Scientific Open Access Journals
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Journal of Hepatology & Gastroenterology

Research Article Open Access

Non-Alcoholic Fatty Liver Responsiveness to Food-Fiber Adequacy in a Community-Based Lifestyle Modification Program

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Received: 10 January 2018; **Accepted:** 06 March 2018; **Published:** 13 March 2018

Abstract

Nonalcoholic fatty liver disease (NAFLD) is an increasingly condition seen in patients with obesity, type 2 diabetes (T2DM) and cardiovascular diseases. Previous data pointed out sedentary behavior and inadequate fiber intake as environmental factors associated with a community-based NAFLD patients. Now, we intended to engage them in a lifestyle-change protocol with dietary counseling and physical exercises (LiSM), complemented with dietary fiber intervention. Among the NAFLD voluntaries (diagnosed by Fatty Liver Index-FLI>60), 20 fulfilled the inclusion criteria and assembled groups G1(regular diet) and G2 (fiber adequacy to 30g/day) that stayed on 20wk-LiSM complying combined physical exercise (walking and strength, 100min./day). Clinical, dietary, anthropometric and biochemical assessments were undertaken at baseline, 10 and 20 wks. The statistical analyses used software SAS for Windows, version 9.3 with $p<0.05$. NAFLD sample was predominantly female (84.2%), 56.6 ±9.3 years of age, 84.2% obese, 21% metabolic syndrome and 15.8% T2DM. G1 and G2 were similar at baseline and responded similarly to LiSM. The overall FLI reduction in G2 achieved 14.4%, more steeply in 10 week (12%), exactly when G2 presented the highest ingested level of fiber ($r= -0.44$; $p=0.057$). The lacking of responsiveness of FLI to the intervention might be attributed to the higher values of FLI components at baseline and their slower decreasing during LiSM. The effect of fiber adequacy on NAFLD normalization was specifically by reducing abdominal fatness, triglycerides and insulin resistance associatively to a general anti-inflammatory action of LiSM.

Keywords: Non-alcoholic Fatty Liver Disease; Dietary fiber; Exercise

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic condition characterized by the accumulation of fat in the liver in the absence of other causes of steatosis, including excess consumption of alcohol or drugs [1]. The prevalence of NAFLD varied from 20% to 30% in different countries [2]. Approximately 10–30% have the potentially progressive form of NAFLD, non-alcoholic steatohepatitis (NASH), which is associated with hepatocellular injury and inflammation [3-5]. Approximately 25–40% of patients with NASH will develop progressive liver fibrosis, ultimately resulting in cirrhosis in 20–30% [3,6-9]. The 10-year mortality rate is 20% for subjects with Child-Pugh A disease and 45% will decompensate within 10 years of diagnosis [10]. The leading cause of death in patients with NAFLD is cardiovascular mortality [11].

Although liver biopsy is the gold standard method for diagnosing and staging NAFLD, the majority of patients could be effectively diagnosed non- invasively with tests that are routinely available in the clinic today [12-16]. Fatty liver index (FLI) is one of these indices developed as a convenient tool. The greatest contribution to the prediction of FLI came from waist circumference (WC), followed by body mass index (BMI), triglycerides (TG), and gamma glutamyl transferase (GGT) levels [12]. The FLI is a surrogate marker of a fatty liver that was validated in a large group of subjects with or without suspected liver disease [12]. In population, hepatic steatosis as detected by ultra- sonography can be rule out if FLI < 30 (SN = 87%; LR- = 0.2) and a FLI ≥ 60 rule in hepatic steatosis (SP = 86%; LR+ = 4.3). When the index value is greater than or equal to 60 (FLI ≥ 60), the probability of having a fatty liver is >78% [17].

The epidemics of NAFLD, for a long time unnoted in the metabolic field, is becoming recognized as a condition possibly involved in the pathogenesis of obesity, metabolic syndrome (MetS), type 2 diabetes (T2DM), and atherosclerosis, whose epidemics are increasing worldwide [18]. In a cross-sectional analysis of baseline data from a local dynamic cohort [19], we found 52.8% NAFLD in a sample of 995 patients presenting 45.5% obesity with 69.8% abdominal obesity [19]. The found main dietary inadequacy was higher food-energy intake in its fat components (polyunsaturated fatty acid (PUFA), monounsaturated fatty acid (MUFA), saturated fatty acid (SAT), cholesterol and oil servings) [19]. Additionally, they showed high intake of processed food such as refined cereals and sugar, as well as sodium and, lower fiber intake. Added to the poor diet-quality and inadequate food intake, the NAFLD patients showed also low physical activity [20]. Thus, we might accept that behavioral factors are involved in the pathophysiology of fatty liver. In this aspect, an increased energy intake is considered to represent a major player and, a sedentary lifestyle with reduced physical activity, independent of diet, represents a determinant for fatty liver[20]. Having physical activity as common background, and dietary fiber adequacy as tool for diluting energy intake, we have found reductions in MetS [21] and WC [19]. Considering these previous data, we now consider to investigate the possible positive effects of adequate fiber intake-physical exercise intervention in NAFLD patients.

Methods

A longitudinal, randomized intervention- controlled study was conducted with subjects participating in a Lifestyle Modification Program ("Move for Health"), a community-based dynamic cohort study conducted by professionals linked to the Metabolism Exercise and Nutrition Center (CeMENutri) at UNESP Medical School (Sao Paulo, Brazil), since 1991. This lifestyle changing program (LiSM) introduces healthy lifestyle into subject's daily activities as alternative care for chronic non-communicable diseases. Participants come to the Center spontaneously either by mouth to mouth or doctor indication, looking for preventive health examination with further non-medicated interventions including nutrition reeducation and supervised physical exercises [21-23].

Among the voluntaries for this study (2015-2016), 20 fulfilled the inclusion criteria. The inclusion criteria involved men and women over 35 years of age, without liver disease and/or alcohol ingestion above 20 g/day, presenting WC higher than 88 cm for females and higher than 102 cm for males along with higher than normal, plasma enzymatic activity of aspartate transaminase (AST) and alanine transaminase (ALT) [24,25].

They were randomized distributed into two groups: Control (G1) and Fiber Adequacy (G2) groups. There was one drop out in G2. Both groups were kept in the LiSM during 20-week experiment, commonly receiving physical exercises and nutrition re-education with dietary counseling.

Subjects were aware of the study and signed a consent form based on the "experiments involving humans" of the Brazilian "National Council of Health, Ministry of Health" and the declaration of Helsinki. Both the design and consent form were submitted and approved by the Research Ethics Committee (CAAE: 36533814.5.0000.5411) of the UNESP-Botucatu (SP) Medical School.

Body weight and height measurements were taken [26] with subsequent calculation of body mass index (BMI = kg/m^2). The WC was measured with millimeter tape inextensible and inelastic on the midpoint between the last intercostal space and iliac crest [26]. Abdominal Sagittal Diameter [ASD] was determined by the highest point of the abdominal surface with the individual in the supine position, during normal breathing by means of an abdominal caliper [27]**.** Body fat composition was performed in the supine position by bioelectrical impedance (BIA) (Biodinâmics®, model 450, USA).

Nutritional histories were recorded individually by 24-hour recall by a trained nutricionist. Nutritionist interview were taken in three non-consecutive days, being one in weekend [28]. The 24-hour recall was applied at baseline, after 10 weeks and at the end of the study (20 weeks). Dietary data were obtained in household measures and converted into grams and milliliter enabling chemical analysis of food consumption. The analyzed nutrients were: Fibers, Carbohydrate, Protein, Total fat, SAT, MUFA, PUFA and Cholesterol. An average of the 3 records of each patient was performed after calculation. Data were processed by the NDSR (Nutrition data system for research, Minnesota University) program.

The antecubital-vein blood sampling was drawn after an overnight fast (8-12 hours), using standard venipuncture vacuum. Lipid parameters (total and HDL-cholesterol and TG), blood glucose, uric acid, GGT, ALT and AST were performed within 4 hours after blood collection by dry chemistry method (Vitros® 5600, Ortho Clinical Diagnostics, Johnson & Johnson Company, Raritan, NJ, USA). Serum insulin concentrations were measured by chemiluminescent method (Immulite 2000®, Siemens Healthcare Diagnostics, Marburg, Germany). The serum C-reactive protein (CRP) was measured by a high-sensitivity immuno-nephelometric assay (Siemens Healthcare Diagnostics, Marburg, Germany) [29]. Plasma malondialdehyde (MDA) was performed by high performance liquid chromatography with fluorimetric detection (HPLC; system LC10A®, Shimadzu, Japan) as previously described [30].

Metabolic Syndrome (MetS) was diagnosed following the NCEP-ATP III criteria[10], using updated glycemic limits of 100mg/dl [31]. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated based on the following formula:

HOMA-IR = [insulin (mU/mL) × Glucose (mg/dL)]/405 [32].

The "fatty liver index" (FLI) was calculated based on laboratory and anthropometric measures, including TG, GGT, BMI, and WC, by using the formula:

$$FLI = [e^{0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745}/(1 + e^{0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745})] \times 100$$

The algorithm varies between 0 and 100 with a FLI ≥ 60 ruling in the fatty liver [12].

The physical exercise protocol was composed by daily sessions of 100 min, 3-5 times/week, including 20 minutes warm up/stretching, 30 minutes walking (60%-80% VO_{2max}), 40 minutes strength in academy (3x 8-12 rep, 60%-70% 1RM) and 10 minutes stretching and cool down. This protocol is validated and is in accordance with the ACSM's guidelines for exercise prescription and treatment of chronic non-communicable diseases [33]. Protocol consisted by supervised exercise sessions, Monday to Friday. They should attend three or more sessions during the week, otherwise would be excluded from the study [23,29].

Nutritional counseling was applied weekly through lectures in groups with relevant nutritional context in which subjects were comprised. Dietary counseling is provided by dietitians that meet the participants to discuss benefits of a healthy diet to achieve an adequate body weight. A special session encouraged participants to increase the daily intake of fruit, vegetables, whole grain cereals, legumes, low-fat dairy products, and lean meat, fish or poultry as recommended by the Food Guide for the Brazilian population [34].

To achieve the goal of fiber adequacy (30 g/day), the fiber-adequate group (G2) received a weekly menu listing the fiber-rich foods and their daily recommended intakes. Complementary, they received saches containing one soup spoon size (15 g) of oats (1.4 g fiber) or linseed (5 g fiber) to be ingested twice a day [35,36].

Variables were expressed as mean and standard deviation. After checking homogeneity (Shapiro Wilk test) the groups were compared either by ANOVA (parametric data) or Gamma distribution (non-parametric data) for p=0.05 using SAS, version 9.3 (Windows®).

Results

The NAFLD sample was composed predominantly by females (84.2%), 56.6 ± 9.3 years old, referring fair good state of health (73.7%) and, 94.7% accomplishing the recommended daily-physical activity. The prevalence of obesity was 84.2%, T2DM 15.8% and MetS 21%.

G1 responded to 10 week of LiSM by increasing energy intake, carbohydrates (g) and and fat (g) (Table 1) without changes in anthropometry (Table 2), FLI and MetS (Table 3). The biochemistry showed significant reduction in all three-enzymes activity without changes in other variables (Table 4). After 20 week-LiSM, the energy intake decreased, returning to its baseline levels, as well as carbohydrates (g) and fat (g) (Table 1). Related to baseline, 20 week-LiSM resulted in unaltered mean anthopometric data (Table 2), food intake (Table 1), blood biochemistry (excepted CRP) (Table 4), and FLI (Table 3). Actually, the reduction of CRP was the only detected change (Table 4).

G2 increased the fiber intake from 14.7 g (Mo) to 19.3 g (M1) and 18.2 g (M2) with Mo< (M1=M2) therefore, G2 showed a significantly higher mean fiber intake than G1 at M2 (Table 1).

In 10 week-LiSM, G2 decreased energy intake (leading to G2=G1), increased carbohydrates (g) (leading to G2<G1), and Protein (g) (leading to G2=G1) and decreased Fat (g) (leading to G2<G1) (Table 1). Regarding the blood biochemistry, LiSM had similar effects on G2 and G1 (Table 4). However, differentially from G1, the plasma -glucose decreased steeply (10.3%) leading G2=G1 (Table 4) as well as FLI (12%), maintained G2=G1 (Table 3). After 20 week-LiSM, G1 and G2 end up with similar values of FLI, energy intake, anthropometry and biochemistry.

Assembling the G2 subjects according to their FLI normalization during the 20 week-experiment, we've composed responsive (G2A) and

Table 1: Control (G1) and Fiber-Intervention (G2) groups: characteristics and statistical differences at baseline (M0), 10-wk (M1) and 20-wk (M2) of intervention. 24-h Food intake.

	Groups	M0	M1	M2	p
Fiber** (g)	G1	11.0 ± 6.0	12.3 ± 6.8	10.4 ± 5.7^{A}	0.49
	G2	14.7 ± 5.0	19.3 ± 5.3	18.2 ± 4.6^{B}	
Energy* (kcal)	G1	1,127.8 ± 548.2^{a}	1,341.7 ± 681.6^{b}	1,161.6 ± 510.4^{a}	0.29
	G2	1,658.7 ± 1276.3^{a}	1,246.1 ± 814.3^{ab}	1,123.8 ± 281.4^{b}	
CHO* (g)	G1	138.1 ± 66.9^{ac}	162.8 ± 82.1^{a}	139.1 ± 67.1^{bc}	0.04
	G2	200.5 ± 125.3^{a}	131.6 ± 33.3^{b}	143.2 ± 41.2^{ab}	
CHO* (%)	G1	46.5 ± 9.2	49.1 ± 10.6	47.2 ± 10.0	0.52
	G2	52.2 ± 11.4	49.9 ± 11.2	48.5 ± 11.5	
Protein* (g)	G1	58.9 ± 23.8	63.8 ± 25.4	53.5 ± 21.5	0.13
	G2	79.7 ± 27.6^{a}	61.1 ± 18.6^{b}	66.7 ± 25.7^{c}	
Protein* (%)	G1	23.4 ± 7.5	20.6 ± 7.6	18.4 ± 6.7	0.34
	G2	23.2 ± 10.4^{a}	22.8 ± 7.8^{b}	23.4 ± 8.2^{ab}	
Fat* (g)	G1	38.5 ± 22.3^{a}	47.4 ± 29.5^{bA}	45.1 ± 24.0^{ab}	0.2
	G2	61.5 ± 84.3^{a}	31.1 ± 8.2^{bB}	36.4 ± 13.7^{ab}	
FAT* (%)	G1	29.5 ± 6.0	29.6 ± 8.0	34.0 ± 9.3	0.63
	G2	24.6 ± 9.5	27.2 ± 8.8	28.1 ± 9.5	
Cholesterol* (mg)	G1	223.9 ± 144.0	216.1 ± 136.3	180.7 ± 85.7	0.44
	G2	200.3 ± 71.8	164.3 ± 92.6	223.2 ± 171.7	
Sat. fat* (%)	G1	10.9 ± 3.7	10.1 ± 3.7	12.2 ± 5.6	0.92
	G2	7.8 ± 4.6	7.8 ± 4.1	9.5 ± 4.4	
MUFA* (%)	G1	10.0 ± 2.6	10.9 ± 4.4	12.0 ± 4.1	0.94
	G2	8.5 ± 3.7	9.0 ± 3.9	9.9 ± 3.5	
PUFA* (%)	0	5.5 ± 2.0	6.0 ± 3.3	7.0 ± 4.0	0.13
	1	5.9 ± 3.4	7.9 ± 3.2	6.1 ± 3.4	

*mean ± SD values; ** n(%) values; *GAMMA and Wald's statistics for variable distribution and repeated measures; **ANOVA for repeated measures presenting normal distribution; a.b.c p<0.05 for Moments(Mo. M1. M2); A.B.C p<0.05 between groups.

Table 2: Control (G1) and Fiber-Intervention (G2) groups: characteristics and statistical differences at baseline (M0), 10-wk (M1) and 20-wk (M2) of intervention- Anthropometric data.

	Groups	M0	M1	M2	P
BMI** (kg/m^2)	G1	35.0 ± 6.2	34.7 ± 5.9	34.5 ± 6.7	0.99
	G2	32.7 ± 2.9	31.9 ± 3.3	31.7 ± 3.8	
WC** (cm)	G1	110.0 ± 12.3	109.2 ± 13.7	105.0 ± 17.1	0.85
	G2	107.5 ± 10.4	102.1 ± 9.9	101.1 ± 9.8	
ASD** (cm)	G1	25.9 ± 4.0	25.8 ± 4.0	25.8 ± 4.3	0.97
	G2	23.7 ± 2.8	23.1 ± 3.1	23.2 ± 3.0	
Body Fat* (%)	G1	42.7 ± 10.4	42.9 ± 10.3	42.9 ± 10.5	0.19
	G2	41.4 ± 7.8*	40.9 ± 7.9	39.7 ± 8.0*	

*Mean ± SD values; *p<0.05 for Moments (M0, M1, M2); **n(%) values; GAMMA and Wald's statistics for variable distribution and repeated measures;. BMI: body mass index, WC: waist circumference and ASD: abdominal sagittal diameter.

Table 3: Control (G1) and Fiber-Intervention (G2) groups: characteristics and statistical differences at baseline (M0), 10-wk (M1) and 20-wk (M2) of intervention. Age, gender, Fatty-liver Index (FLI), Physical Activity (PA), Health status perception (HSP) and chronic diseases.

	Groups	M0	M1	M2
Age*	G1	54.2 ± 11.6	54.3 ± 11.5	53.9 ± 11.5
	G2	58.7 ± 6.5	58.9 ± 6.5	58.9 ± 6.6
Gender**				
Male	G1	1 (11.1)	1 (11.1)	1 (11.1)
	G2	2 (20.0)	2 (20.0)	2 (20.0)
Female	G1	8 (88.9)	8 (88.9)	8 (88.9)
	G2	8 (80.0)	8 (80.0)	8 (80.0)
FLI* (points)	G1	83.2 ± 18.5	79.4 ± 19.3	69.9 ± 29.5
	G2	80.7 ± 18.7^{a}	71.0 ± 27.4^{b}	69.1 ± 29.4^{b}
PA(min/wk)*	G1	799.4 ± 788.4	990.4 ± 574.4	705.0 ± 454.8
	G2	677.0 ± 872.2	819.5 ± 297.8	846.0 ± 471.0
Good HSP**	G1	5 (55.5)	6 (66.7)	5 (55.5)
	G2	9 (90.0)	8 (80.0)	9 (90.0)
Obese**	G1	8 (88.9)	8 (88.9)	7 (77.8)
	G2	9 (90.0)	10 (100.0)	8 (80.0)
T2D**	G1	1 (11.1)	0 (00.0)	0 (00.0)
	G2	2 (20.0)	1 (10.0)	1 (10.0)
MetS**	G1	2 (22.2)	1 (11.1)	2 (22.2)
	G2	2 (20.0)	3 (30.0)	2 (20.0)

*mean ± SD values; ** n(%) values; GAMMA and Wald's statistics for variable distribution and repeated measures; a,b,c p<0.05 for Moments(Mo, M1, M2); A,B,C p<0.05 between groups.

no-responsive (G2B) subgroups (Table 5). Both groups were similar in fiber intake but G2B presented higher baseline values of FLI, BMI, WC, glucose, and TG. All these, but BMI, remained higher than G2A throughout LiSM. Overall, the responsiveness (G2A) was associated with highly decreased FLI and TG and the non-responsiveness (G2B) to the increased BMI, WC and HDL-cholesterol (Table 5).

Discussion

Currently no single diagnostic procedure has been shown to be reliable enough in the diagnosis of fatty liver [37-39]. The two most common methods used in the diagnosis of fatty liver are histologic methods and imaging procedures. Despite liver biopsy being the gold standard procedure for the diagnosis of NAFLD, it is an invasive and expensive tool that has some health risks and economic costs [38-41]. As a result, it may be better that a multifaceted non-invasive approach is implemented in order to diagnose NAFLD in population- based studies. FLI is one of these indices developed as a convenient tool.

Table 4: Control (G1) and Fiber-Intervention (G2) groups: characteristics and statistical differences at baseline (M0), 10-wk (M1) and 20-wk (M2) of intervention-Plasma biochemistry and blood pressure.

	Groups	M0	M1	M2	P
GGT (U/L)*	G1	63.5 ± 42.2[a]	43.5 ± 21.5[b]	40.9 ± 28.2[b]	0.8
	G2	51.9 ± 29.6[a]	34.8 ± 21.9[b]	33.8 ± 19.9[b]	
ALT (U/L)*	G1	54.5 ± 23.8[a]	33.3 ± 9.9[b]	34.9 ± 14.7[b]	0.75
	G2	53.9 ± 36.5[a]	33.5 ± 16.8[b]	31.0 ± 18.2[b]	
AST (U/L)*	G1	48.7 ± 14.9[a]	36.6 ± 11.6[b]	35.3 ± 20.9[b]	0.36
	G2	46.0 ± 17.9[a]	30.8 ± 8.7[b]	36.8 ± 16.6[b]	
CRP* (mg/dL)	G1	0.6 ± 0.2[a]	0.6 ± 0.2[a]	0.5 ± 0.2[b]	0.81
	G2	0.7 ± 0.2[a]	0.5 ± 0.2[ab]	0.5 ± 0.2[b]	
HOMA-IR*	G1	2.7 ± 3.3	2.7 ± 3.3	1.9 ± 2.6	0.96
	G2	4.5 ± 4.5	4.5 ± 4.5	3.0 ± 3.2	
MDA**	G1	0.6 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.93
	G2	0.6 ± 0.1	0.5 ± 0.1	0.5 ± 0.2	
TG* (mg/dL)	G1	151.5 ± 85.2	127.2 ± 47.4	129.6 ± 67.9	0.17
	G2	137.0 ± 65.2	181.3 ± 160.2	184.5 ± 163.5	
HDL-chol.** (mg/dL)	G1	53.4 ± 9.5	49.9 ± 9.8	56.0 ± 9.4	0.96
	G2	55.8 ± 13.2	53.1 ± 11.9	57.1 ± 11.7	
Glucose* (mg/dL)	G1	98.2 ± 17.9	92.2 ± 11.3	92.9 ± 12.8	0.71
	G2	109.7 ± 25.8[a]	98.4 ± 17.0[b]	104.2 ± 23.2	
SBP** (mmHg)	G1	119.8 ± 13.6	116.9 ± 14.6	126.0 ± 16.1	0.61
	G2	124.6 ± 13.4	116.6 ± 13.4	122.0 ± 10.8	
DBP** (mmHg)	G1	77.8 ± 9.2	75.3 ± 9.8	73.8 ± 11.6	0.89
	G2	79.0 ± 5.1	74.4 ± 9.5	75.4 ± 6.5	
Uric acid (mg/dL)	G1	4.5 ± 1.1	4.1 ± 1.2	4.1 ± 1.4	0,09
	G2	4.1 ± 0.8	3.9 ± 0.9	3.9 ± 1.2	

*mean ± SD values; ** n(%) values; *GAMMA and Wald's statistics for variable distribution and repeated measures; **ANOVA for repeated measures presenting normal distribution; a,b,c $p<0.05$ for Moments(Mo, M1, M2); A,B,C $p<0.05$ between groups; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamiyltransferase; HDL-chol.: *high density lipoprotein cholesterol*; HOMA-IR: *homeostatic model assessment insulin resistance*; MDA: malondialdehyde; CRP: high-sensitive C-reactive protein; SBP: systolic blood pressure; DBP: dyastolic blood pressure; TG: triglycerides.

A significantly strong association between NAFLD and FLI was confirmed by binary regression, to the point that a one-unit increase in FLI led to a 5.8% increase in the chance of developing NAFLD. There is an association between FLI and all-cause mortality in middle-aged individuals. FLI was associated not only with hepatic-related mortality but also with cardiovascular disease (CVD) and non-hepatic cancer mortality independently of the diabetes/IGT status and metabolic syndrome (MetS) [42]. Potential clinical uses of FLI include the identification of patients for intensified lifestyle counseling [43,44], and researchers to select patients for epidemiologic studies. Our sample of NAFLD patients had the characteristics of eating a poor quality diet, 84.2% obesity, 21% MetS and 15.8% T2D. However, despite having these pathologies they referred being physical active and in good state of health.

As described earlier, at baseline, we found 69.8% abdominal obesity (and 45.5% BMI obesity) and 52.8% NAFLD [19]. It is well known the prevalence of NAFLD substantially increases in obese individuals [45]. Here, among NAFLD patients we found 84.2% BMI-obesity, 21% MetS and 15.8% T2D. Thus it seems clear that not all abdominal obese are BMI-obeses and, 15.8% of the NAFLD patients were in non BMI-obese. Thus, NAFLD might have to do with something else than body fatness. Similarly, it occurs with MetS and T2DM, while insulin resistance is considered a key mediator that links NAFLD and the metabolic syndrome [13]. Approximately one third of patients with NAFLD have the full MetS and >90% have at least one feature [46]. The severity of NAFLD is associated with the severity of the MetS being more prevalent in patients with more metabolic risk factors. Accordingly, in our sample MetS prevalence was 21%, suggesting that NAFLD might precede MetS. On the other hand, T2D, one of the main MetS complication [47] was 15.8%, a double of the rate found previously in the same community-based dynamic cohort [48].

The present LiSM minimally affected the FLI value and, therefore its components. The possible concurrent factors associated with this lacking of response would be the high degree of fatness (BMI and FLI) at baseline. Previously, our LiSM was proved to be efficient in decreasing body weight and promoting eutrophy from overweight, but nothing from obesity [21,22]. The leaning response to LISM is negatively related to previous physical conditioning therefore, the 20wk-LiSM might be insufficient to decrease BMI and fatness of these (94.7%) subjects previously considered active. On the other hand, It is known that body fatness as well as FLI, correlates with surrogate markers of low-grade inflammation [29], such as fibrinogen, CRP and tumor necrosis factor a soluble receptor II. It is also well described the multiplus anti-inflammatory effects of chronic physical exercises [49,50].

In the present work, both groups responded similarly to LiSM by decreasing CRP, a systemic marker of body inflammation. Similarly to CRP, both groups reduced GGT. It is known that GGT increases following liver inflammation and, this enzyme increases in NAFLD to protect against the adverse effects of insulin resistance. Additionally, GGT has antioxidant activity [51,52]. Among liver enzymes, such as AST, ALT and GGT, only GGT is considered an independent predictor of FL while AST is not associated with FL and ALT is not an independent predictor of FL [12].

Fiber intervention associatively to 20wk-LiSM reduced obesity and T2DM by 10%, without changes in MetS. These values were lower than seen before and particularly unexpected for MetS once it was found a 25% reduction in 10wk-LiSM/fiber intervention [21,22,53]. Actually, the averaged adequacy of 30 g fiber/day was not achieved in spite

Table 5: Responsive (G2A) and Non-responsive (G2B) groups according to Fatty-liver index (FLI) values (above and below 60 points, respectively) after 20-wk intervention: characteristics and statistical differences at baseline (M0), and 20-wk (M2) of intervention. Age, gender, Fatty-liver Index (FLI), Physical activity(PA), Health status perception(HSP) and chronic diseases.

	Group	M0	M2	Delta (M2/M0)
FLI(points)	G2A	63 ± 18.8^{aA}	37 ± 17.0^{bA}	-26^{A}
	G2B	93 ± 5.2^{B}	88 ± 11.1^{B}	-5^{B}
BMI(kg/m^2)	G2A	29.8 ± 1.8^{A}	32.3 ± 7.2	2.5
	G2B	36.1 ± 4.4^{B}	33.4 ± 4.3	-2.7
Fibers (g)	G2A	13.3 ± 5.2	15.9 ± 6.5	2.6
	G2B	12.7 ± 6.1	13.7 ± 6.5	1
WC (cm)	G2A	98.9 ± 6.6^{A}	99.4 ± 14.4^{A}	0.5^{A}
	G2B	114.9 ± 4.0^{aB}	105 ± 13.1^{bB}	-9.9^{B}
Glucose (mg/dL)	G2A	99.4 ± 14.4^{A}	90.5 ± 7.0^{A}	-8.9
	G2B	107.1 ± 26.5^{B}	103.7 ± 22.8^{B}	-3.4
SBP (mmHg)	G2A	119.4 ± 13.3	116.6 ± 8.9	-2.8
	G2B	124.0 ± 13.7	128.2 ± 13.9	4.2
DBP (mmHg)	G2A	76.9 ± 6.0	69.7 ± 6.2	-7.2
	G2B	79.3 ± 7.8	77.5 ± 9.4	-1.8
TG (mg/dL)	G2A	115.9 ± 75.9^{A}	111.5 ± 43.8^{A}	-4.4^{A}
	G2B	160.2 ± 70.2^{B}	185.9 ± 152.5^{B}	25.7^{B}
HDL-chol. (mg/dL)	G2A	52.3 ± 8.6	60.7 ± 12.7	8.4^{A}
	G2B	56.0 ± 12.6	54.2 ± 8.5	-1.8^{B}
CRP (mg/dL)	G2A	0.5 ± 0.2	0.4 ± 0.2	-0.1
	G2B	0.7 ± 0.2	0.5 ± 0.2	-0.2
HOMA IR	G2A	2.7 ± 2.8^{A}	1.2 ± 0.5^{A}	-1.5
	G2B	4.2 ± 4.6^{B}	3.1 ± 3.4^{B}	-1.1
MDA	G2A	0.6 ± 0.2	0.3 ± 0.06	-0.3
	G2B	0.6 ± 0.1	0.6 ± 0.1	0

*mean ± SD values; ** n(%) values; *GAMMA and Wald's statistics for variable distribution and repeated measures; **ANOVA for repeated measures presenting normal distribution; a,b,c $p<0.05$ for Moments(Mo, M1, M2); A,B,C $p<0.05$; BMI body mass index, WC waist circumference; HDL-chol.: *high density lipoprotein cholesterol*; HOMA-IR: *homeostatic model assessment insulin resistance*; MDA: malondialdehyde; CRP: high-sensitive C-reactive protein; SBP: systolic blood pressure; DBP: dyastolic blood pressure; TG: triglycerides.

of intake increasing from 14.7 to 19.3 g/d. This 31.3% increasing in fiber intake led to a 211% increase in plasma beta-carotene, suggesting an overall intake of colorful fiber sources and, consequently, a better quality diet [21].

Ten weeks of higher fiber intake(M1) reduced FLI in 12%, keeping a relationship of r=-0.444(p=0.057). However, this trend was not maintained at M2, when the FLI reduction dropped to 2.7%, ending up to 14.7% in 20 weeks of intervention. The FLI responsiveness to the intervention (LiSM+fiber adequacy) could be attributed (G2A) to a FLI's pattern: lower value at baseline followed by a higher declining, during the LiSM(first 10wk=M1). Conversely, the lack of responsiveness (G2B) of FLI was associated with its higher- component values of BMI, WC and TG as well as glucose. Interestingly, all these, but BMI, maintained higher than G2A from baseline throughout the LiSM. Therefore, the decreasing rate of BMI seemed to discriminate the success of fiber adequacy in normalizing FLI.

Presently, G2A ended up LiSM with lower values of glucose, HOMA-IR and TG, than G2B. TG was the FLI component that mostly responded to the LiSM-fiber adequacy (G2A) as well as glucose and both, have in common the insulin sensitivity, as regulating mechanism. Insulin is an independent risk factor for FL in the general population [54] GGT was the only component of FLI, along with hs-CRP that did not discriminate the success of G2A over G2B. GGT can be considered an independent predictor for NAFLD but, compared to the other components, GGT is the weakier component of FLI [12].

Conclusion

The higher fiber association to LiSM reduced FLI in a inverse relationship, normalizing NAFLD mainly by reducing abdominal fatness, TG and insulin resistance which in great part is probably associated with the non-fiber specific anti-inflammatory action of LISM.

Authors' contributions

Dr. Fernanda Maria M Ramos: The principal investigator, conducted the dietary protocol and nutritional assessments.

Dr. Hugo Tadashi Kano: Contributed with biochemistry assessments and analysis.

Dr. Loraine Gollino: Organized the data file and tables.

Acknowledgements

The authors are grateful to CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico).

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Citation: Ramos FMM, Kano HT, Gollino L, et al. Non-Alcoholic Fatty Liver Responsiveness to Food-Fiber Adequacy in a Community-Based Lifestyle Modification Program. J Hepatol Gastroenterol 2018; 2:009.