Original Article

Association between physical activity and serum liver aminotransferases in Southwestern Iran: A Cross-sectional study

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Background: The main aim of the present study is to investigate the independent association objectively measured level of physical activity (PA) and serum concentration of liver aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) among seemingly healthy individuals. **Materials and Methods:** The current secondary study was conducted in the framework of Khuzestan Comprehensive Health Study, a large population-based multicentric cross-sectional study, conducted between 2016 and 2019 on 18,966 individuals living in Khuzestan province, southwestern Iran. International PA Questionnaire was used for evaluating PA levels, and participants were divided into three groups: low, moderate, and high PA, and ALT and AST were compared between these groups. **Results:** The mean ± standard deviation age of participants was 38.65 ± 11.40 years. The majority of participants were female (71%). The mean concentration of ALT in total sample was 18.22 ± 13.06 (male: 23.65 ± 16.26 and female: 15.57 ± 10.06), while the mean concentration of ALT in total sample was 19.61 ± 8.40 (male: 22.44 ± 10.03 and female: 18.23 ± 7.08). A statistically significant inverse correlation was found between AST ($r = -0.08$, $P = 0.02$) and ALT ($r = -0.038$, $P < 0.001$) with total PA score. The mean concentration of ALT was 19.96 ± 13.63 in people with low PA, 17.62 ± 12.31 with moderate PA, and 18.12 ± 13.47 with high PA ($P < 0.001$). The mean concentration of AST in total sample was 20.37 ± 8.85 in people with low PA, 19.21 ± 8.83 with moderate PA, and 19.75 ± 8.85 with high PA ($P < 0.001$). The difference between people in different levels of PA in terms of mean concentration of AST was remained significant ($P = 0.003$); however, the difference for ALT was not remained significant after adjusting potential confounders. **Conclusion:** The current study based on large sample showed that PA had a statistically negative association with the concentration of liver aminotransferases in the seemingly healthy individuals; however, the observed associations were weak. People in the lowest levels of PA had the highest levels of ALT and AST.

Key words: Alanine aminotransferase, aspartate aminotransferase, liver aminotransferase, physical activity

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INTRODUCTION

At the present time, the serum concentrations of the liver aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) have been routinely considered as markers of hepatocellular injury, including a wide range of etiologies from viral hepatitis to fatty liver.[1] Although ALT is the

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most specific to this feature, AST may also be elevated in other conditions such as thyroid disorders and celiac disease.[2] Abnormal liver enzymes may be also present in the absence of symptoms and signs of liver disease.[1,2] Mild-to-moderate increase in the serum concentration of liver aminotransferases might also be found in asymptomatic patients with liver disorders, particularly in fatty liver or chronic hepatitis C.[3]

Lifestyle factors, especially physical activity (PA), can irrefutably modulate the risk of developing several chronic diseases, including liver diseases.[4] The global prevalence of physical inactivity was about 22% in 2011.[5] Among the Iranian population, 40.0%, 24.7%, and 35.3% of individuals were categorized into low, moderate, and high PA, respectively.[6] Calorie restriction and PA are important factors for the management of nonalcoholic fatty liver disease (NAFLD). Patients with compensated cirrhosis, in addition, have withstood PA well.[4] Adults need to perform at least 150 min/week of moderate intensity exercise or 75 min/week of vigorous intensity exercise to achieve the beneficial and protective effects of PA.[7]

Some previous studies showed that although PA in adults may be associated with decreased likelihood of abnormal liver function in apparently healthy asymptomatic individuals, severe PA can lead to increase in liver enzymes.[8] As a result, the main aim of the current study was to evaluate the independent relationship between objectively measured level of PA and serum concentration of ALT and AST among seemingly healthy individuals in Khuzestan Province, Iran. Our data can be a new baseline of liver aminotransferase for Iranian population.

MATERIALS AND METHODS

Participants and study design

The current secondary study was conducted in the framework of Khuzestan Comprehensive Health Study (KCHS), a large population-based multicentric cross-sectional study. KCHS, a cross-sectional population-based study, was conducted between October 2016 and November 2019 in Khuzestan Province (Southwest), Iran, on 30,506 participants. The individuals in KCHS were recruited from primary care centers, called "Health Houses," in 27 counties of Khuzestan province by applying a stratified, multistage, clustered probability sampling method. A total of 30,506 people aged 20–65 years who met the inclusion criteria were enrolled in KCHS. Written informed consent was obtained from all participants at the beginning of the study. The protocol of the KCHS study was approved by the Ethics Committee and the Review Board of the university (Project No. RDC-9908, Ethics Committee and the Review Board Certificate NO. IR.AJUMS. REC.1399.224). This study was funded by the National Institute for Medical Research Development (NIMAD, grant number: 940,406).[9]

Exclusion criteria consisted of any history of alcohol ingestion, the harmful use of hepatotoxic agents (an amount of drug or nondrug agent that induce hepatocyte damage), chronic liver diseases, alcoholic liver disease, the infection of hepatitis C virus (HCV) or hepatitis B virus (HBV), glomerular filtration rate (GFR) <30, metabolic syndrome, and a disinterest to participate.[10] We also did not include the NAFLD in the study. We calculate GFR using MDRD (Modification of Diet in Renal Disease) Formula.[11] In this study, metabolic syndrome was defined based on the National Cholesterol Education Program Adult Treatment Panel-III (ATP-III) report of 2001 (updated in 2004) criteria (three items or more) including Fasting plasma glucose level ≥100 mg/dL and/or specific medication or previously diagnosed Type 2 diabetes, Hypertension (blood pressure ≥130 mmHg systolic and/or ≥85 mmHg diastolic and/or specific medication), Hypertriglyceridemia (triglyceride [TG] level ≥150 mg/dL and/or specific medication), Low high-density lipoprotein [HDL] cholesterol (<40 mg/dL for men and < 50 mg/dL for women, respectively, and/or specific medication), and central obesity (waist circumference >102 cm for male, >88 cm for Female).[12]

Study instruments and assessment of variables

In the KCHS, a multipart questionnaire was completed for each participant, which included basic sociodemographic variables, physical examination and anthropometric features (body weight, height, and waist and hip circumferences), sleep quality, PA, history of fertility, history of chronic diseases, habitual history, drug history, smoking, family history of chronic diseases, risk factors related to disease transmission, and history of psychological disorders. All questionnaires were completed by trained interviewers.

Physical activity assessment

International Physical Activity Questionnaire (IPAQ) (short version, PA in the last 7 days, issued in 2002).[13] Self-reporting method were performed to complete all items related to IPAQ.

IPAQ is a scoring system of 27 questions divided into five parts, including job-related PA, transportation PA, domestic and gardening (yard) activities, leisure-time PA, and time spent sitting. Job-related PA includes any paid and unpaid work that people did outside their home. Transportation PA is about how to travel from place to place. Domestic and gardening (yard) activities are some of the physical activities that have been done in the last 7 days in and around your home. Leisure-time PAs are all the physical activities of the last 7 days that have been done solely for recreation, sport, exercise, or leisure. Time spent sitting is the time spends for sitting while at work, at home, while doing course work, and during leisure time. The score of each main part of the questionnaire was calculated using the mean of metabolic equivalent of task (METs)-minutes per week (MET-min/week) and the total score of PA for each participants was obtained from addition of all parts. According to this score, each eligible participant was classified into one of the three categorical levels of PA. Low PA described the participants who do not have the criteria for moderate and high categories (<599 MET-min/week). Moderate PA represented individuals who achieve a minimum of at least 600 MET-min/week. High PA showed individuals who accumulate at least 1500 MET-min/week, usually meet vigorous-intensity activity on at least 3 days or any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum of at least 3000 MET-min/week for 7 or more days. Vigorous-intensity activities were defined as activities that take hard physical effort and make individuals breathe much harder than normal. Moderate-intensity activities referred to activities that take moderate physical effort and make individuals breathe to some degree harder than normal. Validity and reliability of IPAQ-SF were approved in Iranian population. Cronbach's alpha coefficient (0.7) indicated a good internal consistency for this instrument. Spearman–Brown correlation coefficient (0.9) showed good test–retest reliability. Furthermore, exploratory factor analysis showed five factors.[13,14]

Clinical and biochemical measurements

The venous blood samples were taken from all participants, fasted for at least 8 h. Serum samples were immediately processed and transported to reliable certified laboratories of each cities. All samples were analyzed within 24 h to determine the level of TG, total cholesterol, low-density lipoprotein, HDL, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, and gamma-glutamyl transpeptidase. The same analyzer and the α-ketoglutarate reaction were utilized measurement of ALT and AST. The upper limit of normal ALT and AST level was accepted for magnitude under 40 U/L in both men and women.[15]

Vital signs including systolic and diastolic blood pressures (mmHg), respiratory rate (breath/minute), heart rate (pulse/minute), and temperature (degree of centigrade) were also recorded.

Other variables

Body mass index (BMI) (kg/m^2) was calculated as the individual's weight (kg) divided by the square of the height (in meters). The following categories were considered for BMI: underweight, BMI of <18.5; normal weight, BMI of 18.5–24.9; overweight, BMI of 25–29.9; and obesity, BMI of 30 or greater.[16,17] Age, gender, level of education (elementary school degree, guidance school degree, associate's degree, bachelor's degree, master's degree, and doctorate/PhD), marital status (single, married, divorced, and widowed), cigarette smoking, and opium use were also recorded.

Statistical analysis

Continuous and categorical variables were reported as mean ± standard deviation (SD) and frequency (percentage), respectively. Normality of continuous variables was evaluated using Kolmogorov–Smirnov test and Q-Q plot, and nonnormally positively skewed data were subjected to logarithmic transformation. Basic demographic and clinical continuous variables were compared between three levels of PA using analysis of variance (ANOVA) and categorical data using Chi-squared test.

The bivariate association of total PA score with serum concentration of liver aminotransferases (ALT and AST) was evaluated using Spearman's rank correlation coefficient. Multiple linear regression was used for evaluating association between total PA score with ALT and AST when adjustment was made for potential confounders.

We also evaluated the mean value of serum concentration of liver aminotransferases (ALT and AST) between people in three levels of PA using multivariate ANOVA (MANOVA) and multivariate analysis of covariance by adjusting confounders. Bonferroni *post hoc* test was used for pairwise comparisons after MANOVA/MANOCVA. Statistical analyses were performed using SPSS statistical software (IBM Corp. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA: IBM Corp.).

RESULTS

The data of 30,506 participants were assessed for eligibility. We removed the data of 11,402 participants due to alcohol ingestion, fatty liver disease, HCV infection, HBV infection, chronic liver diseases or liver cirrhosis, GFR <30, and metabolic syndrome sequentially. Finally, 18,966 participants with complete data on our study's main variables were included in the data analysis. The flow diagram of participants' recruitment is shown in Figure 1.

The classification of participants in terms of PA led to 3524 (18.58%) participants with low PA, 8784 (46.31%) participants with moderate PA, and 6658 (35.10%) participants with high PA.

Table 1 shows the basic demographic and clinical characteristics of the study participants for total sample and across categories of PA. The mean ± SD age of the total

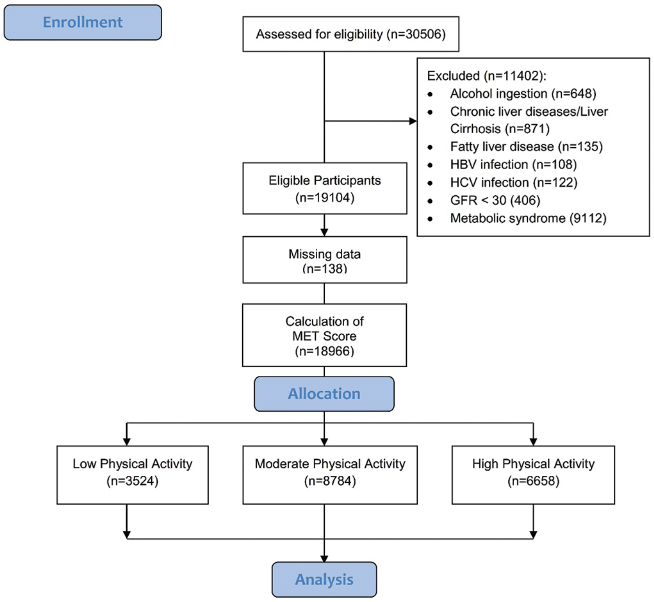

Figure 1: The flow diagram of participant eligibility assessment for the study. Legend*:* HBV: Hepatitis B virus; HCV: Hepatitis C virus; MET: Metabolic equivalents of task

participants was 38.65 ± 11.40. Of total sample 12,749 were women (71%) and the remaining were men. The mean age of participants was significantly different between categories of PA ($P < 0.001$), in which people in low levels of PA were older. People in different categories of PA had significant different BMI ($P < 0.001$), and surprisingly, participants with low PA had lower mean BMI due to lower age. Other basic variables of participants were significantly distributed across categories of PA ($P < 0.001$, for all). More details are presented in Table 1.

The association between PA scores with AST and ALT was evaluated using Spearman's rank correlation coefficient in bivariate setting and multiple linear regression when adjustment was made for potential cofounder, i.e., age, gender, BMI, systemic blood pressure, and cigarette and opium use. A statistically significant inverse correlation was found between AST ($r = -0.08$, $P = 0.02$) and ALT ($r = -0.038$, $P < 0.001$) with PA scores. The association of PA scores with AST based on regression analysis resulted that each SD increase in PA led to a significant decrease in AST: crude regression coefficient B = –0.00067 ($P = 0.005$) and adjusted B = 0.00076 ($P = 0.001$). We did not observe a significant association between total PA score with ALT in adjusted model (adjusted B = –0.00026, $P = 0.62$).

The mean concentration of ALT in total sample was 18.22 ± 13.06 (male: 23.65 ± 16.26; female: 15.57 ± 10.06), while the mean concentration of ALT in total sample was 19.61 ± 8.40 (male: 22.44 ± 10.03; female: 18.23 ± 7.08). The mean concentration of ALT was 19.96 ± 13.63 in people with low PA, 17.62 ± 12.31 with moderate PA, and 18.12 ± 13.47 with high PA ($P < 0.001$). Bonferroni *post hoc* test showed a significant difference between all pair-wise groups ($P \leq 0.001$). The mean concentration of AST was 20.37 ± 8.85 in people with low PA, 19.21 ± 8.83 with moderate PA, and 19.75 ± 8.85 with high PA ($P < 0.001$). Bonferroni *post hoc* test resulted significant difference between people with low PA and high and moderate PA levels ($P < 0.001$, for all) but the difference was significant between moderate and high PA levels. The difference between people in different levels of PA in terms of mean concentration of AST was remained significant ($P = 0.003$); however, the difference for ALT was not remained significant ($P = 0.47$) after adjusting potential confounders.

Subgroup analysis by gender showed similar results as total sample in terms of AST, in which the mean concentration of AST was significantly different between people in different categories before adjusting the confounders in both gender ($P < 0.001$, for male, $P = 0.008$, for female) and after adjusting confounders ($P = 0.012$, for male, $P = 0.015$, for female). However, in both crude and adjusted difference in terms of ALT in different categories of PA, we did not significant results for men however it was significant for women [Table 2].

DISCUSSION

The main finding of our study was that PA can affect serum liver aminotransferases using a province database. Our data showed that there was a significant difference in the serum level of liver aminotransferases in participants with moderate PA in comparison to whom with low PA, probably owing to abundant number of participants [Table 2].[18] The novelty of our study is the evaluation of this association in seemingly healthy individuals. Our data can be a new baseline for Iranian population according to racial diversity in Khuzestan province.

High BMI (as increasing factor) and aging (as decreasing factor) are considered independent confounding factors to evaluate the association between the serum liver aminotransferases and PA.[10,19] Among individuals with normal total bilirubin level, serum AST and ALT concentrations are significantly lower in the females than in the males.[20] In our comparison, we statistically adjusted the effect of the age, gender, and BMI on serum level of liver aminotransferases to remove these confounding effects.

Some previous studies under adjusted models indicated among the participants with NAFLD, high PA has only an independent association with lower ALT level but not with AST level. These independent negative associations were not observed in participants with the moderate PA comprising

Table 1: Demographic characteristics of participants by physical activity level

Variable	Total* (18,966) (%)	Low PA (3524) (%)	Moderate PA (8784) (%)	High PA (6658) (%)	*P***
Age (year)	38.65±11.40	40.35±12.87	38.39±11.87	38.10±11.05	<0.001
Gender					
Male	6217 (32.78)	1941 (10.24)	2348 (12.38)	1928 (10.16)	<0.001
Female	12,749 (67.22)	1528 (8.06)	6494 (34.24)	4727 (24.92)	
Level of education					
Illiterate	3368 (17.76)	593 (3.12)	1514 (7.99)	1261 (6.65)	<0.001
Elementary school degree	4882 (25.74)	840 (4.43)	2332 (12.30)	1710 (9.01)	
Middle school degree	3348 (17.65)	639 (3.37)	1504 (7.93)	1205 (6.35)	
High school degree	4599 (24.25)	849 (4.48)	2152 (11.35)	1598 (8.42)	
Academic degrees	2765 (14.51)	547 (2.88)	1338 (7.05)	880 (4.63)	
Marital status					
Single	2931 (15.45)	633 (3.34)	1406 (7.41)	892 (4.70)	<0.001
Married	15,294 (80.63)	2708 (14.27)	7067 (37.26)	5519 (29.10)	
Divorced	223 (1.17)	39 (0.20)	112 (0.59)	72 (0.38)	
Widowed	518 (2.73)	89 (0.47)	257 (1.36)	172 (0.90)	
BMI (kg/m^2)	26.16±4.94	25.61±4.93	26.26±4.95	26.31±4.92	<0.001
BMI category					
Underweight (BMI <18.5)	772 (4.1)	179 (0.9)	355 (1.9)	238 (1.3)	<0.001
Healthy BMI: 18.5–24.9)	7381 (38.9)	1474 (7.8)	3398 (17.9)	2509 (13.2)	
Overweight (BMI: 25–29.9)	6954 (36.7)	1212 (6.4)	3219 (17)	2523 (13.3)	
Obese (BMI≥30)	3744 (19.7)	572 (3)	1830 (9.7)	1342 (7)	
Systemic hypertension	845 (4.45)	178 (0.93)	402 (2.12)	265 (1.40)	0.02
Cigarette/cigar smokers	1261 (6.64)	435 (2.30)	470 (2.47)	356 (1.87)	<0.001
Opium users	225 (1.18)	89 (0.47)	75 (0.39)	61 (0.32)	<0.001

*Continuous and categorical data are presented as mean±SD and frequency (%); **P*-values resulted from ANOVA for continuous and Chi-squared test for categorical data. SD=Standard deviation; PA=Physical activity; ANOVA=Analysis of variance

Table 2: Mean values of liver aminotransferases across categories of physical activity in total sample and both genders

Variable	Total	Low PA	Moderate PA	High PA	*P**	*P***
ALT						
Male	23.65±16.26	23.01±13.94	23.98±16.76	23.87±17.72	0.12	0.47
Female	15.57±10.06	16.08±12.17	15.32±9.22	15.77±10.39	0.007	0.007
Total	18.22±13.06	19.96±13.63	17.62±12.31	18.12±13.47	<0.001	0.47
AST						
Male	22.44±10.03	21.79±8.89	22.41±10.52	23.13±10.45	<0.001	0.012
Female	18.23±7.08	18.57±8.46	18.05±6.18	18.37±7.69	0.008	0.015
Total	19.61±8.40	20.37±8.85	19.21±7.83	19.75±8.85	<0.001	0.003

**P*-values resulted From MANOVA; ***P*-values resulted from MANCOVA (adjustment was made for age, gender and BMI, hypertension, cigarette and opium use). All data are reported as mean±SD. PA=Physical activity; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; BMI=Body mass index; MANCOVA=Multivariate analysis of covariance

to the inactive ones except for the risk of lean NAFLD.[10,19] In this study, serum level of liver aminotransferases (both ALT and AST) was significantly higher among the ostensibly health participants with low PA in comparison ones who had moderate PA [Table 2]. The present study demonstrated that PA can be an effective factor to prevent liver disorders, especially in apparently healthy asymptomatic individuals with no previous history of liver diseases.

Gender can be a contributing factor on the concentration of liver aminotransferases in healthy population. Some studies revealed independently of the PA level, the mean serum concentration of ALT has apparently lower range among female healthy individuals than male ones.[8,20] Our data showed that the mean levels of AST and ALT were significantly higher in males than females in the population of study and also between three categories of PA [Table 2].

Regular PA has irrefutable benefits in the primary and secondary prevention of several chronic diseases, particularly NAFLD.[4] NAFLD is the most common chronic liver disease with an estimated global prevalence of 25.2% and 2.9% to 37.8% in Iranian adult general population.[21,22] Although among the global population, NAFLD is strongly associated with high weight/obesity, insulin resistance, and dyslipidemia,[23] it is particularly common in male sex and those with old age in Iranian population.[22] In addition, PA has been tolerated acceptably in patients with compensated cirrhosis and might modulate the risk of hepatocellular carcinoma (HCC), especially in NAFLD patients.[4] Regular adequate PA can also improve underlying metabolic disorders in NAFLD and particularly nonalcoholic steatohepatitis (NASH).[24] Following an increase in liver aminotransferase in asymptomatic individuals, NAFLD is usually detected by imaging techniques.[25] Thus, we suggest that it can be a good idea that PA presumably can be used to predict the likelihood of metabolic liver disease including NAFLD and NASH.

The strength of the present study was the existence of a large sample sizes with various ethnicities. Therefore, the total mean serum concentration of liver aminotransferases can be used as reference for Iranian population. Oppositely, our study had some limitations. First, similar to other cross-sectional studies, this study has inherently limitation to clarify causal relationships. Therefore, more longitudinal cohort studies and randomized controlled trials are needed to explain the underlying causal relationships between PA and the level of the liver aminotransferases. Second, we had some limitations of charge and skilled sonographer for screening of all participants. Third, we measured PA using self-reporting questionnaire rather than an objective measurement such as accelerometer readings, while we have no information on the validity of older individuals.[12] Furthermore, the results of this study showed no time that PA should be continued to make good effects on ALT and AST. Finally, we did not follow individuals. We assessed them only at the first visit and evaluate the PA and also LFT.

CONCLUSION

Our results suggest that the level of PA has a statistically negative association with the concentration of liver aminotransferase in the seemingly healthy individuals. Although among the participants with vigorous PA, the concentration of ALT and AST is statistically lower than individuals who have low PA, this difference was not clinically significant.

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Conflicts of interest

There are no conflicts of interest.

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