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PHYSICAL ACTIVITY AND HEPATIC STEATOSIS

E. RUSU[1,2] G. ENACHE[3] M. JINGA[1] R. DRAGUT[1] R. NAN[1] H. POPESCU[1] C. HOMENTCOVSCHI[1] M. POSEA[1] M. STOIAN[1] S. ATEIA[1] A. COSTACHE[1] F. RUSU[4] D. GRIGORIE[1] D. MISCHIANU[1,4] G. RADULIAN[1] I. PANTEA[5] L. NEDELCU[5]

Abstract: *The objective was to evaluate the relationship between self-reported physical activity level and hepatic steatosis index non-invasively measured in patients with hepatic steatosis. We conducted a cross-sectional study that evaluated a number of 104 people, 60 with hepatic steatosis (HS group) and 44 healthy individuals (control group CG). In these patients we analyzed anthropometric parameters (height, weight, body mass index, waist circumference, hip circumference, ratio waist hip), biochemical parameters (fasting plasma glucose (FPG), fasting plasma insulin (FPI), alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase), adipocytokines (adiponectin, leptin, resistin) and proinflammatory cytokines (TNF alpha, IL-6). IR was determined using the homeostasis model assessment (HOMA-IR). Hepatic steatosis (HS) was evaluated by ultrasound and also using a mathematical algorithm (hepatic steatosis index - HSI). Physical activity level (min/week) was self-reported, physical activity less than 100 minutes per week was considered sedentary. The overall model fit was R^2 = 0.14. Sedentary individuals with or without steatosis have an increased index of fatty liver. Sedentary individuals associate also an increased pro-inflammatory status and a higher degree of insulin resistance.*

Key words: *Physical activity, hepatic steatosis, hepatic steatosis index.*

1. Background and Aims

The prevalence of nonalcoholic steatohepatitis (NASH) varies between 20-30% in European countries reaching 58-98% in certain populations (those with diabetes, obesity) [9], [11]. Regular physical activity favorably affects multiple chronic diseases such as obesity, diabetes, nonalcoholic steatohepatitis.

Current recommendations regarding physical exercise in patients with NASH are

[1] University of Medicine and Pharmacy "Carol Davila".
[2] National Institute of Diabetes, Nutrition and Metabolic Diseases Prof. N. Paulescu.
[3] Calarasi County Emergency Hospital.
[4] Clinical Emergency Military Hospital "Carol Davila".
[5] University Transilvania Brasov

150-300 minutes per week of physical activity (aerobic exercise) of moderate-high intensity (50-70% of maximum heart rate) performed minimum 3 days a week [7].

The objective of this study was to evaluate the relationship between self-reported physical activity level and fatty liver non-invasively assessed through hepatic steatosis index in patients with hepatic steatosis.

2. Materials and Methods

2.1. Study population

Participants were recruited from three hospitals from Bucharest, ”Prof. N. Paulescu” National Institute of Diabetes, Nutrition and Metabolic Diseases, “Dr. Carol Davila” Clinical Central Military Emergency Hospital, and Dr. I. Cantacuzino Clinical Hospital Romania. The inclusion and the exclusion criteria were previously published [15]. For this analysis we selected 104 persons (the NASH group (n=60) and the control group (44 healthy people)) from the patients included in the research project " Adipocytokines, link between virus C hepatitis and type 2 diabetes mellitus (DIADIPOHEP)"; this study was approved by the Romanian National Authority for Scientific Research. Written informed consent was obtained from all participants.

3. Procedures and Measurements

Anthropometric assessment was performed by measuring the following parameters weight, height, BMI (body mass index), waist circumference (AC), waist hip ratio (WHR). Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Based on World Health Organization classification, overweight was defined as BMI between 25 and 29.9 kg/sqm and obesity was defined as BMI of over 30 kg/sqm [7]. We also measured waist circumference (in centimeters), midway between the 12th rib and the iliac crest. Hip circumference was measured to the major trochanter.

Blood pressure was measured three times at the end of the physical examination with the patient in a seated position. Participants whose average blood pressure was greater or equal to 140/90 or receiving antihypertensive drugs were classified as hypertensive subjects [19].

4. Laboratory assays

Laboratory tests included biochemical analyses (glucose, glycosylated hemoglobin, lipid profile (cholesterol, triglyceride, HDL-cholesterol (HDL-C)), liver profile (aspartat-aminotransferase (ALT), alanin-aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), bilirubin), blood count. Adipocytokines (adiponectin, leptin, resistin) and proinflammatory cytokines (tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6)) were determined by enzyme-linked immunosorbent assay.

IR was determined using the homeostasis model assessment (HOMA-IR) [12].

Hepatic steatosis (HS) was evaluated by ultrasound and also using a mathematical algorithm (hepatic steatosis index - HSI) [5]. Hepatic fibrosis was non-invasively assessed using Forns index [4] and AST/platelet ratio [18].

Physical activity level (min/week) was self-reported, physical activity less than 100 minutes per week was considered sedentary.

5. Statistical Analyses

Data are presented as means and standard deviation of the mean. Comparisons among groups were made by use of ANOVA for quantitative variables. Chi-square tests were used to calculate the association between categorical variables. The Pearson's correlation coefficient was used to correlate physical activity with HSI, HOMA-IR. Statistical Package for Social Science (SPSS) version 18.0 was used for analyses. The values of $p<0.05$ were considered statistically significant.

6. Results

Characteristics of participants (n=104) include descriptive results for the anthropometric parameters and for biological markers (Table 1).

Of the 104 patients 75% were sedentary (physical activity <100 min/week) (59.1% (n=26) in the control group and 86.7% (n=52) in patients with SH group). In the control group the active patients were younger, with lower FPG, FGI, HOMA-IR, leptin, and TNF-α (all $p<0.05$). HSI, AST/ALT ratio were significantly increased in sedentary individuals (all $p<0.05$). In HS group active patients had lower BMI, WC, cholesterol, triglycerides, HOMA-IR, and lower levels of proinflammatory cytokines; HSI was higher in sedentary persons; active persons with steatosis associate a lower degree of liver fibrosis (lower Forns Index, $p=0.048$).

Characteristics of participants Table 1

	Control group					**Hepatic steatosis group**				
	Sedentary (n=26)		**Active (n=18)**			**Sedentary (n=52)**		**Active (n=8)**		
	Mean	**SD**	**Mean**	**SD**	**p**	**Mean**	**SD**	**Mean**	**SD**	**p**
Age (years)	46.58	8.60	42.50	6.35	0.040	51.19	7.87	46.63	7.44	0.040
Physical activity (min/week)	75.00	14.49	142.22	11.14	<0.001	79.42	15.14	133.75	10.61	<0.001
Weight (kg)	70.59	16.05	75.72	12.35	NS	91.26	14.73	81.64	7.84	NS
BMI (kg/mp)	25.54	5.65	25.08	2.90	NS	32.12	4.57	27.90	2.51	0.014
WHR	0.81	0.10	0.78	0.09	NS	0.94	0.09	0.87	0.10	NS
WC (cm)	81.85	10.42	79.00	6.96	NS	99.25	9.08	89.00	9.13	0.004
HC (cm)	101.14	6.11	101.24	5.65	NS	105.91	6.52	102.14	7.00	NS
Cholesterol (mg/dl)	184.69	25.69	188.89	18.07	NS	223.20	44.69	188.25	25.34	0.036
Triglyceride (mg/dl)	106.00	49.10	107.33	34.57	NS	192.48	94.44	111.50	25.36	0.020
HDL-C (mg/dl)	50.46	10.02	52.02	10.33	NS	38.49	7.00	43.05	9.46	0.030
FPG (mg/dl)	84.54	5.82	80.89	6.29	0.045	99.51	18.44	91.00	7.76	NS

	Control group					Hepatic steatosis group				
	Sedentary (n=26)		Active (n=18)			Sedentary (n=52)		Active (n=8)		
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
FPI (uUI/ml)	6.17	1.62	5.16	1.62	0.047	11.67	3.07	8.38	3.73	0.008
HOMA-IR	1.31	0.42	1.05	0.40	0.046	2.92	1.07	1.93	0.95	0.017
HSI	32.48	5.28	30.72	3.78	NS	39.74	5.38	34.77	3.85	0.015
AST (UI/L)	16.08	7.32	13.59	5.04	NS	48.70	21.33	49.38	21.91	NS
ALT (UI/L)	22.98	8.41	22.73	6.41	NS	64.40	30.97	73.50	41.02	NS
GGT (UI/L)	20.20	7.66	23.96	13.72	NS	74.24	42.03	62.13	36.77	NS
AST/ALT	0.69	0.16	0.59	0.09	0.025	0.78	0.18	0.73	0.24	NS
Forns Index	4.90	0.82	4.85	0.62	NS	6.47	0.99	6.16	1.24	0.048
APRI	0.17	0.07	0.15	0.07	NS	0.58	0.33	0.63	0.47	NS
Adiponectin (ng/ml)	5.97	1.63	6.81	1.17	0.020	3.79	1.73	6.48	3.65	0.001
Leptin (ng/ml)	10.91	2.61	9.33	1.75	0.031	18.23	7.48	9.89	4.17	0.003
TNF alpha (pg/ml)	7.24	2.13	6.28	1.65	0.048	14.88	5.32	10.06	4.74	0.019
IL-6 (pg/ml)	7.85	2.04	6.08	1.59	0.037	15.58	5.64	11.20	5.05	0.043
Resistin (ng/ml)	10.03	4.16	8.39	2.40	NS	21.14	13.12	18.08	13.51	NS

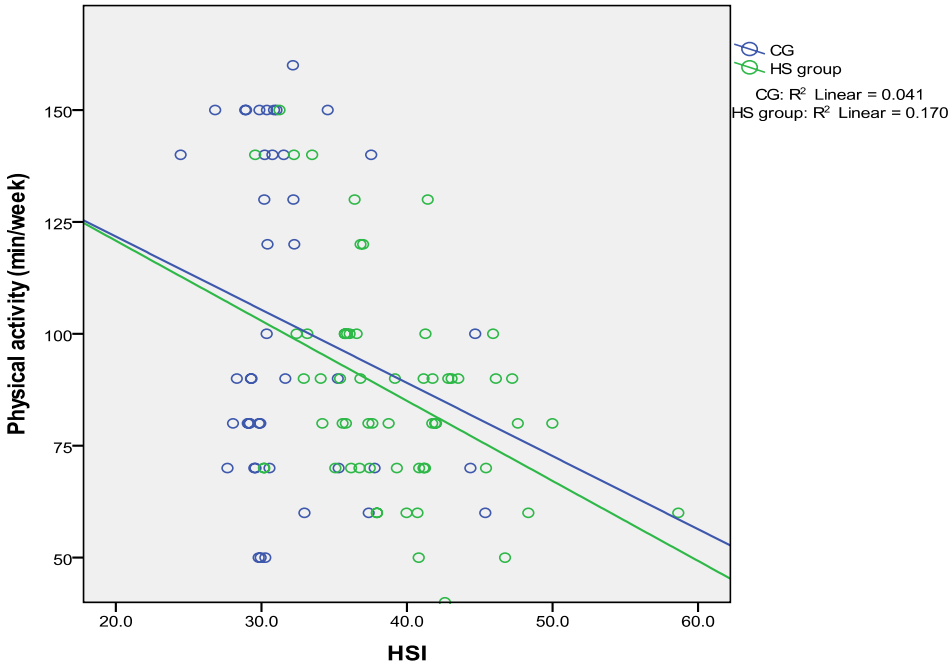
Table 2

Pearson's correlations between PA, HIS

	PA	HSI	HOMA-IR
HSI	-0.386**	1.00	0.619**
HOMA-IR	-0.270**	0.619**	1.00
BMI (kg/mp)	-0.301**	0.965**	0.613**
WC (cm)	-0.312**	0.830**	0.729**
AST (UI/L)	-0.195*	0.552**	0.767**
GGT (UI/L)	-0.14	0.552**	0.649**
AST/ALT	-0.230*	0.317**	0.276**
APRI	-0.197*	0.537**	0.739**
HDL-C (mg/dl)	0.280**	-0.508**	-0.550**
FPI (uUI/ml)	-0.278**	0.622**	0.988**
Adiponectin (ng/ml)	0.288**	-0.761**	-0.613**
Leptin (ng/ml)	-0.417**	0.583**	0.549**
TNFalfa (pg/ml)	-0.301**	0.607**	0.660**
IL-6 (pg/ml)	-0.300**	0.646**	0.679**
Resistin (ng/ml)	-0.327**	0.564**	0.556**

Table 2 shows the Pearson's correlations between PA, HSI and other parameters. In all patients, in univariate analysis (Pearson's correlation) PA was negatively

correlated with hepatic steatosis index (r=-0.386, p=0.01)(Graphic 1), HOMA-IR (r=-0.270, p=0.01), FPI (r=-0.278, p=0.01), AST/ALT ratio (r=-0.230, p=0.05), APRI (r=-0.197, p=0.05), BMI (r=-0.301, p=0.01) and positively correlated with HDL-c (r=0.280, p=0.01). Hepatic steatosis index was positively correlated with HOMA-IR (r=0,629, p=0,01), FPI (r=0,622, p=0,01), BMI (r=0,965, p=0,01), AST (r=0,552, p=0,01) and negatively with HDL-C (r=-0,508, p=0,01). The correlation between PA and HSI remained significant after adjustment for BMI (B=-0.079 95% CI-0.116, -0.042, p<0.001). The overall model fit was R^2 = 0.14.



Graphic 1. *Correlation between physical activity and hepatic steatosis index*

7. Discussions

The present study has highlighted an inverse correlation between the degree of physical activity and the index of hepatic steatosis; this correlation remains significant after adjustment for BMI. In our study, sedentary patients in both groups had higher levels of proinflammatory cytokines (TNF-α, IL-6). We also found an inverse correlation between the physical activity level and proinflammatory cytokines. This suggests that physical activity may reduce the progression of steatosis by reducing inflammation. Moreover recently published data confirm these results; increasing the level of physical activity of moderate/vigorous intensity with 30 minutes / day is associated with reduced risk of hepatic steatosis [10].

Prospective studies have shown that physical activity can reduce inflammatory markers in certain groups [14].

A recent meta-analysis demonstrated the effectiveness per se of physical activity in patients with NAFLD [8]. In the short term in diabetic patients diet and physical

activity is associated with reduced intrahepatic lipid content measured by the magnetic resonance [16].

Including regular physical activity (30 min/day, at least 5 days/week) into lifestyle intervention optimization programs was associated with reduced liver enzymes, insulin resistance and improved insulin signal [3], decrease of steatosis and necroinflammatory activity [2], reducing inflammation and oxidative stress [13], reduction of cellular apoptosis. The beneficial effects of physical activity may be associated with redox changes and improvement of antioxidant activity [1], the decrease of inflammatory cytokines [3], decreasing the expression of TNF-alpha, IL-6 and Toll-like receptors [6], [17].

The main limitation of this study is the cross-sectional design. Another limitation of the study is the diagnosis of liver steatosis based on ultrasound examination and using a mathematic model. A further limitation is the assessment of insulin resistance using HOMA-IR.

8. Conclusions

Sedentary individuals with or without steatosis have an increased index of fatty liver. Sedentary individuals associates also an increased pro-inflammatory status and a higher degree of insulin resistance. Structured programs focused on increasing physical activity should be promoted among the population in order to prevent the occurrence of fatty liver and of other associated metabolic diseases.

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The authors declare that they have no conflict of interests regarding the publication of this paper.

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