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The Influence of Progression of Liver Fibrosis to Exersice Blood Pressure Response

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ABSTRACT

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) being linked to the metabolic syndrom may represent a cardiovascular (CV) risk factor. This study was designed to estimate the association between the stage of fibrosis in normotensive patients with NAFLD and exercise blood pressure response.

METHODS*:* We carried out a prospective study on normotensive 70 patients with biopsy-proven NAFLD. We divided the study group into 3 different groups as group 1: simple steatosis (n=20); group 2: NASH with fibrosis stage 1 (n=36) and group 3: NASH with fibrosis stage 2 or 3 (n=14). These patients underwent several cardiovascular investigations by twenty-four hour blood pressure monitoring and treadmill effort testing.

RESULTS: The values for recovery diastolic blood pressure (DBP) in group 3 was higher in comparison with group 2 in 1 st min (79,6±9,7 vs 69,5±9,3, p<0,05); in 2 nd min (77,8±12,4 vs. 66,3±11,7, p<0,05); in 3 rd min (78,3±10,7 vs. 67,8±11,6, p<0,05); in 4 th min (79,3±11,4 vs. 67,8±11,6, p<0,01) and in 5 th min (79,3±11,4 vs. 68,9±10,4 p<0,01) of treadmill testing.

CONCLUSIONS: The patients with steatohepatitis had progression in Recovery DBP in accordance with stage of fibrosis. These findings suggest that exercise testing can provide valid information that may help identify patients with steatohepatitis with normal BP at a greater risk for future hypertention.

KEY WORDS*:* exercise, blood pressure response, steatohepatitis.

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INTRODUCTION

It has been proved by hyperinsulinaemic–euglycaemic clamp studies that increased intrahepatic triacylglycerol (IHTG) content strongly correlates with insulin resistance in liver, skeletal muscle and adipose tissue across a large range of liver fat percentages. Hence, it is considered that even small amounts of IHTG content associated with metabolic dysfunction (1,2).

In other studies it has been showen that the patients with NASH had significantly worse endothelial dysfunction in comparison with patients with simple steatosis and healthy controls. It is evident that endothelial

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dysfunction has significant predictive value for the development of cardiovascular disease (3).

The recent across sectional studies suggest that the severity of liver histology is closely associated with markers of early atherosclerosis such as carotid artery wall thickness and lower endothelial flow-mediated vasodilatation, independently of insülin resistance. In additional, it was showen that endothelial dysfunction leads to exercise-induced hypertention as a result of endothelium-dependent vasodilatation.

Thus, we designed the study to evaluate association between severity of liver fibrosis and exercise blood pressure response.

METHODS

Study design and groups

The study enrolled 70 patients who were under supervision with the diagnosis of NAFLD and documented to have normal blood pressure at rest. All patients underwent exercise test according to the Bruce protocol. Liver biopsy was performed at the discretion of the attending gastroenterologist and all biopsy specimens was evaluated according to the criteria proposed by Brunt et al (4). Based on biopsy results we divided the study group into 3 different groups as group 1: simple steatosis (n=20); group 2: NASH with fibrosis stage 1 (n=36) and group 3: NASH with fibrosis stage 2 or 3 (n=14). These patients underwent several cardiovascular investigations by twenty-four hour blood pressure monitoring and treadmill effort testing.

Exclusion criteria included age > 60 years, consumption of more than 20 g of alcohol per day, evidence for hepatitis B or C infection, autoimmune liver disease, use of medication linked to hepatic steatosis including glucocorticoids, amiodarone, tamoxifen, tetracycline, methotrexate, Wilson disease, hemochromatosis, α1- antitripsin deficiency, overt diabetes, thyroid dysfunction, hypertention (blood pressure higher than 130/85).

Diagnosis of NAFLD and Metabolic Syndrome

The diagnosis of NAFLD was made on the basis of fatty liver on ultrasonographic examination by criteria of at least 2 of the following findings: diffuse hyperechoic echo-texture, increased echo-texture compared with kidneys, vascular blurring and deep attenuation, focal sparing, or narrowing of the lümen of the hepatic veins.

Metabolic syndrome was defined by the International Diabetes Foundation (IDF) criteria. Three of following five criteria were necessary for definition: waist circumference >102 cm (40 inches) in men, > 88 cm in women,; triglycerides ≥150 mg/d L or on drug treatment for elevated triglycerides; reduced high density lipoprotein < 40 mg/ d L in men and <50 mg/ d L in women; systolic blood pressure ≥130 mmHg or diastolic ≥85 mm Hg or on antihypertensive drug treatment; fasting glucose >100 mg/ d L or on drug treatment for elevated glucose.

Measurement of waist circumference

Measurement was made at the end of a normal expiration. The measuring tape was placed in a horizontal plane around abdomen at level of iliac crest.

Histopathological evaluation of the liver

All patients underwent liver biopsy. The procedure was performed using a 16-G disposable needle by gastroenterologist. All specimens included 12 or more complete portal tracts and were longer than 20-25 mm. Hematoxylin and eosin (HE) and Masson trichrome stains were used for histopathological diagnoses of formalin-fixed paraffin-embedded liver tissues. Simple steatosis was defined as macrovesicular steatosis without any additional histological findings more than 5% of the weight of normal liver (5). The diagnosis of NASH was evaluated on Brunt's Criteria . Fibrosis was also scored as 0=no fibrosis;1=periportal or perisinusoidal fibrosis;2=perisinusoidal and portal/periportal fibrosis;3=bridging fibrosis; and 4=cirrhosis. Simple steatosis in association with pattern of fibrosis was classified as NASH.

Blood sampling

The venous blood samples were obtained from the antecubital vein from all patients and were collected in vacutainer tubes with gel clot activator.

Insulin resistance index was assessed by homeostasis model assessment IR (HOMA-IR)

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index and calculated by the formula of 'fasting insulin'(μIU/ml)×fasting glucose(mmol/L)/22.5. In a previous study concerning an İtalian population, the cut-off HOMA values indicative of insülin resistance was at 2.7.

Total cholesterol , HDL cholesterol, triglyceride, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP) were measured using common standardized laboratory techniques (Abbott Diagnostics, Toshiba Corp, Otawara-Shi, Japan).

Blood pressure measurement

All patients were asked for home blood pressure (BP)monitoring. BP was measured daily on 7 consecutive days; in the mornings as well as in the evenings. BP was measured in a quiet room, with the patient in the seated position, back and arm supported, after 5 min of rest and with two measurements per occasion taken 1–2 min apart: the results were reported in a standardized logbook immediately after each measurement. Resting BP was taken in a seated position after the patients had rest for at least 5 min. The measurement was performed 3 times per each visit, and the average of three measurement was accepted to be a representative value.

All 70 patients with baseline HBPM (home blood pressure monitoring) and resting systolic (SBP) and diastolic (DBP) designated to be normal according to the classification of hypertention (SBP <130 mmHg, DBP <85 mmHg) underwent tredmill effort testing.

Tredmill effort test

All patients underwent multistage exercise treadmill test according to the Bruce protocol. The patients remained on the treadmill for up to five 3-minute stages. Systolic and diastolic BPs were recorded by cuff while the participants were standing before testing and during the last minute of each 3-minute exercise stage. The duration of recovery phase was 5 minutes, with BP and heart rate recorded in the sitting position at the end of per minute. Exaggerated BP response at exercise was defined as systolic BP of ≥200 mm Hg or diastolic BP of ≥95 mm Hg.

Statistical analysis

All analyses were conducted using a computer based statistics software (IBM SPSS 20.0) and all data are expressed as mean±standard deviation (SD). Because the number of groups were more than two, the comparison of mean values of quantitative features was performed by one- way ANOVA test. In case where results of ANOVA test were positive, post hoc Tukey HSD test was used to clarify which groups had signifficant differences. Statistical significance was accepted at $p<0.05$.

Ethics Statement

All participants provided written consent for participation in the study. Ethics approval for conducting this study was received from the Ethical Committee of the Bezmialem Vakıf University (Istanbul, Turkey). All procedures were in accordance with the ethical standards of the committee on human experimentation of our institution and with the Declaration of Helsinki.

RESULTS

Demographic, clinical and laboratory details

Seventy biopsy-proven NAFLD patients were recruited. The madian ages of patients with steatosis, fibrosis stage 1 and fibrosis stage 2 and 3 were 44,2±10, 44,6±8,9 and 49,4±8,9, respectively. There were no statistically significant difference between the gender and ages of participants. There were no significant difference in waist circumference measurements and in lipid profile between groups. A comparison of postprandial plasma glucose among group 1 and group 2 (117,8±34,6 vs 191,7±93,1, $p<0,01$) and among group 2 and group 3 (141,5±0,26 vs 191,7±93,1, $p<0,05$) revealed significant difference. Hemoglobin A1c value were higher in group 3 in comparison with group 1 (6,62±1 vs 5,54±1,07, $p<0,01$) and in comparison with group 2 (6,62±1 vs 5,9±0,67, $p<0,05$), respectively. Therefore, the severity of metabolic syndrome increased in accordance with progression of liver fibrosis.

The clinical and laboratory data of patients are summarized in Table 1.

Treadmill testing details

We observed that there was progression in recovery diastolic BP (Rec-DPB) in accordance

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with progression of liver fibrosis. The values for recovery DBP in group 3 was higher in comparison with group 2 in 1 st min (79,6±9,7 vs 69,5±9,3, p<0,05); in 2 nd min (77,8±12,4 vs. 66,3±11,7, p<0,05); in 3 rd min (78,3±10,7 vs. 67,8±11,6, p<0,05); in 4 th min (79,3±11,4 vs. 67,8±11,6, p<0,01) and in 5 th min (79,3±11,4 vs. 68,9±10,4 p<0,01) of treadmill testing. There was no signifficant difference in recovery sistolic BP (Rec-SBP) between groups. The features of treadmill testing are summarized in Table 2. Comparison of rec-DBP within groups showed in Figure 1.

Table 1: Demographic and laboratory features of groups

Variables	Group 1 (n=20)	Group 2 (n=36)	Group 3 (n=14)	F value	P value	Tukey HSD p<0,05
BMI	28,80±4,09	28,42±3,81	29,79±5,32	0,530	0,591	
Waist circ, sm	44,75±9,98	44,69±8,96	49,43±8,92	1,454	0,241	
Trigliserid, mg/dl	169,10±92,53	229,51±174,59	164,31±47,77	1,752	0,182	
LDL, mg/dl	145,20±45,37	137,26±137,26	146,38±39,13	137,26	0,761	
HDL, mg/dl	41,70±9,15	43,71±5,37	41,15±12,49	0,241	0,786	
HOMAIR	4,16±2,34	11,20±21,25	10,76±16,65	1,170	0,317	
FPG, mg/dl	108,45±18,58	116,69±42,93	132,08±38,10	1,647	0,200	
PPG,mg/dl	117,80±34,58	141,49±62,57	191,69±93,13	93,13	0,007	1,2 vs 3
AST, IU/L	31,89±17,39	35,67±24,25	72,15±31,69	12,966	0,000	1,2 vs 3
ALT, IU/L	52,58±37,21	54,94±44,47	97,57±44,85	5,79	0,005	1,2 vs 3
ALP, IU/L	70,37±15,49	80,25±31,3	89,71±25,55	2,140	0,126	
GGT, IU/L	40,42±20,31	54,17±35,41	74,86±57,92	3,328	0,042	1,2 vs 3
CRP, IU/L	0,36±0,43	0,49±0,39	0,43±0,26	0,757	0,473	
HbA1c, mg/dl	5,55±1,08	5,91±0,68	6,63±0,99	6,133	0,004	1,2 vs 3
Neutrophil, 103/mL	4,93±2,14	4,53±1,67	4,29±0,71	0,608	0,548	
Lymphocyte, 103/mL	2,64±0,93	2,42±0,59	2,73±0,98	0,923	0,403	
NLR	2,04±0,97	1,93±0,96	1,74±0,62	0,422	0,657	
MPV	9,95±1,04	12,75±13,25	10,55±1,06	0,620	0,541	

Circ: Circumference LDL- low density lipopritein, HDL- high density lipoprotein, FPG- fasting plasma glucose, PPG- postprandial plasma glucose, AST-aspartate aminotransferase, ALT-alanine aminotrasferase, GGT-gamma-glutamyl trasferase, ALP-alkaline phosfatase, HbA1c: Hemoglobine A 1c NLR- neutrophil-to-lymphocyte ratio, MPV-mean platelet volume, APRİ- aspartate aminotransferase to platelet ratio index, FİB4- Fibrosis 4 score.

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Table 2. Comparison of treadmill effort test features within groups.

Variables	Group 1 (n= 20)	Group 2 (n=36)	Group 3 (n=14)	F value	P value	Tukey HSD p<0,05
Pretest systolic blood pressure(mmHg)	125,85±15,69	130,78±15,59	130,91±19,19	0,461	0,633	
Pretest diastolic blood pressure(mmHg)	76,92±11,04	75,16±12,07	79,91±8,83	0,737	0,483	
Stage 1 systolic blood pressure(mmHg)	134,46±21,01	151,16±21,88	146,45±22,96	2,687	0,077	
Stage 1 diastolic blood pressure(mmHg)	70,54±12,39	72,50±11,41	78,73±6,33	1,872	0,164	
Stage 2 systolic blood pressure(mmHg)	153,62±17,36	160,44±23,85	158,55±24,15	0,421	0,658	
Stage 2 diastolic blood pressure(mmHg)	73,00±15,63	71,22±11,69	78,91±4,37	1,745	0,184	
Stage 3 systolic blood pressure(mmHg)	161,92±20,69	168,53±22,96	175,8±28,29	1,035	0,362	
Stage 3 diastolic blood pressure(mmHg)	75,15±15,49	73,22±10,37	82,09±10,10	2,365	0,104	
Rec- systolic blood pressure 0(mmHg)	155,92±23,07	167,34±21,22	172,55±27,53	1,750	0,184	
Rec-diastolic blood pressure 0(mmHg)	72,00±13,24	72,06±9,03	81,27±11,93	3,296	0,045	2 vs 3
Rec-systolic blood pressure 1(mmHg)	153,38±21,67	164,31±22,63	170,27±26,43	1,710	0,191	
Rec-diastolic blood pressure 1 (mmHg)	73,69±9,68	69,53±9,30	79,64±9,73	4,800	0,012	2 vs 3
Rec-systolic blood pressure 2(mmHg)	147,69±19,65	156,16±23,19	165,64±30,23	1,671	0,198	
Rec-diastolic blood pressure 2(mmHg)	71,77±7,43	66,34±11,66	77,82±12,44	4,699	0,013	2 vs 3
Rec-systolic blood pressure 3(mmHg)	146,23±20,68	151,28±23,17	158,55±25,45	0,852	0,432	
Rec-diastolic blood pressure 3(mmHg)	71,46±7,11	67,78±11,63	78,36±10,75	4,119	0,022	2 vs 3
Rec-systolic blood pressure 4(mmHg)	145,31±21,00	151,19±23,13	157,45±26,33	0,810	0,450	
Rec-diastolic blood pressure 4(mmHg)	71,38±7,16	67,78±11,63	79,36±11,41	4,778	0,012	2 vs 3
Rec-systolic blood pressure 5(mmHg)	143,77±21,00	147,13±19,66	157,45±26,33	1,349	0,268	
Rec-diastolic blood pressure 5(mmHg)	71,23±6,61	68,91±10,42	79,36±11,41	4,572	0,015	2 vs 3
Maximum heart rate	164,31±10,80	164,25±11,48	159,45±12,00	0,783	0,462	

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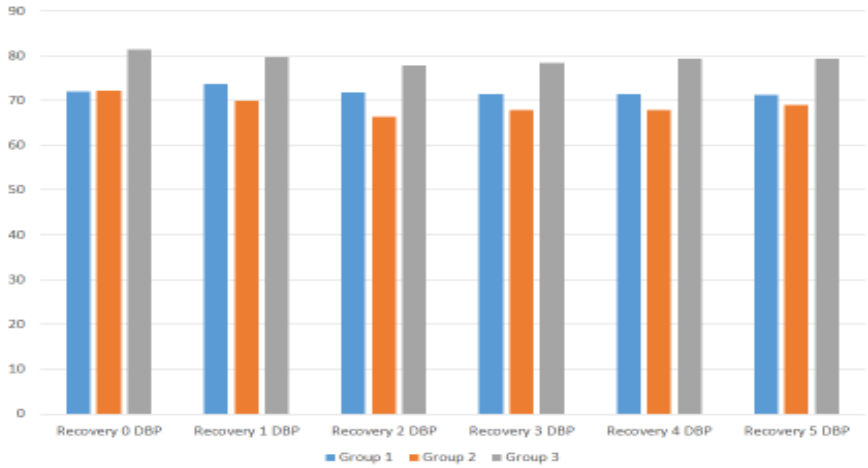

Figure 1: Comparison of rec-DBP within groups.

DISCUSSION

It was well established in the previous studies that an exercise testing appears to be an important diagnostic and prognostic procedure in the assessment of patients with hypertension (6-8). Also, an exaggerated diastolic BP response to exercise among normotensive patients was associated with 2-to-4-fold risk for new-onset hypertention.

During exercise in normal subjects the systolic pressure rises, the diastolic pressure falls, and the mean pressure does not change significantly (9). Reduction in diastolic blood pressure during exercise causes complete emptying of the left ventricle into the aorta. This leads to increased cardiac output and decreased myocardial oxygen consumption. Also physical activity increases intra- thoracic pressure and reduces venous return to heart, accumulates blood in general blood circulation, and, finally, increases systolic blood pressure (10). Exercise-induced rise in diastolic BP in the prehypertensive stage and borderline hypertensives was explained by increased resting peripheral vascular resistance in the early stages of hypertension (11) and impaired capacity for exercise-induced vasodilatation (9,12,13). Wilson et al. explained exaggerated response as a poor compliance of peripheral adaptation in proportion to the increment of cardiac output (14). It was demostrated that endothelium-dependent vasodilation was impaired in patients with exaggerate response to exersice. Thus, the endothelial dysfunction and impaired vasodilatory capacity of peripheral vasculature suggested to be responsible for inappropriate accomodation for increased cardiac output during exersice. Several studies has shown that the patients with NASH being linked to the metabolic syndrome and its components had significantly worse endothelial dysfunction compared with patients with simple steatosis (15). And metabolic syndrome is associated with endothelial dysfunction, impairing the vascular response to physiologic and pharmacologic stimuli (16).

The current study shows the association of diastolic blood pressure response to exersice and progression of liver fibrosis. We did not find any correlation between other components of metabolic syndrome, despite postprandial and hemoglobin A1c levels showed progression in accordance with fibrosis score. Also there were no signifficant difference between waist circumference and progression of fibrosis. We revealed a positive correlation between Rec-DBP and fibrosis score. Because the immediate postexercise period is associated with a reduction of sympathetic tone and a rebound

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increase in vagal tone (17), it suggested that abnormalities of autonomic control and vasoreactivity could extend into the early recovery phase of exercise. Consequently, endothelial dysfunction presenting in patients with NAFLD and which leds to increased periferal vascular resistance and impaired capacity for exercise-induced vasodilatation can explain the elevated recovery DBP in accordance with our study.

CONCLUSIONS

The exaggerated increase of BP in response to exercise has a negative correlation with endothelium-dependent vasodilation. It is considered that liver fibrosis accompanies endothelial dysfunction which appears to be predictor of early arherosclerosis. In our study we revealed that the patients with steatohepatitis had progression in Recovery DBP in accordance with stage of fibrosis. These findings suggest that exercise testing can provide valid information that may help identify patients with steatohepatitis with normal BP at a greater risk for future hypertention and that treatment modalities for the improving of endothelial function might be effective for prevention of cardiovascular events.

Conflicts of interest: No conflict to declare. Authors' contribution: R.A., J.C.: conception of idea and final review for academic content; R.A., M.McM.: review of clinical data and writing of manuscript; S.W., N.O'C.: patient recruitment and review of clinical data; J.S.,R.S.: statisical support and review of data; K.D.B., C.U.N.: review of manuscript for intellectual content.

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