levels of flaxseed oil compared to safflower oil consumers by gender. Data (N = 32) is reported as mean ± standard error of the mean (S.E.M, v =visit.).

parameter	Male Flaxseed oil N=10	Male Safflower oil N=8	Female Flaxseed oil N=8	Female Safflower oil N = 6
Lag time (minutes) v1v2	128.1 ± 24.4	136.8 ± 28.4	130.7 ± 36.4	133.7 ± 38.4
Lag time (minutes) v3	133.7 ± 21.5	137.4 ± 25.7	138.1 ± 41.5	137.4 ± 45.7
Maximal propagation rate (AU/min) v1v2	0.149 ± 0.028	0.144 ± 0.024	0.145 ± 0.052	0.134 ± 0.035
Maximal propagation rate (AU/min) v3	0.152 ± 0.043	0.148 ± 0.036	0.141 ± 0.048	0.148 ± 0.031
Maximal conjugated diene formation (AU) v1v2	0.680 ± 0.074	0.695 ± 0.077	0.729 ± 0.114	0.721 ± 0.099
Maximal conjugated diene formation (AU) v3	0.702 ± 0.083	0.725 ± 0.097	0.741 ± 0.105	0.751 ± 0.162

Table 7: Systolic and blood pressure levels of flaxseed oil compared to safflower oil consumers by gender. Data (n = 32) is reported as mean ± standard error of the mean (S.E.M., v = visit).

parameter	Male Flaxseed oil N=10	Male Safflower oil N=8	Female Flaxseed oil N=8	Female Safflower oil N = 6
Systolic (mm Hg) v1v2	141.5 ± 6.0	133.4 ± 5.1	137.4 ± 4.4	153.0 ± 8.4
Systolic (mm Hg) v3	144.8 ± 8.1	134.7 ± 6.2	147.3 ± 4.7	148.0 ± 9.7
Diastolic (mm Hg) v1v2	83.6 ± 2.8	85.0 ± 2.9	80.7 ± 2.7	91.4 ± 4.1
Diastolic (mm Hg) v3	87.0 ± 3.0	84.9 ± 1.2	86.5 ± 3.1	86.4 ± 2.9

Table 8: Anthropometric levels of flaxseed oil compared to safflower oil consumers by gender. Data (n = 32) is reported as mean ± standard error of the mean (S.E.M., v = visit).

parameter	Male Flaxseed oil N=10	Male Safflower oil N=8	Female Flaxseed oil N=8	Female Safflower oil N = 6
Weight (kg) v1v2	93.5 ± 5.7	86.0 ± 1.2	90.5 ± 5.7	79.8 ± 7.0
Weight (kg) v3	92.7 ± 5.7	86.5 ±1.6	90.6 ± 6.1	80.9 ± 6.9
Waist circumference (cm) v1v2	103.5 ± 3.5	99.8 ± 1.4	104.3 ± 4.1	98.4 ± 4.7
Waist circumference (cm) v3	105.0 ± 4.1	99.0 ±1.6	102.8 ± 4.3	98.5 ±4.6
Hip circumference (cm) v1v2	103.8 ± 2.2	102.0 ± 1.0	120.1 ± 5.3	113.1 ± 6.0
Hip circumference (cm) v3	103.8 ±2.4	102.0 ± 1.7	119.0 ±5.2	115.5 ± 5.0
BMI v1v2	30.8 ±1.2	29.5 ± 0.5	35.8 ±2.2	31.6 ± 2.6
BMI v3	30.5 ±1.7	29.7 ± 0.6	35.7 ± 2.1	32.0 ± 2.5
Waist to hip ratio v1v2	0.99 ± 0.02	0.99 ± 0.01	0.87 ± 0.01	0.87 ± 0.02
Waist to hip ratio v3	1.01 ± 0.03	0.97 ± 0.01	0.86 ± 0.01	0.86 ± 0.02
Waist to height ratio v1v2	0.595 ±0.014	0.584 ± 0.009	0.656 ± 0.022	0.602 ± 0.031
Waist to height ratio v3	0.604 ± 0.018	0.580 ± 0.011	0.650 ± 0.023	0.620 ± 0.030

complication.[109] However, flaxseed oil can lower platelet reactivity in human type 2 diabetics.[110]

The blood pressure data is validated by its consistency between visits one and two. The subjects of this study, each by gender population, are not meeting the Canadian Diabetes Association (CDA) 2008 Clinical Practice Guidelines[111] for systolic (< 130 mm Hg) and diastolic (< 85 mm Hg) pressures. This appears to be the first study addressing flaxseed oil supplementation, gender and hypertension in type 2 diabetics.

There is growing concern about anthropometric measures in terms of exacerbation of various phenotypic expressions of type 2 diabetes. Control of these anthropometric measures is key to diabetic management and dietary intake is key to management of anthropometric measures. Males and females had statistically identical weights, BMI and waist circumferences for the average of visits 1 and 2. There was a trend toward higher BMIs in females consistent with Wauters and associates,[103] de Azeredo-Passos and associates[112] and Sekikawa and associates[113] though inconsistent with Shah and associates[114] and Duc Son and associates.[115] This trend is not surprising given statistically gender identical weights and higher waist to height ratios in females. However, Shah and associates [114] and Duc Son and associates[115] observed Nepalese and Vietnamese persons, respectively indicating that gender differences may be ethnically based. The BMIs are greater and waist to hip ratios are about the same for Caucasian males and females in the current study compared to Widjaja and associates[116] and Morris and Rimm.[117] The higher waist to hip ratios seen in males in the current study and in Han and associates [118] differ inexplicably from a lack of gender difference in this ratio seen by Wauters and associates [103] in similar type 2 diabetics. Regardless, the elevated waist to hip ratio in males confers no advantage in type 2 diabetic management[119] while the lower waist to height ratio would appear to place the males in better position to manage their type 2 diabetes. Indeed, as indicated by Lee and associates [65], it would appear from the waist to height ratio data from the current study that females are perhaps at particular risk of complications of type 2 diabetes, given their significantly higher waist to height ratios. The waist to height ratio gender imbalance is consistent with that of Lorenzo and associates,[120] Mannucci and associates,[121], Hadaegh and associates,[122] and Tulloch-Reid and associates.[123] However Lorenzo and associates[120] have indicated that no single measure of obesity confers discriminatory advantage in prevalence differences in type 2 diabetes among different populations. This is consistent with the findings of Poll and associates[124] who found no good relation of any of these measures with fat volume. However, the consensus is that higher BMI, waist circumference, waist to hip and waist to height ratios are reasonable indicators of increased risk of complications arising from type 2 diabetes.

This clinical trial is the only one to show a significant decrease in total serum cholesterol, albeit it only in females, as the result of flaxseed oil consumption in type 2 diabetics. Thus it appears that only type 2 diabetic females may be sensitive to higher doses of ALA in terms of total serum cholesterol level reduction compared to any other human population examined for the impact of flaxseed oil on total serum cholesterol. Goh and associates[71] have reported a decrease in LDL-c due to flaxseed oil consumption in type 2 diabetics, though none have examined sd-LDL-c. Thus it may be that the lower dose used by Goh and associates[71] more specifically targets the cholesterol in the LDL fraction.

Harris[125] has observed that it takes very high doses of flaxseed oil to produce a lowering of triglycerides. The dose used in this study was insufficient to cause a drop in triglycerides and consequent decrease in sd-LDL-c and rise in HDL-c and HDL_2-c. Yet the drop in triglycerides is not necessary to produce a flaxseed oil induced decrease in HDL-c in dyslipidemic non type 2 diabetics.[72] Thus, type 2 diabetes may make flaxseed oil induced decreases in HDL-c independent of any change in total triglycerides. The absence of changes in lipid profile, with the exception of the drop in cholesterol in the current study, are mirrored by Pang and associates [74], Schwab and associates[75], Kaul and associates[76], Layne and associates[126], using normal humans and by Kelley and associates [127] who observed no change in lipid profile in healthy men consuming diets enriched in ALA. The ratios of TC:HDL-c, and LDLc:HDL-c showed no change due to flaxseed oil similar to Pang and associates[74] and Schwab and associates.[75] No other study in any human population has looked at the impact of flaxseed oil consumption on non-HDL-c, Lp(a) or free fatty acids.

Apolipoprotein E is a significant determinant of serum lipid levels and their distribution among lipoproteins.[79-81] Yet no one has ever published on apolipoprotein E genotype associated responsiveness of lipids to flaxseed oil administration in human type 2 diabetics. Differing sensitivity to changes in lipid profiles as the result of flaxseed oil administration (trend of apo E 3/4 for the greatest drop in triglycerides in females, statistical significance of apo E 4/4 for the greatest increase in HDLc and the trend of apo E 2/4 for the greatest drop in sd-LDL-c in females) occurred. Further, the apo E 3 homozygote males showed the greatest resistance to the change in total serum cholesterol. Donnelly and associates[128] have indicated the importance of apo E 4 to the sensitivity in change of lipids to change in response to statin drugs with the current results suggesting that the mechanism of enhanced sensitivity via apo E 4 may extend beyond the statins. This is confirmed via a calorie restricted diet methodology used by Saito and associates[82] to alter blood plasma lipid profiles. Further, Saito and associates[82] also noticed a statistically significant resistance to lipid profile changes in apo E 3 homozygotes compared to the apo E 3/4 genotype. However, only the current study has examined the responsiveness of blood serum lipid parameters to flaxseed oil in terms of apo E genotype in type 2 diabetics.

The flaxseed oil induced decrease in CRP, [72, 73] and adiponectin observed by Paschos and associates [74] and Nelson and associates[75] was not observed in this study, though the reasons for such are not clear. The absence of change in leptin or adiponectin in this study is consistent

with the relation between various lipid levels and each of leptin and adiponectin with the exception of the mild decrease in cholesterol seen in females in the current study,[8-19] Leptin is inversely correlated with HDL-c.[11,17] The explanation(s) for positive changes due to flaxseed oil seen in various published studies versus the lack of changes seen in this study is (are) not readily apparent. The validity of this study is in part assured by the consistency in gender data going from visit 1 to visit 2 and an absence of change for either gender in the safflower oil group between visit 3 and the averages of visits 1 and 2.

The finding of an absence of effect of flaxseed oil on propagation rate or maximal oxidation level using conjugated diene formation as a measure of oxidation is consistent with the observations of Nestel and associates.[83] The current study used a $CuSO_4$ challenge protocol very similar to that of Nestel and associates.[83] However, this is the first study done in type 2 diabetics and the first study comparing males to females in terms of ex vivo conjugated diene formation as the result of a $CuSO_4$ challenge to LDL isolated from flaxseed oil and safflower oil consumers. The absence of impact of dietary polyunsaturated fatty acids on LDL oxidisability in type 2 diabetics is consistent with that of Bos and associates,[129] Finnegan and associates[130] in hyperlipidemic persons, Higdon and associates[131] in post-menopausal women and Egert and associates[132] in healthy persons. However, this data contrasts with those of Hargrove and associates.[107]

The decrease in systolic and diastolic pressures observed by Paschos and associates[85] were not observed in this study. If there were any ALA-induced increases in arterial compliance as shown by Nestel and associates [84] they did not translate into decreases in blood pressure. Thus, despite the potential to alter eicosanoid formation mediating blood pressures, this potential did not manifest, for whatever unknown reasons, in changes in blood pressure. Males and females had similar pre-intervention systolic and diastolic pressures. Thus, it seems that males may be in no greater need of intervention or intensity of intervention [133] to decrease blood pressures than females and that both require intervention to overcome this risk factor for myocardial infarction and potential subsequent death. However, Bebb and associates[134] have observed that it appears very difficult at the present time to meet the CDA targets, though intensive intervention did improve target achievement in one study.[133]

The impact of diet combined with flaxseed or safflower oil did not confer any advantage to either gender in terms of anthropometric measures. Caloric intakes were similar to those reported in male type 2 diabetics but lower in females compared to values reported by Rivellese and associates.[135] Despite the higher caloric intake by males, a better anthropometric profile was not achieved by females suggesting that females in particular need to much more aggressively manage their anthropometric features by an appropriate combination of diet, exercise and medications. It is evident that the females despite a significantly lower caloric consumption are further away from target levels of various anthropometric measures.[64,111,136,137] Similar dietary intakes of OA indicate that males and particularly so females are not consuming this fatty acid in a manner advantageous to reductions in anthropometric measures key to better management of risk of complications arising from type 2 diabetes. Increased OA intake as the result of either flaxseed oil or safflower oil and increased ALA intake as the result of flaxseed oil intake did not cause any change in anthropometric measures and thus did not suppress appetite in any meaningful way.[8,85-91] Thus, ALA alone or perhaps as the result of insufficient conversion to EPA and DHA did not sufficiently suppress caloric intake. That said, it is clear that neither males nor females are meeting anthropometric guidelines and thus remain at significantly risk of serious complications of type 2 diabetes and thus both need to better manage their anthropometric features by a combination of diet, exercise and medications.

It is concluded that neither gender significantly improved any of the anthropometric measures as the result of increased ALA and similar but elevated OA consumption as the result of combined diet and nutraceutical intake. It may be that both genders need to much more aggressively manage exercise patterns and dietary consumption, including perhaps OA and ALA consumption, to bring their anthropometric measures into line with recommendations. It is also concluded that flaxseed oil was without impact on lipid levels and distribution, CRP, LDL oxidation and blood pressure.

Finally, the mean HDL-c and LDL-c levels and the ratios of: TC: HDL-c and LDL-c : HDL-c and blood pressures do not meet the 2008 Clinical Practice Guidelines[111]set by the Canadian Diabetes Association consistent with the work of Harris and associates[138] examining type 2 diabetes management in Canada. Thus, much more aggressive intervention ranging from improved diet, aerobic exercise, reduced or preferably eliminated smoking and alcohol consumption are required. Should these approaches fail increased doses of anti-atherosclerotic drugs or drugs that have not yet been tried in a given patient will be necessary. If the current study's patient data is representative of the Cape Breton type 2 diabetic population, then more aggressive intervention is required on this island. Such aggressive intervention is required to reduce or eliminate atheromatous plaque. When such plaque ruptures, collagen fibrils in the media of the artery are exposed to blood platelets. Collagen fibrils cause aggregation of these blood platelets resulting in thrombus and/or embolus formation which in turn may precipitate myocardial infarction. It has been previously observed that this population of type 2 diabetics has dramatically shortened bleeding times thus enhancing the risk of platelet aggregation and subsequent thrombus and/or embolus formation thus enhancing the opportunity for myocardial infarction[110], however, no statistically significant effect of the flaxseed oil was seen on glucose management.[139]

Acknowledgments
Ms. Pat Collins, R.N. of the Cape Breton University Health Centre is thanked for help with blood taking and

anthropometric measures. The authors also acknowledge the contribution of Dr. J. Wawrzyszyn of Sydney for drawing this study to the attention of his patients. We also thank Dr. E. Rudiuk of Cape Breton University for his assistance with statistical analyses. Bioriginal of Saskatoon, Saskatchewan is thanked for their generous contribution of the flaxseed and safflower oil capsules. The Canadian Institutes of Health Research and the Cape Breton University Research Assistance grant program funded this work.

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