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Association between Serum Liver Enzymes and Hypertension: Findings from Shahedieh Yazd Cohort Study, Iran

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ABSTRACT

Background: Hypertension, known as a silent killer, leads to various complications and may influence serum liver enzymes, potentially resulting in liver diseases. This study aims to investigate the relationship between hypertension and serum liver enzymes in Yazd, Iran.

Methods: This cross-sectional study analyzed data from the first phase of Shahedieh Yazd Cohort Study (2015–2016), including 9,550 individuals aged 35–70. Statistical analyses were performed using Chi-square tests and multivariable logistic regression in STATA 17, with a significance level of $P < 0.05$.

Result: Among 9,550 participants (mean age 49.68 ± 9.54, 50.02% male), hypertension prevalence was 7.53%. Hypertensive individuals showed significant differences in age, sex, education, smoking, diabetes, cardiac diseases, and cholesterol levels compared to normotensive individuals. However, no significant associations were found with fatty liver history, alcohol consumption, low-density lipoprotein (LDL), high-density lipoprotein (HDL), serum glutamic-oxaloacetic transaminase (SGOT, also known as aspartate aminotransferase [AST]), or serum glutamic-pyruvic transaminase (SGPT, also known as alanine aminotransferase [ALT]) levels. Liver enzymes, including AST, ALT, gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP), were significantly associated with hypertension, particularly in younger age groups. GGT was related to hypertension in individuals aged 30–39 and ≥50, while ALP showed an association only in those aged ≥ 60 ($P < 0.05$).

Conclusion: A significant association between liver enzymes (ALT, AST, GGT) and hypertension was observed, especially in younger individuals. These findings suggest liver enzymes as potential hypertension indicators, emphasizing the need for early screening. Public health policies should incorporate liver function tests alongside hypertension management, particularly for younger populations.

Key words: Hypertension, Blood pressure, Risk factors, Liver enzymes, Age factors, Cross-sectional studies

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Introduction

Hypertension is known as a silent killer disease which may lead to several complications and diseases such as kidney, cardiovascular, and stroke diseases if left undiagnosed and untreated in the early stages (1). According to the statistics, more than half of the individuals have hypertension by the age of 60 (2). It is predicted that its prevalence will increase by 30% by 2025, reaching 1.5 billion people in developing countries (3, 4). Also, this disease causes almost 10 million deaths every year making it an important cause of disability and death (5).

The prevalence of hypertension varies from 20% to 50% in different regions of the world. Differences in the study protocols and definitions, as well as environmental or even genetic factors, might be the reason for this variation. In addition, modifiable risk factors including obesity, lack of physical activity, alcohol consumption, and unhealthy eating style, as well as non-modifiable risk factors including age, sex, and family history of the disease, can be other causes of these differences (1, 4, 6 ,7). Increased blood pressure may cause damage to liver tissues and lead to increased ALT and AST enzymes, which indicate liver damage and can be a sign of serious liver problems. Elevated liver enzymes may indicate serious health problems and require immediate treatment. Therefore, careful monitoring of blood pressure and liver tests in adults with hypertension is very important to prevent serious health problems and ensure the health of the liver and other organs (7) .

Few studies have addressed the relationship between high blood pressure and liver enzymes. In a 9-year prospective cohort study, it was shown that the increase of gamma-glutamyl transferase level over time is associated with the risk of developing hypertension (8). Serum levels of liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) can be an early indicator of liver diseases (6) of which, ALT and GGT are more common (12). Immediately after liver damage, the ALT enzyme increases faster because it has a longer half-life compared to the others. ALT level shows the progress of the liver damage. The liver plays different roles in the body's metabolism. So, diseases that disrupt the body's metabolism, such as high blood pressure, metabolic diseases, or diabetes, can cause changes in liver enzymes (1).

Each liver enzyme has its functionalities, and its changes are related to specific disorders. For instance, ALT and AST enzymes are responsible for the metabolism of amino acids. Moreover, they play a role in liver glucogenesis. Also, the relationship between oxidative stress and alcohol consumption with the GGT level has been investigated. In addition, the liver enzyme ALP is investigated more in biliary disorders (1). In some hypertensive individuals, the level of all or some of the liver enzymes might be changed. A cross-sectional study showed that an increase in serum ALP level is significantly associated with an increase in the possibility of high blood pressure among both sexes (6). Other studies have also showed the relationship between liver enzymes, metabolic diseases, and diabetes (9, 10).

Studies conducted both in Iran and abroad have explored the relationship between liver enzymes and hypertension. In many countries, research has emphasized the connection between elevated GGT levels and cardiovascular diseases and hypertension, as GGT is known to be a marker for oxidative stress and damage caused by alcohol consumption and liver diseases (11). Several foreign studies have also examined the relationship between ALT and AST with metabolic diseases such as diabetes and metabolic syndrome (12). Additionally, in Western countries, more research has been conducted on the connection between ALP and biliary disorders and liver diseases (13, 14).

In Iran, studies have focused more on non-alcoholic fatty liver disease (NAFLD) and obesity, which are closely linked to hypertension. Many studies in Iran have emphasized the high prevalence of NAFLD, Hepatitis B and C, and metabolic syndrome in the Iranian population. In

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this context, increased levels of ALT and AST are more commonly observed in individuals with hypertension and diabetes (15, 16). Moreover, some Iranian studies have reported a significant relationship between ALP levels and hypertension, especially in older individuals. These differences highlight the varying prevalence of diseases and risk factors in different populations, which can influence health outcomes and public health policies (17, 18).

Given the increasing prevalence of hypertension as well as the increase in risk factors for this disease and other factors that are common with liver diseases (19, 20), the present study aims to investigate the relationship between serum liver enzymes (ALT, GGT, SGPT, SGOT) and hypertension.

Methods

Study design: This is a cross-sectional study in which data is obtained from the Yazd Shahedieh Cohort study from 2015 to 2016 in Yazd Province ,as part of the prospective Persian cohort study conducted in 18 regions of Iran.

Data collection: This study extracted its data from the first phase of the Yazd Shahedieh Cohort Study. Demographic data (age, gender, marital status, and education), lifestyle factors (smoking, physical activity, and nutrition), and medical history (diabetes, heart disease, hypertension, and liver diseases) were collected. Blood pressure was measured in two stages using an electronic sphygmomanometer. Additionally, biochemical and blood tests, including liver enzymes (ALT, AST, GGT, ALP), triglycerides (TG), cholesterol, HDL, and LDL, were performed after 9 to 12 hours of fasting.

Inclusion and Inclusion Criteria: The inclusion criteria for this study consisted of adults aged 35 to 70 who participated in the first phase of Shahedieh Yazd Cohort Study between 2015 and 2016. Only individuals with complete demographic, clinical, and laboratory data who had provided informed consent were included. Conversely, participants who did not complete the study protocol or had incomplete demographic and laboratory information were excluded. Additionally, individuals with conditions that could significantly affect liver enzyme levels, such as acute liver failure, chronic viral hepatitis, or cirrhosis, were not included in the study. Furthermore, those with uncontrolled confounding conditions, such as active malignancies, were also excluded.

Variables selection and definitions: The data included clinical laboratory results, blood tests, urine tests, and para-clinical tests as well as the data gathered from questionnaires in 2015-2016. The study variables included socio-demographic information, chronic disease records, and laboratory tests.

All study participants whose data was available were included in the study. The participants who did not complete the study protocols, as well as those with incomplete laboratory and demographic information, were excluded (Figure 1).

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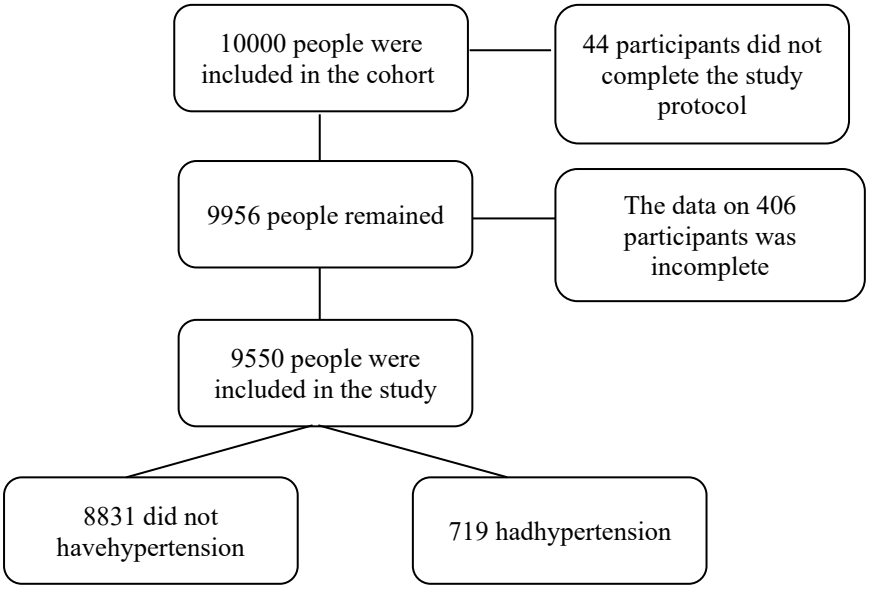

Figure 1. The flowchart of the number of participants in the study

The laboratory tests in both stages were performed after 9 to 12 hours of fasting. After separating serum from the blood, the TG level was determined using standard Pars test kits. Bionic kits (Bionic Company, Tehran, Iran) were also utilized to analyze HDL and cholesterol levels. All analyses were performed using a biochemical auto-analyzer (BT 3000, Italy).

Definitions of hypertension and abnormal levels of liver enzymes (AST, ALT, ALP, GGT)

According to the study protocol, the blood pressure was measured using an electronic sphygmomanometer in two stages on both arms. The first measurement was taken in the sitting position, after at least 5 minutes of rest. Similarly, the second measurement was also performed 10 minutes after the first one. The average was taken as the result. The blood pressure values greater than 140 mmHg (systolic) and 90 mmHg (diastolic) were considered as hypertension (21).

Normal levels of laboratory tests were as follows (22):

Test	Normal Range
ALT (IU/L)	< 35 (Women), < 40 (Men)
AST (IU/L)	< 35 (Women), < 40 (Men)
GGT (IU/L)	< 37 (Women), < 54 (Men)
HDL (gr/dl)	> 40 (Men), > 50 (Women)
ALP (IU/L)	< 306 (Both sexes)
LDL (gr/dl)	< 160 (Both sexes)
CHOL (mg/dl)	≤ 240 (Both sexes)
TG (mg/dl)	≤ 200 (Both sexes)

Data analysis: In this study, data analysis was performed using the Chi-square statistical test and a multivariable logistic regression model in STATA 17, with a significance level of 5%. The assumptions of statistical tests were examined, ensuring the independence of observations, categorical nature of the data, and adequacy of expected cell counts for the Chi-square test. In the

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logistic regression model, the binary nature of the dependent variable, absence of multicollinearity among independent variables, sufficiency of observations in each group, and lack of influential outliers were assessed and validated. Additionally, potential confounding variables, including sex, education level, smoking status, history of diabetes, history of cardiac diseases, and cholesterol level, were adjusted to minimize bias and isolate the independent effects of liver enzymes on hypertension across different age groups.

Results

A total number of 9,550 participants who had enrolled in the baseline phase of the Shahedieh Cohort study in Yazd, Iran, were included in the present study. Their mean age (± SD) was 49.68 (± 9.54) while 4,777 (%50.02) of them were males and 4,773 (%49.98) were females.

Table 1 presents the baseline characteristics of normotensive and hypertensive participants, including their socio-demographic characteristics, personal habits, and clinical risk factors. Accordingly, age, sex, educational status, smoking cigarettes, history of diabetes, history of cardiac diseases, cholesterol, GGT, and statistically significant relationships were observed between ALP levels and hypertension. This was while no statistically significant relationship was observed between previous history of fatty liver, alcohol consumption, LDL, HDL, SGOT, and SGPT levels and hypertension according to chi-squared test results ($P > 0.05$) (Table 1).

Table 2 presents the association between serum liver enzymes and hypertension across different age groups, adjusting for potential confounders such as sex, educational status, smoking, history of diabetes, history of cardiac diseases, and cholesterol levels. The findings indicated that SGOT was significantly associated with hypertension only in the 30-39 age group. Similarly, SGPT showed a significant association with hypertension in 30-39 and 40-49 age groups, but not in older individuals. GGT exhibited a broader association, showing statistically significant relationships with hypertension in the 30-39, 50-59, and ≥60 age groups, suggesting its potential role in hypertension across different life stages. Additionally, ALP was significantly related to hypertension in the 50-59 age group, but no significant associations were found in other age groups. These results suggest that the relationship between liver enzymes and hypertension may vary with age, emphasizing the importance of considering age-specific risk factors in hypertension research and clinical evaluations (Table 2).

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Table 1. Baseline characteristics of participants by hypertension status

Variables		Normotensive n(%)	Hypertensive Number n(%)	P-value
sex	Male	4,386 (91.81)	391 (8.19)	0.01
	Female	4,445 (93.13)	328 (6.87)	
Age	30-39	1,670 (97.78)	38 (2.22)	<0.001
	40-49	3,233 (95.85)	140 (4.15)	
	50-59	2,422 (89.97)	270 (10.03)	
	≥60	1,506 (84.75)	271 (15.25)	
Educational status	Illiterate	1,337 (84.67)	242 (15.33)	<0.001
	Below highschool diploma	6,441 (93.84)	423 (6.16)	
	Bachelor's degree and higher	1,053 (95.12)	54 (4.88)	
History of having diabetes	Yes	1,492 (86.64)	230 (13.36)	<0.001
	No	7,339 (93.75)	489 (6.25)	
History of having cardiac diseases	Yes	680 (88.54)	88 (11.46)	<0.001
	No	8,151 (92.81)	631 (7.19)	
History of having fatty liver	Yes	950 (91.79)	85 (8.21)	0.37
	No	7,881 (92.55)	634 (7.45)	
Alcohol consumption	Yes	335 (91.53)	31 (8.47)	0.48
	No	8,496 (92.51)	688 (7.49)	
Smoking cigarettes	Yes	1,968 (91.24)	189 (8.76)	0.01
	No	6,863 (92.83)	530 (7.17)	
Cholesterol	Normal	7,949 (92.74)	622 (7.26)	0.01
	Abnormal	882 (90.09)	97 (9.91)	
LDL	Normal	8,375 (92.58)	671 (7.42)	0.14
	Abnormal	432 (90.76)	44 (9.24)	
HDL	Normal	6,751 (92.44)	552 (7.56)	0.84
	Abnormal	2,080 (92.57)	167 (7.43)	
SGOT	Normal	8,530 (92.53)	689 (7.47)	0.27
	Abnormal	300 (90.91)	30 (9.09)	
SGPT	Normal	7,732 (92.61)	617 (7.39)	0.17
	Abnormal	1,099 (91.51)	102 (8.49)	
GGT	Normal	7,614 (92.96)	577 (7.04)	<0.001
	Abnormal	1,216 (89.54)	142 (10.46)	
ALP	Normal	620 (96.27)	24 (3.73)	<0.001
	Abnormal	8,210 (92.20)	695 (7.80)	

Chi-square test

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Table 2. Association between serum liver enzymes and hypertension

Variables	30-39 AOR* (%95 CI) *Ref (Normal)	P-value	40-49 AOR (%95 CI) *Ref (Normal)	P-value	50-59 AOR (%95 CI) *Ref (Normal)	P-value	≥60 AOR (%95 CI) *Ref (Normal)	P-value
SGOT	5.5 (2.1-14.5)	0.00	1.16 (.52- 2.58)	0.70	1.05 (.56- 1.94)	0.87	.92 (.35-2.44)	0.88
SGPT	2.76 (1.34-5.69)	0.00	1.81 (1.18-2.77)	0.00	0.94 (.63-1.38)	0.75	1.33 (.82-2.17)	0.24
GGT	2.22 (1.03- 4.79)	0.04	1.04 (.65-1.66)	0.85	1.48 (1.07-2.04)	0.01	1.41 (1.00-1.99)	0.04
ALP	0.68 (.23-2.00)	0.49	1.80 (.78-4.16)	0.16	2.40 (1.05- 5.52)	0.03	1.63 (.77-3.44)	0.19

Adjusted by sex, educational level, smoking cigarettes, history of diabetes, history of cardiac diseases, cholesterol level.
AOR: Adjusted Odds Ratio
Multivariable Logistic Regression Model

GGT

The changes of two enzymes including ALP and GGT are more common in liver diseases. In this study, a positive relationship between GGT enzyme and hypertension was observed among almost all age groups. Similar results were obtained in other studies. In a cross-sectional study that investigated the relationship between GGT enzyme and blood pressure levels, levels of this enzyme were higher in people who had hypertension or pre-hypertension, while about 90% of them were older than 35 years old. In addition, another study proved the relationship between high GGT enzyme and high blood pressure among both men and women. In this study, factors such as age, sex, increased cholesterol, history of cardiac disease, and history of diabetes were among the factors that showed a relationship with the occurrence of hypertension, and the authors considered age as the only confounding factor by grouping it into 4 subgroups, so that a relationship between age groups from 30 to 60 and GGT enzyme and hypertension was observed. In another study, the relationship between GGT enzyme and the occurrence of hypertension was investigated according to BMI and waist circumference in different age subgroups, which indicated the existence of a relationship between hypertension and people with central obesity and high BMI (23) Therefore, it is very likely that this enzyme is related to hypertension among most age groups due to high BMI and obesity, especially among the people of Yazd province (24). In addition, in another longitudinal study in which the relationship between the GGT enzyme and the occurrence of hypertension was confirmed, the most important determinants were sex (more men than women), alcohol consumption, and waist circumference (25). It seems that waist circumference index and BMI are very important and should be controlled as a confounding factor during the investigation of this relationship.

ALP

The relationship between ALP enzyme and the occurrence of hypertension was only observed among the age group of 50-59 which is also confirmed in a cross-sectional study conducted in Rafsanjan (Iran) (6). Moreover, a relationship between ALP and hypertension was found in Tehran Sugar and Lipid Study (TLGS), which was conducted to investigate the relationship between liver enzymes and cardiometabolic indicators (26). In some other studies in which this relationship was investigated, it was not confirmed (4, 27). This might be due to the difference in the mean age of people with hypertension, which was around 30 and 40 in those two studies mentioned above. Therefore, it seems that ALP enzyme levels are higher in older people. In another study, the relationship between hypertension and ALP enzyme was observed among alcoholic men and non-alcoholic women, and drinking alcohol was considered as a confounding factor (19). However, no relationship between drinking alcohol and hypertension was observed in this study, so it was not included in the final model as a confounding factor. It might be due to the small number of alcoholics in the country, especially in Yazd province as a religious one compared to the others. However, it should be noted that this may increase among people and should be considered in future studies.

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AST (SGOT) ALT (SGPT),

A relationship between two enzymes AST (SGOT) and ALT (SGPT) and hypertension was observed in the age group of 30-39, and only between ALT enzyme and hypertension in the age group 40-49, while there was no relationship between these two enzymes and hypertension in other age groups. ALT enzyme has a longer half-life compared to AST and increases faster in case of liver damage (10). The lower half-life of these enzymes might be a reason for that increase in younger age groups, which was observed by removing its other confounding factors. In a study conducted in China, it was also shown that the probability of developing hypertension among people with high ALT, compared to people with normal one, has increased by 55%. Also, this relationship was significant in two age groups older and younger than 35 years old. In addition, it was demonstrated that being overweight or obese, drinking alcohol, and smoking can increase the risk of developing hypertension among people with high ALT levels in this study (27). Although the mechanism between ALT enzyme and hypertension is unclear, some studies have shown that it is a sing for excess fat deposition in the liver, which can be an alarm for metabolic syndrome and related diseases (28, 29). In another study among Thai military personnel with an approximate sample size of 22,000 people, the chance of increased AST and ALT among hypertensive men was respectively 92% and 43% higher, compared to those with normal blood pressure. Similarly, it was 1.42 and 1.38 times higher than normal people for women, respectively. In this study, confounding variables such as the amount of cholesterol, smoking and alcohol consumption, BMI, TGs, and blood glucose were controlled, and the average age of the people was 47 (30). Therefore, hypertension can cause long or short-term changes in liver enzymes in any age group, which needs further investigation, especially in different age groups and obesity categories in Yazd province, where the prevalence of obesity is high.

One of the strengths of this study was the sample size of almost 10,000 people and the fact that the data was collected in a cohort study where the quality of data is mostly adequate, so the results can be more trustable. Due to the cross-sectional nature of the study, it was not possible to investigate the causal relationship between outcome and its effect, as well as other factors such as BMI index and waist circumference, which were included in the literature review as potential risk factors in other studies.

Conclusion

In conclusion, this study highlights a significant relationship between liver enzymes, particularly ALT, AST, and GGT, and hypertension, with the strongest association observed in individuals aged 30-39. Additionally, GGT levels were found to be significantly associated with hypertension across a broader range of age groups (30-39 and 50 and older), while ALP showed a positive relationship only in individuals aged 60 and above. These findings underscore the importance of considering age as a confounding factor in understanding the relationship between liver enzymes and hypertension.

From the public health policy perspective, these results suggest that monitoring liver enzyme levels could be an important component of hypertension prevention and management, particularly in younger populations where the relationship between liver function and hypertension is more pronounced. Health policies should focus on early screening and intervention strategies that include both liver health and blood pressure management, especially in age groups most at risk. Additionally, further research into the mechanisms behind these associations is necessary to refine preventive strategies and improve healthcare outcomes.

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Conflict of interest

The authors declared no conflict of interest.

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Ethical considerations

All participant information was kept confidential and used solely for research purposes, ensuring that data analysis was conducted without mentioning names or personal details. Additionally, this was an observational study with no interventions affecting participants' health, ensuring no harm was caused. Furthermore, all data analyses were performed with impartiality, free from bias, and the results were reported based on scientific evidence and rigorous statistical methods.

Code of ethics

IR.SSU.SPH.REC.1401.143

Author contributions

0 process, conducted the final data analysis, and approved the final manuscript for submission.

Open access policy

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