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Behavioral Determinants of Fatty Liver Index and of Nafld Responsiveness to a 10-Week Lifestyle Modification Program with Supervised Physical Exercises and Dietary Counseling

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Abstract

Environmental-behavior determinants of Fatty-Liver Index (FLI) and of Non-Alcoholic Fatty-Liver Disease (NAFLD) responsiveness to a Lifestyle Modification (LiSM) were investigated in a dynamic cohort study. Baseline-data analysis of 1030 subjects (2005-2017) included medical, dietary (24h-food intake questionnaire and Healthy Eating Index-HEI calculation), physical activity (IPAQ), anthropometry, and plasma biochemistry. An algorithm based on BMI (Body Mass Index), waist circumference, triglycerides, and GGT (Gamma Glutamyl Transferase) was used to develop the FLI, which varies between 0 and 100 with FLI ≥ 60 ruling in NAFLD. Longitudinal analyses from 583 subjects submitted to a 10-wk LiSM intervention with daily supervised mixed-physical exercises (5x/wk, 80min/session/60-80% VO_{2max}) and dietary counseling. FLI values were split into quartiles (Q1-Q4) for comparison with co-variables and submitted to ANOVA with Tukey's post hoc and significance level set at p=0.05. The top quartile of FLI was predominantly male, with lower schooling, lower income, lower physical activity, and inadequate HEI (98.8%). Multiple regression analysis revealed that increased FLI is associated with higher intake of fats, Carbohydrates (CHOs), and higher Na/K ratio in the diet. FLI was influenced by altered LDL-c and HDL-c, HOMA-IR, hs-CRP and MDA. After 10-wk LiSM, 95 subjects (16.3%) had reduced the>60 (M0) FLI. Hs-CRP and MDA were the main factors for positive responsiveness of FLI to LiSM. Thus, FLI was associated with low-quality diet with high-energy manufactured foods along with insulin resistance, pro- inflammatory, and elevated oxidative stress. The responsiveness to LiSM was associated with the decreasing of processed-refined foods and the reduced inflammatory-oxidative state.

Keywords: Fatty liver index • Risk factors • Lifestyle modification intervention

Introduction

Non-Alcoholic Fatty-Liver Disease (NAFLD) is the most frequent liver disease in western countries and has obesity as its main risk and cardiovascular mortality as Its leading cause of death [1].

Hepatic lipid accumulation plays a key role in the development of non-alcoholic fatty liver diseases. The term NAFLD is used to describe a condition of fat accumulation in the liver in the absence of excessive alcohol consumption (less than 20 g/d) and specific causes of hepatic steatosis. Among them, nutritional (*e.g.*, malnutrition, rapid weight loss), metabolic (*e.g.*, abetalipoproteinemia, lipodystrophy), and drug-induced (*e.g.*, glucocorticoids, methotrexate) causes as well as other conditions (*e.g.*, jejunal diverticulitis with bacterial overgrowth, inflammatory bowel disease) are relevant [2]. The prevalence of NAFLD varied from 20% to 30% in different countries [3]. A prevalence of about 34% among adults in the United States was described earlier in this century [4].

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Similarly to metabolic syndrome, it is widely accepted that behavioral factors are involved in the pathophysiology of fatty liver [5]. In this aspect, an increased energy intake is considered to represent a major player. In addition, diet composition was found to be relevant, associated with the plasma redox-markers [6]. A sedentary lifestyle with reduced physical activity, independent of diet, represents another determinant for fatty liver [2,5].

The aim of this study was to confirm environmental-behavioral (dietary and physical activity) factors affecting NAFLD in a community-based sample and, the effectiveness of a 10-wk lifestyle modification protocol (dietary counseling and supervised physical exercise) on NAFLD regression.

Materials and Methods

Subjects and study design

Cross-sectional and longitudinal studies were 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, looking for preventive health examination with further non-medicated interventions including nutrition reeducation and supervised physical exercises [7].

Baseline data from 1030 individuals, selected for the LiSM, from 2005 to 2017, were cross-sectionally analysed for medical, dietary (24h-food intake questionnaire and healthy eating index-HEI calculation), anthropometry, plasma biochemistry, physical activity (IPAQ version 8) and fitness (hand

grip, flexibility and cardiorespiratory-Balke's treadmill protocol). The algorithm based on BMI (Body Mass Index), Waist Circumference (WC), Triglycerides (TG) and GGT (Gamma Glutamyl Transferase) was used to develop the "fatty liver index" (FLI), which varies between 0 and 100 with a FLI ≥ 60 ruling in the NAFLD.

Longitudinal analysis were undertaken in data from 583 subjects submitted to a 10-wk LiSM intervention with daily supervised mixed-physical exercises (5x/wk, 80min/session/60-80% VO_{2max}) and dietary counseling [7].

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 of the UNESP-Botucatu (SP) Medical School.

Assessments

The anthropometry included body weight and height with Body Mass Index calculation [8]; waist circumference (cm) [9]; abdominal sagittal diameter [10]. Body fat was measured by Bioelectrical Impedance (BIA) (Biodinâmics®, model 450, USA).

From the antecubital-vein blood sampling drawn after an overnight fast it was undertaken biochemical analysis for Lipid (total and HDL-c (High Density Lipoprotein Cholesterol) and TG), blood glucose, uric acid, GGT, ALT (Alanine Aminotransferase) and AST (aspartate aminotransferase) by dry chemistry method (Vitros® 5600, Ortho Clinical Diagnostics); insulin by chemi-luminescent method (Immulite 2000®, Siemens Healthcare Diagnostics); high sensitivity C-reactive protein (hs-CRP) by a High-Sensitivity Immune-Nephelometric Assay (Siemens Healthcare Diagnostics) and Malondialdehyde (MDA) by High Performance Liquid Chromatography with fluorimetric detection (HPLC; system LC10A®). The Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was calculated based on the formula: HOMA-IR=[insulin (mU/mL) × Glucose (mg/dL)]/405 [11].

The algorithm based on BMI, Waist Circumference (WC), Triglycerides (TG) and Gamma Glutamyl-Transpeptidase (GGT) was used to develop the "Fatty Liver Index" (FLI), by using the formula: FLI=[e0.953 × ln (TG)+0.139 × BMI+0.718 × ln (G-GT)+0.053 × WC-15.745/(1+e0.953 × ln (TG)+0.139 × BMI+0.718 × ln (GGT)+0.053 × WC -15.745)] × 100. The algorithm varies between 0 and 100 with a FLI ≥ 60 ruling in the fatty liver [12].

The dietary Intake was calculated from a 24-hour recall taken in three non-consecutive days, being one in weekend. An average of the 3 records of each patient was performed after calculation [13]. Data were processed by the NDSR (Nutrition Data System for Research, Minnesota University) program [14].

The cardiorespiratory fitness (VO_{2max}) was determined by the treadmill test (Balke protocol) [15].

Interventions

The Lifestyle Modification (LiSM) intervention was by daily supervised mixed-physical exercises and dietary counseling. The supervised physical exercise protocol was composed by daily sessions of 100 min, 3-5 times/week, including warm up/stretching, walking (60%-80% VO_{2max}), strength in academy (3 × 8-12 rep, 60%-70% 1RM) and stretching and cool down [16].

The dietary counseling was applied weekly through lectures in groups. Benefits of a healthy diet to achieve an adequate body weight were stressed. 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 [7].

Statistics

FLI values were split into quartiles for comparison with co-variables. The groups were compared either by parametric (ANOVA) or non-parametric (Gamma distribution) data, for p=0.05 using SAS, version 9.3 (Windows®). Tukey`s post hoc was applied with significance level set at p<0.05.

Results

In the cross-sectional analysis, the found FLI quartiles were Q1 (<36.5), Q2 (36.6-59.8), Q3 (59.9-84.7) and Q4 (>84.8). The FLI for rule in NAFLD (≥ 60) corresponded to Q3 and Q4, though accounting for 50% of the sample (Table 1).

Compared to Q1, Q4 was predominantly male, presenting lower schooling, lower income and in (self- perceptive) bad health additionally to be heavier, fatter and leaner, referring lower physical activity and showing lower aerobic fitness without changes in flexibility and hand grip strength (Table 1).

Compared to Q1, Q4 presented inadequate HEI (98%) with the lowest intake of fruits and vegetables and higher TEI (Total Energy Intake) along with higher total fat, saturated and PUFA (Polyunsaturated Fatty Acid) intake than the other quartiles. Additionally, NAFLD (Q3 and Q4) showed higher intake of CHO (carbohydrate), (refined) grain and sugar, and higher ratio of CHO/fiber and sodium/potassium. Overall, Q1 presented the greater variety of dietary components of all (Table 2).

When compared to Q1, FLI>60 (Q3 and Q4) was characterized by similar albumin and higher values of triglycerides, total and LDL-c (low density lipoprotein cholesterol), fasting glucose and HOMA-IR, γ-GT, ALT, hs-CRP and MDA (Table 3). Differences in HDL-c. Happened only in Q4<Q1 (Table 3).

FLI correlated negatively with VO_{2max} and time to exhaustion but not with physical activity (IPAQ) (Table 4).

In a stepwise analysis, FLI > 60 was associated with lower VO_{2max} and lower time to exhaustion (Table 5).

Similarly, FLI correlated positively with TEE, its fat (excepted MUFA, monounsaturated fatty acid) and CHO components as well as with the ratios of CHO/fiber and sodium/potassium. On the other hand, FLI correlated negatively with the intake of fibers, MUFA, fruits and legumes. In a stepwise analysis, FLI ≥ 60 was associated with inadequacy intake of sugar, fiber, CHO and cereal (and CHO/fiber ratio), SAFA (saturated fatty acid) and PUFA, as well as with higher ratio of sodium/potassium. Similarly, FLI ≥ 60 was associated with lower VO_{2max} and lower time to exhaustion (Table 6).

In the longitudinal analysis, among the 583 subjects that started LiSM, 95 (16.3%) had reduced their FLI from>60 (M0) to<60 (M1). The 10-wk LiSM increased VO_{2max} and hand grip, without changes in flexibility. Additionally, there was reduction in BW and fatness with an increased Muscle-Mass Index (MMI) (Table 7).

Simultaneosly, LiSM decreased TEI and its components CHO (sugar) and fats (excepted MUFA) and increased the intake of fiber and grains leading to a decreased CHO/fiber ratio. There was also a decreasing in the sodium/potassium ratio (Table 8). Thus, LiSM increased physical activity and improved physical fitness of aerobics and strength. Similarly, LiSM led to dietary improvements by reducing TEI and by increasing the intake of natural/whole foods.

In general, LiSM led to a significant decreasing in all biochemical variables, excepted insulin, albumin and urea (Table 9). All four components of FLI responded to the LiSM with different OR (gender and age adjusted): GGT (OR=0.22), TG (OR=0.22) and WC (OR=0.63). Therefore, from the 583 subjects that started LiSM, 95 subjects (16.3%) had reduced their FLI from>60 (M0) to<60 (M1). Besides these four components of the FLI, the responsiveness to LiSM was associated with reduced ASD, increased VO_{2max}, adequate intake of CHO, Lipids (total and SAFA), adequate sodium/potassium and CHO/fiber ratio and plasma normalization of ALT, hs-CRP, HOMA-IR and MDA (Table 9).

The logistic regression and adjustments the 10-wk LiSM responsive subjects (to 10-wk LiSM), with FLI normalization, showed as protecting factors: ASD reduction, total lipid (%) and SAFA (%) adequacy, VO_{2max} increasing and HOMA-IR normalization. The stronger OR were for MDA (0.35), ALT (0.43), Fiber (0.85) and %CHO (0.87) intakes. Thus, after adjustments, the influence of fat intake disappeared, remaining the decreasing of CRP and MDA as the main factors for positive responsiveness of FLI to the present LiSM.

Table 1. Cardiorespiratory and fitness data according the quartiles of FLI.

Parameters	Fatty Liver Index (FLI)			
	FLI ≤ 36.5 ≤ p25 n=254	FLI:36.6-59.8 p25-50 n=215	FLI:59.9-84.7 p50-75 n=288	FLI ≥ 84.8>p75 n=253
VO_{2max} (mL/kg·min^{-1})	33.9 (17.7-60.9)[a]	33.1 (14.1-60.9)[a]	29.3 (12.3-50.1)[b]	26.7 (15.9-42.9)[c]
Time to exhaustion (s)	663 (142-1565)[a]	626 (95.0-1568)[a]	518 (64.0-1032)[b]	493 (68.0-977)[b]
Flexibility (cm)	22.5 (0-101)	21.0 (0-101)	21.2 (0-47.0)	21.0 (0-101)
Dynamometer (kgF)	28.0 (14.0-72.0)	28.0 (13.0-78.0)	28.0 (10.0-74.0)	26.5 (11.0-69.0)

Data presented as median (min-max). FLI: Fatty Liver Index; VO_{2max}: Maximum Oxygen Uptake; different letters expressed statistical difference. $p<0.05$.

Table 2. Significant food intake distribution among fat liver quartile in a community-based adult.

Parameters	Fatty Liver Index (FLI)			
	FLI ≤ 36.5 ≤ p25 n=254	FLI:36.6-59.8 p25-50 n=215	FLI:59.9-84.7 p50-75 n=288	FLI ≥ 84.8>p75 n=253
TEI (kcal/day)	1448 (538-2469)[a]	1372 (611-2376)[a]	1651 (608-4018)[b]	1991 (1217-4662)[c]
CHO (%)	52.4 (24.6-69.9)[a]	52.2 (23.0-71.0)[a]	65.8 (43.9-84.7)[b]	73.0 (47.2-87.1)[b]
CHO (g)	184 (71.8-317)[a]	183 (31.3-376)[a]	222 (83.0-463)[b]	287 (94.0-748)[b]
CHO/fiber	11.6 (3.90-71.5)[a]	12.6 (4.00-85.9)[a]	17.8 (8.90-176)[b]	21.1 (9.30-194)[b]
SAFA (%)	7.40 (1.50-18.9)[a]	7.90 (1.20-20.6)[a]	8.00 (1.10-25.7)[a]	9.10 (1.90-36.3)[b]
SAFA(g)	10.2 (2.10-35.2)[a]	11.5 (2.50-45.2)[a]	12.9 (3.30-66.5)[a]	15.8 (3.90-80.0)[b]
PUFA (%)	6.00 (1.50-18.1)[a]	6.10 (1.40-18.0)[a]	6.30 (0.700-21.1)[a]	7.50 (0.800-21.4)[b]
PUFA (g)	8.10 (1.50-18.1)[a]	8.80 (0.400-37.3)[a]	10.3 (0.500-43.3)[a]	13.7 (1.10-47.5)[b]
Total Lipids (%)	29.8 (5.90-54.9)[a]	29.7 (8.00-54.1)[a]	30.9 (10.0-63.8)[a]	35.8 (13.7-87.6)[b]
Oil (servings)	1.50 (0.100-6.70)[a]	1.40 (0.200-10.9)[a]	2.00 (0.200-10.5)[a]	3.10 (0.100-21.3)[b]
Cholesterol (mg)	140 (0.100-565)	145 (0.200-948)[a]	217 (0-1064)[a]	358 (13.6-4677)[c]
Fiber (g)	15.7 (3.40-45.0)[a]	14.7 (1.00-45.7)[a]	11.5 (1.40-32.4)[b]	8.10 (2.00-26.5)[b]
Fruits (g)	130 (0-995)[a]	140 (0-1050)[a]	134 (0-1463)[a]	110 (0-1158)[b]
Vegetables (g)	90.0 (0-434)[a]	96.0 (0-547)[a]	81.0 (0-575)[a]	64.0 (0-682)[b]
Grains (servings)	3.10 (0.500-11.8)[a]	3.20 (0-12.9)[a]	5.50 (0.600-18.6)[b]	5.90 (0.700-19.0)[b]
Fruits (servings)	2.10 (0-13.5)[a]	2.20 (0-19.0)[a]	1.90 (0-10.2)[a]	1.00 (0-7.00)[b]
Vegetables (servings)	2.30 (0-19.0)[a]	2.10 (0-18.9)[a]	1.10 (0-13.5)[b]	1.10 (0-12.5)[b]
Sugar (servings)	1.00 (0-7.70)[a]	1.50 (0-9.80)[a]	2.30 (0-11.9)[b]	2.50 (0-12.5)[b]
Sodium/Potassium	0.500 (0.100-2.20)[a]	0.500 (0.100-2.40)[a]	1.00 (0-5.70)[b]	1.20 (0.100-10.8)[b]
Variety (points)	16.0 (2.00-29.0)[a]	12.0 (3.00-25.0)[b]	12.1 (2.00-53.4)[b]	11.7 (6.00-21.0)[b]

Data presented as median (min-max). FLI: Fatty Liver Index; TEI: Total Energy Intake; CHO: Carbohydrate; SAFA: Saturated Fatty Acid; PUFA: Polyunsaturated Fatty Acid; different letters expressed statistical difference. $p<0.05$.

Table 3. Biochemical, hormonal and oxidative stress parameters

Parameters	Fatty Liver Index (FLI)			
	FLI ≤36.5≤ p25	FLI:36.6-59.8 p25-50	FLI:59.9-84.7 p50-75	FLI≥84.8> p75
	n=254	n=215	n=288	n=253
SBP (mmHg)	120 (88.0-172)[a]	120 (90.0-165)[a]	125 (85.0-180)[a]	140 (82.0-180)[b]
DBP (mmHg)	78.0 (56.0-114)[a]	80.0 (58.0-103)[a]	80.0 (52.0-110)[a]	95 (58.0-108)[b]
Total cholesterol (mg/dL)	190 (116-292)[a]	199 (114-334)[ab]	201 (113-321)[b]	225 (151-394)[c]
HDL-c (mg/dL)	55.0 (26.8-101)[a]	51.0 (26.4-100)[a]	48.0 (28.0-77.0)[a]	40.3 (28.0-71.4)[b]
LDL-c (mg/dL)	112 (45.9-218)[a]	120 (51.6-245)[a]	142 (93.7-237)[b]	176 (99.2-292)[c]
Triglycerides (mg/dL)	101 (36.0-232)[a]	128 (47.0-353)[a]	158 (82.9-416)[b]	199 (118-630)[c]
Fasting plasma glucose (mg/dL)	90.3 (68.0-188)[a]	94.0 (68.0-221)[a]	110 (72.0-307)[b]	138 (99.7-323)[c]
Insulin (mUI/mL)	9.80 (0.200-50.4)[a]	11.2 (0.400-73.0)[a]	13.0 (1.20-71.9)a	22.5 (5.90-77.1)[b]
HOMA-IR	1.80 (0.040-15.0)[a]	2.60 (0.100-19.8)[a]	5.40 (2.30-24.0)[b]	9.10 (6.00-29.0)[c]
γ-GT (U/L)	18.0 (4.40-68.1)[a]	28.1 (10.6-70.1)[a]	59.5 (38.6-155)b	87.8 (52.0-275)[c]
AST (U/L)	25.8 (10.1-62.0)[a]	28.0 (12.0-75.9)[a]	41.0 (15.6-95.6)a	68.0 (15.5-135)[b]
ALT (U/L)	22.5 (10.0-60.1)[a]	23.0 (10.4-71.2)[a]	50.2 (17.4-113)b	73.7 (32.4-136)[c]
Urea (mg/dL)	30.6 (14.0-78.0)[a]	33.0 (16.0-88.0)	33.0 (14.6-73.1)	32.9 (14.5-66.0)
Uric acid (mg/dL)	4.10 (1.20-7.90)[a]	4.50 (2.10-8.90)[a]	3.50 (1.90-8.20)a	2.70 (1.60-4.80)[b]
hs-CRP (mg/dL)	0.300 (0.010-1.15)[a]	0.300 (0.001-1.29)[a]	0.670 (0.260-1.82)b	0.950 (0.360-3.00)[c]
MDA (µmol/L)	0.400 (0.080-1.01)[a]	0.410 (0.070-1.27)[a]	0.760 (0.250-1.40)b	1.03 (0.390-2.15)[c]
Albumin (mg/dL)	4.0 (2.8-4.8)	4.1 (3.0-4.9)	3.1 (2.5-5.0)	3.1 (2.1-5.1)

Data presented as median (min-max). SBP: Systolic Blood Pressure; DBP: Dystolic Blood Pressure; HDL-c: High Density Lipoprotein cholesterol; LDL-c: Low Density Lipoprotein cholesterol; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance; γ-GT: gamma Glutamyl Transferase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; hs-CRP: High-sensitivity C-Reactive Protein; MDA: Malondialdehyde; different letters expressed statistical difference. $p<0.05$.

Table 4. Spearman rank R correlation of FLI.

Correlation	r value	p value
FLI with VO_{2max}	-0.490	<0.00001
FLI with time to exhaustion	-0.480	<0.00001
FLI witth PA	0.020	0.520

FLI: Fatty Liver Index; VO_{2max}: Maximum Oxygen Uptake; PA: Physical Activity (minutes/week); different letters expressed statistical difference. $p<0.05$.

Table 5. Multiple regression backward stepwise analysis for parameters with influence in fatty liver disease (FLI $\geq$ 60) in basal moment (M0).

Parameters	Fatty Liver Index-FLI≥60		
	β	R^2=0.88 Backward	p
Lower VO_{2max} (mL/kg·min^{-1})	0.42	0.41	0.04
Lower Time to exhaustion (s)	0.4	0.38	0.04

VO_{2max}: Maximum Oxygen Uptake; $p<0.05$.

Table 6. Multiple regression backward stepwise analysis for parameters with influence on fatty liver disease (FLI≥60) at baseline.

Parameters	Fatty Liver Index FLI≥60		
	β	R^2=0.88 Backward	p
CHO% (inadequate)	0.400	0.390	0.030
CHO/fiber ratio (inadequate)	0.560	0.590	0.010
Fiber (inadequate)	0.550	0.550	0.020
Cereal (inadequate)	0.550	0.510	0.020
Sugar (inadequate)	0.650	0.620	0.003
Total lipids (inadequate)	0.360	0.320	0.030
SAFA (inadequate)	0.380	0.370	0.030
PUFA (inadequate)	0.400	0.370	0.020
Sodium/Potassium (higher-inadequate)	0.530	0.48	0.020

CHO: Carbohydrate; SAFA: Saturated Fatty Acid; PUFA: Polyunsaturated Fatty Acid; $p<0.05$.

Table 7. Baseline (M0) and 10wk intervation (M1) data from adult individuals participant of the lifestyle changing program.

Parameters	Fatty Liver Index (FLI)				
	M0 (basal)	n	M1 (10-weeks LSMP)	n	p value
TEI (kcal/day)	1785 (979-4492)	583	1406 (1095-2502)*	583	0.03
CHO (%)	70.4 (45.1-87.1)	583	50.3 (40.2-65.9)*	583	0.01
CHO (g)	265 (50.6-748)	583	193 (43.7-395)*	583	0.01
CHO/fiber	19.6 (7.50-176)	583	11.5 (4.30-58.4)*	583	0.0001
SAFA (%)	9.10 (2.00-36.3)	583	7.30 (1.10-27.5)*	583	0.001
SAFA (g)	14.0 (3.30-77.4)	583	10.1 (1.50-56.8)*	583	0.01
PUFA (%)	7.10 (1.00-20.3)	583	6.00 (1.00-15.9)*	583	0.04
PUFA (g)	12.1 (1.50-46.2)	583	8.20 (0.400-33.5)*	583	0.04
Total Lipids (%)	35.8 (10.0-87.6)	583	28.1 (7.40-59.6)*	583	0.001
Total Lipids (g)	49.3 (8.50-248)	583	40.1 (7.30-190)*	583	0.001
Fiber (g)	12.3 (1.00-37.6)	583	19.1 (7.20-48.1)*	583	0.001
Grains (servings)	5.20 (0-19.0)	583	3.80 (0.300-14.2) *	583	0.04
Sodium/Potassium	0.900 (0.200-9.50)	421	0.500 (0.100-7.70)*	421	0.01

Data presented as median (min-max). TEI: Total Energy Intake; CHO: Carbohydrate; SAFA: Saturated Fatty Acid; PUFA: Polyunsaturated Fatty Acid; different letters expressed statistical difference. $p<0.05$.

Table 8. Significant dietary intake variation in a 10-wk intervation with supervised-physical exercises and dietary- counseling, in a community-based adult.

Parameters	Fatty Liver Index (FLI)				
	M0 (basal)	n	M1 (10-weeks LSMP)	n	p value
TEI (kcal/day)	1785 (979-4492)	583	1406 (1095-2502)*	583	0.03
CHO (%)	70.4 (45.1-87.1)	583	50.3 (40.2-65.9)*	583	0.01
CHO (g)	265 (50.6-748)	583	193 (43.7-395)*	583	0.01
CHO/fiber	19.6 (7.50-176)	583	11.5 (4.30-58.4)*	583	0.0001
SAFA (%)	9.10 (2.00-36.3)	583	7.30 (1.10-27.5)*	583	0.001
SAFA (g)	14.0 (3.30-77.4)	583	10.1 (1.50-56.8)*	583	0.01
PUFA (%)	7.10 (1.00-20.3)	583	6.00 (1.00-15.9)*	583	0.04

PUFA (g)	12.1 (1.50-46.2)	583	8.20 (0.400-33.5)*	583	0.04
Total Lipids (%)	35.8 (10.0-87.6)	583	28.1 (7.40-59.6)*	583	0.001
Total Lipids (g)	49.3 (8.50-248)	583	40.1 (7.30-190)*	583	0.001
Fiber (g)	12.3 (1.00-37.6)	583	19.1 (7.20-48.1)*	583	0.001
Grains (servings)	5.20 (0-19.0)	583	3.80 (0.300-14.2) *	583	0.04
Sodium/Potassium	0.900 (0.200-9.50)	421	0.500 (0.100-7.70)*	421	0.01

Data presented as median (min-max). TEI: Total Energy Intake; CHO: Carbohydrate; SAFA: Saturated Fatty Acid; PUFA: Polyunsaturated Fatty Acid; different letters expressed statistical difference. $p<0.05$.

Table 9. Significant biochemical, hormonal and oxidative stress variation in a 10-wk intervation with supervised- physical exercises and dietary-counseling, in a community-based adults.

Parameters	Fatty Liver Index (FLI)				
	M0 (basal)	n	M1 (10-weeks LSMP)	n	p value
SBP (mmHg)	140.2 (82.0-180.0)	583	120 (75.0-165)*	583	0.03
DBP (mmHg)	84.8 (60.0-110.0)	583	75.0 (60.0-100)*	583	0.04
Total cholesterol (mg/dL)	227.3 (113.0-394.0)	583	210 (118-287)*	583	0.04
HDL-c (mg/dL)	43.8 (28.0-94.2)	583	55.1 (39.6-95.0)*	583	0.04
LDL-c (mg/dL)	153.6 (68.0-291.6)	583	130 (51.2-207)*	583	0.03
Triglycerides (mg/dL)	197.6 (94.1-630.0)	583	122 (89.9-300)*	583	<0.0001
Fasting plasma glucose (mg/dL)	118.9 (80.2-323.0)	583	97.2 (73.6-177)*	583	0.001
Insulin (mUI/mL)	17.5 (2.3-73.0)	412	13.4 (0.900-54.2)	412	0.09
HOMA-IR	8.9 (1.2-29.0)	412	3.30 (0.050-12.6)*	412	<0.0001
γ -GT (U/L)	74.3 (39.7-275.0)	583	42.6 (21.3-111)*	583	<0.0001
AST (U/L)	58.8 (19.5-135.4)	583	40.1 (10.9-102)*	583	0.04
ALT (U/L)	68.4 (25.6-135.7)	583	30.4 (19.5-96.8)*	583	<0.0001
Urea (mg/dL)	33.2 (15.0-81.4)	583	31.9 (14.7-76.5)	583	0.31
Uric acid (mg/dL)	3.5 (1.6-7.5)	583	4.40 (2.40-8.00)*	583	0.04
hs-CRP (mg/dL)	0.65 (0.10-2.45)	473	0.290 (0.050-1.16)*	473	<0.0001
MDA (µmol/L)	0.81 (0.36-2.15)	569	0.550 (0.270-1.13)*	569	<0.0001
Albumin (mg/dL)	3.6 (2.1-4.7)	583	4.20 (2.50-5.20)	583	0.09

Data presented as median (min-max). SBP: Systolic Blood Pressure; DBP: Dystolic Blood Pressure; HDL-c: High density Lipoprotein cholesterol; LDL-c: Low density Lipoprotein Cholesterol; HOMA-IR: Homeostasis Model Assessment - Insulin Resistance; γ-GT: gamma Glutamyl Transferase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; hs-CRP: High-sensitivity C-Reactive Protein; MDA: Malondialdehyde; $p<0.05$.

Discussion

Although liver biopsy has been the gold standard method for diagnosing and staging NAFLD, Fatty Liver Index (FLI) is an algorithm developed as a non-invasive tool validated in a large group of subjects with or without suspected liver disease [12]. Considering FLI ≥ 60 for ruling in the NAFLD [12], our sample presented a prevalence of 50% (Q3+Q4).

NAFLD is considered a hepatic manifestation of metabolic syndrome [17] and as such it might have behavioral factors such as food inadequacy and sedentary lifestyle in its development [5,18].

Here we found FLI correlating positively with TEE, its fat (excepted MUFA) and CHO components. FLI>60 was associated with inadequate intake of sugar, fiber, CHO and cereal (and CHO/fiber ratio), SAFA and PUFA, as well as with higher ratio of sodium/potassium. On the other hand, FLI correlated negatively with the intake of fibers, MUFA, fruits and legumes. Likewise, FLI ≥ 60 was associated to lower VO_{2max} and lower time to exhaustion, lacking significance, however, to physical activity (IPAQ). Thus, physical inactivity and inadequate dietary intake lead to higher FLI. Lower aerobic capacity was the independent-risk factor for NAFLD (FLI>60). Similarly, high energy intake and lower fruits and legumes ingestion were associated with higher FLI. The higher intake of energy dense-processed food was the independent-risk factor for NAFLD. Overall, an increased energy dense-processed food represented a major player and, a sedentary lifestyle with reduced aerobic conditioning, independent of diet, represented the determinants for NAFLD. Intending to overcome these behavioral-misleading factors, we submitted the sample to our protocol of LiSM, looking for the results we have found previously for MetS (Metabolic Syndrome) patients [18].

In fact, once more LiSM increased physical activity and improved physical fitness of aerobics and strength. Additionally, there was reduction in BW and fatness with an increased Muscle Mass Index (MMI). Similarly, LiSM led to dietary improvements by reducing TEI and by increasing the intake of natural/whole foods.

The 10-wk LiSM reduced NAFLD by 16.3%, with higher ORs for reducing WC (OR=0.63) and identically OR=0.22 for GGT and TG. Therefore, WC plays a pivotal role in both, diagnosis of NAFLD and, FLI responsiveness to LiSM. In fact, although FLI had acceptable discriminatory power in the diagnosis of NAFLD, WC was a simpler and more accessible index with a similar performance [19]. In the case of NAFLD, it is believed that, the surplus of FFA (Free Fatty Acids) reaches liver from peripheral adipocytes lipolysis and both, the expansion of visceral fat mass, as well as ectopic fat accumulation in liver and skeletal muscle results from the inability of the body to adequately store energy, a state that is driven by insulin resistance of sub-cutaneous adipose tissue [20].

In previous work NAFLD-patients engaged in a lifestyle-change protocol with dietary counseling and physical exercises (LiSM), complemented with dietary fiber intervention (30g/day) showed an incremental 14.4% decreasing in the FLI. 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 [19].

On the baseline data we found that besides the components of NAFLD-algorithm, higher FLI (Q4) was characterized also by lower HDL-c. And higher values of total and LDL-c, fasting glucose and HOMA-IR, ALT, hs-CRP and MDA. These, enframes NAFLD as a glucolipotoxic- pattern of disease presenting inflammatory background (from ectopic fatness), insulin resistance and oxidative stress as underlying processes [21].

As found for metabolic syndrome, decreased CRP and MDA were the

main factors for positive responsiveness of FLI to LiSM. It is known that body fatness as well as FLI, correlates with surrogate markers of low-grade inflammation [22]. It is well described the multiplus anti-inflammatory effects of chronic physical exercises [23–25]. Similarly, moderate-physical exercises exerts antioxidant properties potentiating our defenses [26].

Previously, changes in plasma Total Antioxidant Performance (TAP) of those patients with MetS were inversely and significantly correlated with changes in MDA (r=-0.45). TAP responsiveness to LiSM was linked to higher Cardio-Respiratory Fitness (CRF) and only plasma-GSH (increasing) levels influenced plasma TAP of subjects with MetS [6].

Presently, we speculate that, by decreasing the intake of energy-dense refined CHO-rich diet and increasing aerobic conditioning there are lower free-fatty acid accumulation in hepatocytes, VLDL (Very Low Density Lipoprotein) secretion and CRP production. Decreased oxidative stress might be consequent either by the aerobic conditioning or by the decreased intake of energy-dense refined CHO-rich diet.

Conclusion

Food inadequacy/high-energy dense-processed food and lower physical inactivity/aerobic fitness were environmental risk factors for higher FLI. The LiSM intervention overcomes mostly of this altered behavior. The effectiveness of LiSM on NAFLD was evidenced through mechanisms of decreasing inflammation and oxidative stress.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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