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Original Article

Physical activity and elevated liver enzymes: A cross-sectional study from the PERSIAN Guilan cohort study

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Abstract

Background: Regular physical activity promotes health that can affect liver health, particularly modulating liver enzymes. The objective of this study was to assess the association between physical activities and elevated liver enzyme levels in the population of the Prospective Epidemiological Research Studies of the Iranian Adults (PERSIAN) Guilan cohort study (PGCS).

Methods: This cross-sectional study was conducted on 10,519 individuals from the PGCS population. The demographical and clinical data of participants were collected. The study involved measuring the levels of physical activity and liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transferase (GGT). The study assessed physical activity intensity using standardized classification based on the energy costs of different activities, which was calculated through questionnaires administered in three tertiles. The relationship between physical activity and elevated liver enzymes was examined using the Cochran–Armitage test for trend and logistic regression.

Results: The average age of individuals was 51.52±8.90 years, and 53.6% were women. The prevalence of elevated ALT, AST, and GGT decreased with increasing physical activity ($p<0.001$, 0.010, and <0.001, respectively). According to fully adjusted model, participants with low physical activity levels had higher odds for elevated ALT and GGT compared to the participants with high physical activity levels (OR=1.15, 95% CI: 1.04–1.31 and OR=1.37, 95% CI: 1.16–1.61, respectively) ($p<0.05$).

Conclusion: Higher physical activity levels were associated with a lower prevalence of elevated liver enzymes, suggesting that regular physical activity may positively affect liver health.

Keywords: Exercise, Liver disease, Aspartate aminotransferase, Alanine aminotransferase.

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Maintaining a healthy lifestyle is crucial for overall well-being, and physical activity promotes good health. Regular exercise is known to have numerous benefits, including improved physical and mental health. In recent years, there has been increasing attention towards comprehending the influence of physical activity on liver health, particularly in relation to elevated liver enzymes (1–3). Elevated liver enzymes are markers of liver damage that show liver dysfunction and can indicate various liver conditions. Liver function and the overall health of the liver can be effectively assessed using specific liver enzymes. These enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transferase (GGT), have demonstrated their reliability as indicators in this regard (4–6).

ALT is widely recognized as a specific marker of liver damage, predominantly found in the liver (7). On the other hand, GGT is an enzyme on the surfaces of many cells but exhibits significant activity in the liver, pancreas, and kidneys. GGTs play a role in facilitating the uptake of glutathione and are believed to be involved in processes related to oxidative stress and chronic inflammation (8, 9). Meanwhile, AST and ALP are present in various tissues throughout the body (10, 11). Research has indicated that engaging in regular physical exercise can lower the risk of developing fatty liver disease, a condition marked by the accumulation of fat within liver cells. Physical activity helps combat this condition by promoting weight loss, improving insulin sensitivity, and reducing inflammation, all of which contribute to better liver health (12, 13). Obesity is closely linked to liver disease, including non-alcoholic fatty liver disease (NAFLD). Physical activity is crucial in weight management, and maintaining a healthy weight can significantly reduce the risk of liver conditions. Regular exercise helps burn calories, increase metabolism, and reduce body fat, decreasing the strain on the liver and minimizing the likelihood of elevated liver enzymes (14, 15). Liver diseases like hepatitis and cirrhosis are frequently linked to chronic inflammation. However, regular physical activity has been proven to possess anti-inflammatory properties that can benefit the body. Exercise helps modulate the immune system, reducing pro-inflammatory cytokines and promoting the release of anti-inflammatory molecules. By reducing inflammation, physical activity may help protect the liver from damage and maintain healthy liver enzyme levels (16, 17). Hence, the objective of the present study was to examine the correlation between physical activity levels and the concentrations of liver enzymes within the population of the Prospective Epidemiological Research Studies of the Iranian Adults (PERSIAN) Guilan cohort study (PGCS).

Methods

Study design and participants: The cross-sectional study involved a sample size of 10,519 individuals from the Guilan population in Iran, who were participants of the PGCS. (18, 19). The demographical and clinical data including age, gender, marital status, education level, employment, habitat, wealth score index (WSI), body mass index (BMI), physical activity (Metabolic equivalents (METS)), cigarette smoking, alcohol use, fatty liver, hepatitis B, hepatitis C, use of lipid lowering drugs, and use of hepatotoxic drugs, lipid profile, and liver enzymes were recorded. Determination of liver diseases was self-report according to previous diagnosis by specialists. MET was employed to assess the intensity of physical activity based on a standardized classification of the energy costs of different physical activities.

Physical activity was calculated using questionnaires given to the participants in face-to-face interviews by trained people in PGCS to measure their activity intensity. The oxygen which is used during rest and immobility is equal to physical activity. The study population was categorized into three tertiles based on their daily activity levels, which were determined by the number of hours spent on activities such as walking, working, exercise, and others. The tertiles were defined as low (<36.1), moderate (36.1-42.8), and high (>42.8) levels of physical activity (20). BMI was classified into different categories: underweight (<18.5 kg/m²), normal weight (18.5–24.99 kg/m²), overweight (25–29.9 kg/m²), and obese (≥30 kg/m²). The levels of liver enzymes, namely ALT, AST, GGT, and ALP, were measured using a Biotecnica analyzer (BT 1500, Italy). Elevated liver enzymes were defined as follows: ALT ≥ 32 U/L in males / ≥ 22 U/L in females, AST ≥ 37 U/L in males/ ≥ 31 U/L in females, GGT ≥ 49 U/L in men/ ≥ 32 U/L in females, and ALP ≥ 307 U/L in both males and females. The reference range for a normal lipid profile was established as follows: cholesterol (Chol) ≤200 U/L, triglyceride (TG) ≤150 U/L, low-density lipoprotein (LDL) ≤100 U/L, and high-density lipoprotein (HDL) ≥40 U/L (21, 22).

Statistical analysis: In the present study, continuous variables were reported as mean ± standard deviation (SD), while categorical variables were presented as numbers and percentages. The relationship between physical activity level and elevated liver enzymes was examined in univariable analysis using the Cochran–Armitage test for trend. Furthermore, we employed logistic regression analysis to assess the relationship between elevated liver enzymes and physical activity levels. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated to quantify the strength of the association.

ORs were adjusted for demographic and clinical characteristics. In the current study, model 1 was employed without any adjustments, while model 2 was adjusted for age and gender. Model 3, was adjusted for age, gender, marital status, education, employment, habitat, WSI, BMI, cigarette smoking, and alcohol use. Model 4 was adjusted for variables in model 3 and total cholesterol, TG, LDL, HDL, fatty liver, hepatitis B, hepatitis C, use of lipid lowering drugs and hepatotoxic drugs. All statistical analyses were carried out by IBM SPSS Version 26.0 and a p-value less than 0.05 was considered statistically significant.

Results

Table 1 presents a comprehensive overview of the demographic and clinical profiles of the study participants. The mean age of the participants was 51.52±8.90 years. About 46.4% were males, 32.6% were obese, 24.7% were smokers, 13.4% consumed alcohol, 75.8% had dyslipidemia, 6.6% had fatty liver, 15.1% reported use of lipid-lowering drugs, and 16.5% reported use of hepatotoxic drugs. The frequency of increased ALT, AST, GGT, and ALP was 19.4%, 4.6%, 11.6%, and 5.1%, respectively. The prevalence of elevated ALT, AST, and GGT was more significant among women than males (p<0.001, p=0.040, p<0.001, respectively). The prevalence of elevated ALT decreased with age (p for trend <0.001), whereas the prevalence of elevated ALP increased with age (p for trend<0.001) (table 2).

Table 1. Demographic and clinical characteristics of the participants in the PERSIAN Guilan Cohort Study

Variables	Mean±SD or n (%)
Age (years)	
35-44	3138 (29.8)
45-54	3854 (36.6)
55-64	2730 (26.0)
≥ 65	797 (7.6)
Mean±SD	51.52±8.90
Gender	
Male	4886 (46.4)
Female	5633 (53.6)
Marital status	
Single	305 (2.9)
Married	9526 (90.6)
Widow	566 (5.4)
Divorced	122 (1.2)
Education level	
Illiterate	1738 (16.5)
1-5	3312 (31.5)
6-12	4831 (45.9)
University	638 (6.1)
Mean±SD	6.63±4.52
Employment	
Unemployed	4781 (45.5)
Employed	5738 (54.5)
Habitat	
Urban	4612 (43.8)
Rural	5907 (56.2)
Wealth Score Index (Z-score)	0±1
BMI (kg/m2)	
Underweight	141 (1.3)
Normal	2746 (26.1)
Overweight	4198 (39.9)
Obese	3435 (32.7)
Mean±SD	28.14±5.09

Variables	Mean±SD or n (%)
Physical activity (MET)	41.26±8.88
Smoking	2584 (24.6)
Alcohol consumption	1395 (13.3)
Total cholesterol	192.79±38.98
Triglycerides	160.27±103.28
LDL-C	112.85±32.05
HDL-C	48.38±10.97
Fatty Liver	696 (6.6)
Hepatitis B	22 (0.2)
Hepatitis C	12 (0.1)
Use of lipid lowering drugs	1584 (15.1)
Use of hepatotoxic drugs	1732 (16.5)

SD: Standard Deviation; BMI: Body Mass Index

Table 2. Prevalence of elevated liver enzymes among the participants in the PERSIAN Guilan Cohort Study

	Elevated ALT n (%)	Elevated AST n (%)	Elevated GGT n (%)	Elevated ALP n (%)
Total	2043 (19.4%)	480 (4.6%)	1222 (11.6%)	536 (5.1%)
Age				
35-44	673 (21.4%)	154 (4.9%)	346 (11.0%)	101 (3.2%)
45-54	779 (20.2%)	168 (4.4%)	431 (11.2%)	170 (4.4%)
55-64	481 (17.6%)	126 (4.6%)	358 (13.1%)	202 (7.4%)
≥ 65	110 (13.8%)	32 (4.0%)	87 (10.9%)	63 (7.9%)
***P* for trend**†	<0.001	0.617	0.111	<0.001
Gender				
Male	873 (17.9%)	201 (4.1%)	350 (7.2%)	244 (5.0%)
Female	1170 (20.8%)	279 (5.0%)	872 (15.5%)	292 (5.2%)
P	<0.001	0.040	<0.001	0.659

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase. † Cochran–Armitage test for trend.

As presented in table 3, the prevalence of elevated ALT among participants in the first, second, and third tertile of physical activity was 21.8%, 19.3%, and 17.2%, respectively. In which the prevalence of elevated ALT decreased with increasing the level of physical activity (*p* for trend<0.001). In the unadjusted model (model 1), participants characterized by a lower level of physical activity exhibited increased odds of elevated ALT compared to those with a higher level of physical activity (OR=1.34, 95% CI: 1.19–1.51) (table 4). The same result but with lower OR was observed for participants with moderate levels of physical activity (OR=1.15, 95% CI: 1.02–0.30). In model 2, after adjusting for age and gender, a low level of physical activity demonstrated a significant association with a 32% higher likelihood of elevated ALT (OR=1.32, 95% CI: 1.17–1.49). In model 3, after adjustment for other socio-demographic characteristics, the OR for those with low level of PA also remained statistically significant (OR=1.21, 95% CI: 1.06–1.38). The similar result was obtained after further adjustment for total cholesterol, triglyceride, LDL-c, HDL-c, fatty liver, hepatitis B, hepatitis C, use of lipid lowering drugs, and use of hepatotoxic drugs (OR=1.15, 95% CI: 1.00–1.31) (model 4). The frequency of elevated AST in the first, the second, and the third tertiles of physical activity was 5.3%, 4.4%, and 4.0%, respectively. Overall, the prevalence of elevated

AST slightly decreased with increasing physical activity (p for trend=0.010) (table 3).

In the unadjusted model, participants with low physical activity had significantly higher odds for elevated AST than participants with high physical activity levels (OR=1.34, 95% CI: 1.07–1.68). Even after adjusting for age and gender, this relationship was statistically significant (OR=1.30, 95% CI: 1.03–1.63). In both, model 3 and 4, there was no significant association between physical activity level and elevated AST (see table 4). The frequency of elevated GGT in individuals in the first, the second, and the third tertiles of physical activity was 14.3%, 11.4%, and 9.2%, respectively. The frequency of elevated GGT in individuals in the first, the second, and the third tertiles of physical activity was 14.3%, 11.4%, and 9.2%, respectively.

The prevalence of elevated GGT decreased with increasing physical activity (p for trend<0.001) (table 3). In model 1, individuals with low and moderate physical activity levels were more likely to have elevated GGT compared to those with high levels of physical activity (OR=1.65, 95% CI: 1.42–1.91, and OR=1.27, 95% CI: 1.09–1.48, respectively). In model 2, after adjusting for age and gender, participants with low physical activity levels were 1.36-fold more likely to have elevated GGT than participants with high physical activity (OR=1.36, 95% CI: 1.17–1.59). A similar result was obtained in model 3 (OR=1.40, 95% CI: 1.19–1.66). The OR also maintained statistical significance in the fully adjusted analysis (model 4), (OR=1.37, 95% CI: 1.16–1.61) (table 4). The frequency of elevated ALP in individuals in the first, the second, and the third tertiles of physical activity level was 4.9%, 5.0%, and 5.3%, respectively (P for trend=0.445) (table 3). According to the logistic regression analyses presented in Table 4, the level of physical activity did not show any significant association with elevated ALP levels. This lack of association was observed in both the unadjusted model (model 1) and all adjusted models, including models 2, 3, and 4.

Table 3. Prevalence of elevated liver enzymes by level of physical activity among the participants in the PERSIAN Guilan Cohort Study

	Elevated ALT n (%)	Elevated AST n (%)	Elevated GGT n (%)	Elevated ALP n (%)
Physical activity				
Tertile 1 (Low)	765 (21.8%)	185 (5.3%)	501 (14.3%)	173 (4.9%)
Tertile 2 (Moderate)	675 (19.3%)	155 (4.4%)	399 (11.4%)	176 (5.0%)
Tertile 3 (High)	603 (17.2%)	140 (4.0%)	322 (9.2%)	187 (5.3%)
***P* for trend†**	<0.001	0.010	<0.001	0.445

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase. † Cochran–Armitage test for trend.

Table 4. Relationship between physical activity and elevated liver enzymes among the participants in the PERSIAN Guilan Cohort Study

	Elevated ALT		Elevated AST		Elevated GGT		Elevated ALP	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Model 1								
Physical activity								
Tertile 1	1.34 (1.19 – 1.51)	<0.001	1.34 (1.07 – 1.68)	0.011	1.65 (1.42 – 1.91)	<0.001	0.92 (0.74 – 1.14)	0.447
Tertile 2	1.15 (1.02 – 1.30)	0.026	1.11 (0.88 – 1.40)	0.372	1.27 (1.09 – 1.48)	0.003	0.94 (0.76 – 1.16)	0.553
Tertile 3	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
Model 2								
Physical activity								
Tertile 1	1.32 (1.17 – 1.49)	<0.001	1.30 (1.03 – 1.63)	0.026	1.36 (1.17 – 1.59)	<0.001	0.87 (0.70 – 1.08)	0.195
Tertile 2	1.11 (0.98 – 1.25)	0.109	1.07 (0.84 – 1.35)	0.600	1.02 (0.87 – 1.20)	0.798	0.91 (0.73 – 1.13)	0.385
Tertile 3	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	

	Elevated ALT		Elevated AST		Elevated GGT		Elevated ALP	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Model 3								
Physical activity								
Tertile 1	1.21 (1.06 – 1.38)	0.004	1.20 (0.94 – 1.54)	0.152	1.40 (1.19 – 1.65)	<0.001	0.99 (0.78 – 1.25)	0.920
Tertile 2	1.05 (0.93 – 1.20)	0.437	1.03 (0.81 – 1.32)	0.801	1.05 (0.89 – 1.24)	0.552	1.02 (0.82 – 1.28)	0.839
Tertile 3	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
Model 4								
Physical activity								
Tertile 1	1.15 (1.00 – 1.31)	0.043	1.16 (0.90 – 1.49)	0.259	1.37 (1.16 – 1.61)	<0.001	0.95 (0.75 – 1.21)	0.703
Tertile 2	1.02 (0.91 – 1.17)	0.711	1.02 (0.79 – 1.30)	0.903	1.03 (0.87 – 1.22)	0.715	1.01 (0.81 – 1.27)	0.904
Tertile 3	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; OR: Odds Ratio; CI: Confidence Interval. Model 1: Unadjusted model. Model 2: Adjusted for gender and age. Model 3: Adjusted for Model 2 plus marital status, years of education, occupation, place of residency, wealth score index, BMI, smoking, and alcohol consumption. Model 4: Adjusted for Model 3 plus total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, fatty liver, hepatitis B, hepatitis C, use of lipid lowering drugs, and use of hepatotoxic drugs.

Discussion

The results of this study provide valuable insights into the association between physical activity and elevated liver enzymes. The findings indicate that individuals with lower physical activity levels had a higher frequency of increased levels of liver enzymes, specifically ALT and GGT. The identified link between physical activity and liver health is in accordance with prior studies, underscoring the favorable effects of exercise on liver function (23, 24). Li et al. revealed a significant inverse relationship between higher levels of moderate-to-high physical activity and the prevalence of elevated ALT (ALT prevalence ratio 0.97 [0.77–1.23], 0.84 [0.66–1.06], and 0.72 [0.54–0.96]; p-trend=0.01). However, this association became non-significant after adjusting for additional factors such as demographic/socioeconomic factors and sedentary time (25). Elevated levels of ALT are commonly associated with liver damage, and it was reported that adding regular exercise led to the normalization of ALT in patients with NAFLD (1, 26). Our findings showed that the prevalence of elevated ALT resulted in a significantly decreased trend by age, with the highest prevalence in the age group under 55. Meanwhile, ALP exhibited a substantial upward trend in correlation with the aging, whereby the age group surpassing 55 years displayed the highest occurrence of elevated ALP levels. Similar to our findings, Elinaz et al. reported that ALT decreases with age (27).

Many studies reported the association between liver enzyme function, liver injury, and age in older people (28, 29). Moreover, a decline in the metabolic and detoxification functions of the liver during old age has been indicated, although the results were controversial according to different investigations (30, 31). Considering that most of the ALP is derived from the bones and liver, upper levels of ALP are often observed in elderly patients (32). Given the liver's crucial role in regulating overall systemic metabolism and safeguarding the body against endogenous and exogenous toxins, any age-related alteration in liver function carries significant implications for age-related conditions and diseases (33, 34). On the other hand, our results revealed that the prevalence of elevated ALT, AST, and GGT increased among women than men. A study by Islam et al. investigated the association between liver enzymes and diabetes. It demonstrated that females in the diabetes group had higher ALT, AST, and GGT levels than males (35). In contrast to our findings, Denova-Gutiérrez et al. reported that men had a higher prevalence of elevated ALT and GGT than women (36).

Due to our results, about 75% of the participants had dyslipidemia. Kathak et al. reported an independent association between the GGT level and lipid profile. They also suggested that individuals with dyslipidemia often have a higher chance of developing elevated liver enzymes compared to those with no dyslipidemia (37). Being overweight increases the risk of dyslipidemia (38), as our results showed that the mean BMI among the participants was over 28 kg/m^2, which also increases the risk of elevated liver enzymes among these individuals. Furthermore, elevated GGT levels are often indicative of liver dysfunction and are associated with conditions such as alcohol abuse, fatty liver disease, and liver inflammation (39, 40). The inverse relationship between physical activity

and these liver enzymes suggests that regular exercise may help protect against liver damage and dysfunction. The current study illustrated a decreasing trend of elevated enzymes by increasing physical activity levels, which was significant for ALT and GGT. Physical exercise promotes fatty acid oxidation within the liver while reducing fatty acid synthesis. Additionally, exercise helps protect against mitochondrial and hepatocellular damage by decreasing the release of damage-associated molecular patterns (41).

It should be considered that the lack of a significant association between physical activity and AST or ALP may be attributed to several factors. AST is present in various tissues throughout the body, including the liver, heart, and muscles, whereas ALT is more specific to the liver (10, 11). Therefore, the influence of physical activity on AST levels may be subject to various factors that extend beyond the realm of liver health. Similarly, ALP is an enzyme found in various organs, including the liver, bones, and intestines (42).

As such, factors unrelated to liver function may influence the relationship between physical activity and mentioned enzymes. Consequently, regular physical activity could be established as a practical therapeutic approach for fatty liver disease.

Due to the cross-sectional nature of the current study, it cannot establish a cause-and-effect relationship between physical activity and liver enzyme levels. Future longitudinal studies and randomized controlled trials would be beneficial in further elucidating the influence of physical activity levels on liver health. Despite these limitations, the findings of this study underscore the potential benefits of regular physical activity in maintaining liver health. Encouraging individuals to moderate to high physical activity levels could significantly affect liver disease prevention and better clinical management. The current study found low physical activity levels associated with higher odds of elevated liver enzymes. The findings suggest that regular physical activity may benefit liver health by reducing the risk of elevated ALT and GGT.

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Conflict of interests: The authors declare that they have no conflict of interest.

Authors' contribution: FMGH, HAB and FJ participated in the research design. MSH and MOG participated in writing the first draft. FJ and SM participated in the performance of the research and analytic tools. SM participated in data analysis. All authors reviewed and confirmed the final manuscript.

Availability of data and materials: The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

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