BMC Endocrine Disorders

RESEARCH Open Access

The relationship between hepatic enzymes, prediabetes, and diabetes in the Azar cohort population

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Abstract

Background Early prediabetes screening holds immense significance in decreasing the incidence of diabetes. Therefore, we aimed to evaluate the association of hepatic enzymes with prediabetes and diabetes in the Azar cohort population in Iran.

Methods This cross-sectional study utilized data from the Azar cohort study, initiated in 2014, with 14,865 participants aged 35–70 years. This study defines prediabetes, according to the American Diabetes Association (ADA), as fasting blood sugar (FBS) of 100–125 mg/dl. An FBS ≥ 126 mg/dL or a history of diabetes indicates diabetes. Serum liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) were measured, and associations with prediabetes and diabetes were analyzed using binary logistic regression.

Results In a study of 14,865 participants, 16% had prediabetes and 14.1% had diabetes. The serum levels of ALT, AST, GGT, and ALP were significantly higher ($P < 0.05$) in the prediabetic and diabetic patients. The adjusted logistic regression model showed a dose-response increase for all hepatic enzymes, with the highest ORs in the fourth quartile for both prediabetes and diabetes. The highest OR for prediabetes and diabetes was in the fourth GGT quartile.

Conclusion Our findings suggest that serum ALT, GGT, and ALP levels are strongly associated with prediabetes and diabetes. These hepatic enzymes may be considered easy and valuable early indicators of diabetes risk, prompting timely interventions to slow disease progression.

Keywords Hepatic enzymes, Prediabetes, Diabetes

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Introduction

The diabetes mellitus epidemic represents a global public health concern [1]. The prevalence and incidence of type 2 diabetes mellitus (T2DM) are rising rapidly worldwide [2]. According to the Centers for Disease Control and Prevention, the prevalence of prediabetes is much higher than diabetes [3]. The International Diabetes Federation reported that approximately 463 million adults (9.3%) were diagnosed with diabetes and 374 million (7.5%) with prediabetes in 2019 [4]. In Iran, the prevalence of T2DM and prediabetes was 15.0% and 25.4% in 2020, respectively. People with prediabetes have a high risk of developing diabetes, and in the past decades, the prevalence of prediabetes has sharply increased in some developing countries. About 70% of subjects with prediabetes may develop T2DM during their lifetime [5]. Prediabetes is, therefore, an urgent health concern, especially in developing countries [6]. These data show that a large number of people are at increased risk of developing T2DM [7].

T2DM has been linked to a shorter life expectancy due to its complications, including eye disease, heart disease, strokes, kidney failure, and bone disease [8]. These chronic illnesses negatively impact productivity and impose enormous costs [9]. Identifying the populations at high risk of developing T2DM and adopting preventive interventions is an important strategy to reduce T2DM incidence and its complications. Understanding the pathophysiological pathways leading to T2DM is vital for planning such predictive measures. The role of the liver in the pathogenesis of T2DM is attracting increasing interest since the liver plays an essential role in regulating blood glucose levels, especially in the fasting state [10–13]. Liver injury, indicated by elevated blood alanine aminotransferase (ALT), aspartate transaminase (AST), or gamma-glutamyl transferase (GGT) levels, has been reported to increase the incidence of T2DM [14]. Alkaline phosphatase (ALP) is another hepatic enzyme that reportedly increases in patients with T2DM [15]. In addition, elevated ALP levels are associated with disruption of inflammatory factors in homeostasis, such as tumor necrosis factor-alpha (TNF-α) and reactive protein C (CRP), which play important roles in insulin resistance and T2DM development [15].

Growing evidence suggests a link between abnormal hepatocellular functions and T2DM incidence, with high levels of hepatic enzymes including ALT, AST, ALP, and GGT associated with the later development of prediabetes and diabetes [16–19]. However, the findings about the relationship between hepatic enzymes and the occurrence of prediabetes and diabetes are inconsistent. Several prospective studies reported that ALT and AST were associated with incident prediabetes and diabetes [13, 19–23]; others showed that AST did not predict incident diabetes [16, 24–26]. A systematic review and meta-analysis of prospective studies demonstrated a moderate association between ALT levels and the risk of developing diabetes but did not find a significant association between AST levels and incident diabetes risk [27, 28]. Thus, the association patterns between these hepatic enzymes and T2DM are complex and inconsistent across different studies [28, 29]. More recent studies examined the association between hepatic enzymes and the incidence of diabetes [15, 17, 18]. Since prediabetes is a transitional and reversible stage [30], early detection is significant in minimizing the incidence of diabetes. Therefore, the current study aimed to evaluate the association of hepatic enzymes with prediabetes and diabetes in the Azar cohort population.

Materials and methods

In this cross-sectional study, to determine the association between serum hepatic enzymes and prediabetes/diabetes, we used the Azar cohort study data, which is a part of the large PERSIAN (Prospective Epidemiological Research Studies in Iran) cohort study [31]. The Azar cohort study is a prospective cohort with three phases: pilot, recruitment, and follow-up [32]. From 2014 to 2017, 15,006 (35–70 years old) participants were recruited during the pilot and recruitment phases. In the present study, we utilized the data collected during both the pilot and recruitment phases. The Azar cohort study is explained in more detail in other published article [32]. Written informed consent was signed by all subjects who participated voluntarily in the Azar cohort study. A total of 14,865 participants were analyzed after excluding those with missing outcome data. This study was conducted following the approval of the Ethics Committee of Tabriz University of Medical Sciences (Code: IR.TBZMED.REC.1400.884).

Data collection

Demographic characteristics

Demographic data including age, gender, educational level, marital status, smoking status, and medical history of chronic diseases were recorded using well-designed questionnaires. The wealth score index (WSI) was calculated by multiple correspondence analysis (MCA) of economic and social variables. Based on WSI, participants were classified into five quintiles. People who continuously smoked at least one cigarette per day for more than six months were defined as smokers; those who had ceased smoking at least a year before were regarded as ex-smokers, and those who had never smoked were labeled as non-smokers.

Subjects who smoked other tobacco products including hookah, water pipe, pipe, or chewed nass were considered as smokers of other tobacco products.

Daily physical activity was measured by a 23-item self-reported questionnaire. The respondents declared their daily (24-hour) activities (light and heavy), rest, and sleep based on hours and minutes. Based on the findings of the physical activity questionnaire, metabolic equivalent tasks (METs) were calculated. Each MET is equal to the amount of energy a person consumes relative to their weight. Then, the results were categorized into three levels (including low, moderate, and high) using the tertile scale.

Biochemical measurements

We took the blood samples from 7:00 to 9:00 AM following 12 h of fasting. We assayed fasting blood sugar (FBS), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), AST, GGT, ALP, and ALT by a Pars Azmoon kit (Tehran, Iran) at the central laboratory of the cohort center.

We categorized participants into the following serum hepatic enzymes quartiles: for AST ≤ 17, 18–20, 21–25, and ≥ 26 IU/L; for ALT ≤ 16, 17–21, 22–29, and ≥ 30 IU/L; for GGT ≤ 14, 15–20, 21–29, and ≥ 30 IU/L; for ALP ≤ 149, 150–181, 182–200, and ≥ 221 IU/L. In the analysis, the first quartile of each hepatic enzyme was considered as the reference group.

Definition of prediabetes and diabetes

According to the American Diabetes Association (ADA), prediabetes was defined as FBS = 100–125 mg/dl. Participants with FBS ≥ 126 mg/dL or a history of diabetes were considered diabetic.

Statistical analysis

We used SPSS version 11.5 (Chicago, IL, USA) for data analysis. Data normality was assessed using Kurtosis and Skewness indices. TG, and liver enzymes are not normally distributed and are reported as mean ± SD, median and interquartile range. Other continuous variables are presented as mean ± standard deviation, while categorical variables are shown as numbers (percentages). The three groups were compared using the chi-square, Kruskal-Wallis, and one-way ANOVA tests where appropriate. Furthermore, logistic regression was conducted to analyze the association of the hepatic enzymes with prediabetes and diabetes (Model 1: unadjusted; Mode 2: adjusted for age, gender (if applicable), Model 3: adjusted for age, gender (if applicable), BMI, socioeconomic status (WSI), physical activity level (MET), and smoking status). The odds ratios (ORs) and related 95% confidence intervals (CIs) were reported. Statistical significance was set at $P < 0.05$.

Results

Of 14,865 participants, 2,382 (16%) and 2,092 (14.1%) had prediabetes and diabetes, respectively. The general characteristics of the participants are presented in Table 1. The frequency of low education level, and low socioeconomic status in prediabetic and diabetic patients was significantly higher than in non-diabetic participants. Moreover, a history of hypertension in prediabetic and diabetic patients was more prevalent than in non-diabetic subjects. The prevalence of prediabetes and diabetes was higher among obese subjects. As illustrated in Table 1, we observed a consistent increase in mean anthropometric measurements and serum TG transitioning from non-diabetic participants to diabetic patients.

The percentage of prediabetic and diabetic patients in the 4th quartiles of ALT, GGT, and ALP (highest level of hepatic enzymes) was significantly higher than the non-diabetic population (Table 2).

Findings of binary logistic regression indicated that in the adjusted models, a dose-response increase was seen in prediabetes in relation to all hepatic enzymes, with the highest ORs in the fourth quartile [OR (95%CI): 1.18 (1.04–1.35), 1.61 (1.40–1.85), 1.85 (1.61–2.13), and 1.60 (1.40–1.83) for AST, ALT, GGT, and ALP, respectively]. In males, after adjusting for age, the fourth quartile of AST was positively associated with prediabetes. The odds of prediabetes also increased with GGT, with the highest OR in the fourth quartiles of the crude and adjusted models. In females, a dose-response increase in prediabetes was seen for all enzymes in the crude and adjusted models, with the highest ORs in the fourth quartile of each enzyme (Table 3).

We found that the odds of diabetes increased with elevated levels of ALT, GGT, and ALP; so that the highest ORs were in the fourth tertile of each enzyme [OR (95%CI): 2.29 (1.97–2.66), 3.40 (2.91–3.97), and 1.85 (1.60–2.13), respectively]. These results were similar in both genders. Among hepatic enzymes, the highest OR for prediabetes and diabetes was in the fourth GGT quartile (Table 4).

Discussion

In the present study, we evaluated the associations of serum AST, ALT, GGT, and ALP levels with prediabetes and diabetes in the Azar cohort population. The findings of this study showed that the serum levels of these enzymes were significantly higher in prediabetic and diabetic patients compared with non-diabetic participants. Moreover, elevated serum levels of

Table 1 Personal characteristics of study groups ($n = 14865$)

	Non diabetes ($n = 10391$)	Pre-diabetes ($n = 2382$)	Diabetes ($n = 2092$)	*P*
	***N* (%)**	***N* (%)**	***N* (%)**	
Gender				*<0.001
Male	4747(45.7)	1075(45.1)	852(40.7)	
Female	5644(54.3)	1307(54.9)	1240(59.3)	
Marital status				*<0.001
Not married	678(6.5)	203(8.5)	204(9.8)	
Married	9713(93.5)	2179(91.5)	1888(90.2)	
Education level				**<0.001
Illiterate	1404(13.5)	539(22.6)	553(26.4)	
Primary school	3962(38.2)	1002(42.1)	840(40.2)	
Diploma	3946(38)	723(30.4)	585(28)	
University	1072(10.3)	118(5)	113(5.4)	
Physical activity level (METs¶)				**<0.001
Low	3304(31.8)	747(31.4)	925(44.2)	
Moderate	3522(33.9)	755(31.7)	653(31.5)	
High	3565(34.3)	880(36.9)	509(24.3)	
Quintiles of wealth index				**<0.001
1 (poorest)	2223(21.4)	675(28.3)	551(26.3)	
2	1639(15.8)	449(18.8)	425(20.3)	
3	2050(19.7)	514(21.6)	455(21.7)	
4	2386(23)	390(16.4)	325(15.5)	
5 (richest)	2093(20.1)	354(14.9)	336(16.1)	
Current Smoking status				**<0.001
Never smoker	7810(75.2)	1866(78.3)	1604(76.7)	
Ex-smoker	810(7.8)	214(9)	215(10.3)	
Smoker	1576(15.2)	267(11.2)	225(10.8)	
Smoking other tobacco	195(1.9)	35(1.5)	48(2.3)	
History of hypertension	1557(15)	563(23.6)	896(42.8)	*<0.001
BMI classification (kg/m^2)				**<0.001
Underweight (< 18.5)	76(0.7)	8(0.3)	4(0.2)	
Normal (18.5–24.9)	2470(23.8)	376(15.8)	233(11.1)	
Overweight (25-29.9)	4327(41.6)	960(40.3)	813(38.9)	
Obese (≥ 30)	3518(33.9)	1038(43.7)	1042(49.8)	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age (years)	[a]48.20 ± 9.07	[a]51.57 ± 9.01	[a]54.76 ± 8.35	¶<0.001
Height (cm)	[a]162.80 ± 9.48	[a]161.76 ± 9.41	[a]160.55 ± 9.37	¶<0.001
Weight (kg)	[a]75.03 ± 13.50	[a]77.61 ± 13.87	[a]78.44 ± 14.19	¶<0.001
BMI (kg/m^2)	[a]28.32 ± 4.84	[a]29.68 ± 4.93	[a]30.41 ± 4.88	¶<0.001
Waist circumference (cm)	[a]92.81 ± 11.09	[a]96.10 ± 11.21	[a]99.83 ± 10.52	¶<0.001
Fasting blood glucose (mg/dl)	[a]86.19 ± 7.31	[a]107.19 ± 6.32	[a]154.61 ± 56.68	¶<0.001
Cholesterol (mg/dl)	[a]190.61 ± 37.51	[a]204±42.44	[a]192.75 ± 47.19	¶<0.001
Triglyceride (mg/dl)	[a]141.06 ± 72.8	[a]163.24 ± 89.69	[a]183.28 ± 118.20	**<0.001
Median(interquartile range)	118(64)	138(87)	153(109)	
LDL (mg/dl)	[a]116.09 ± 32.47	[a]125.11 ± 36.83	[a]112.58 ± 38.523	¶<0.001
HDL (mg/dl)	[bc]46.32 ± 10.89	[c]46.28 ± 11.09	[bc]43.90 ± 10.60	¶<0.001

**P*: chi-square; **P: Kruskal-Wallis; ¶ P: One-Way ANOVA;[a] significant difference exists among all groups ($P < 0.05$).b there is a significant difference between non-diabetes and diabetes groups ($P < 0.05$). c A significant difference exists between the diabetes group and the other two groups

BMI; Body mass index, LDL; Low-density lipoprotein, HDL; High-density lipoprotein, METs; Metabolic equivalent tasks

ALT, GGT, and ALP were significantly associated with higher odds of prediabetes and diabetes, even after adjustment for age, gender, BMI, WSI, physical activity level, and smoking status.

Consistent with our results, Kushkestani et al. indicated that the serum levels of ALT in prediabetic subjects were significantly higher than in healthy subjects [33]. However, they reported no significant difference between serum AST and ALP levels in prediabetic and

Table 2 Comparison of liver enzymes among study groups

	Non diabetes	Pre-diabetes	Diabetes	*P
	Mean ± SD	Mean ± SD	Mean ± SD	
AST(IU/l)	[a]22.17 ± 9.87	[a]22.59 ± 8.70	[b]22.86 ± 11.37	0.001
Median (interquartile range)	20(8)	21(8)	20(10)	
ALT(IU/l)	[c]23.75 ± 13.79	[c]25.76 ± 13.12	[c]26.82 ± 14.56	< 0.001
Median (interquartile range)	21(12)	23(14)	23(14)	
GGT(IU/l)	[c]22.99 ± 17.80	[c]26.31 ± 19.22	[c]31.36 ± 30.37	< 0.001
Median (interquartile range)	18(13)	21(15)	25(14)	
ALP(IU/l)	[c]184±54.99	[c]197.23 ± 56.56	[c]205.23 ± 61.52	< 0.001
Median (interquartile range)	177(68)	189(73)	201(77)	
	N(%)	*N*(%)	*N*(%)	
AST(IU/L)				< 0.001
Q1(≤ 17)	3138(30.2)	634(26.6)	702(33.6)	
Q2(18–20)	2318(22.3)	527(22.1)	399(19.1)	
Q3(21–25)	2666(25.7)	636(26.7)	452(21.6)	
Q4(≥ 26)	2269(21.8)	585(24.6)	539(25.8)	
ALT (IU/L)				< 0.001
Q1 (≤ 16)	2826(27.2)	502(21.1)	366(17.5)	
Q2(17–21)	2810(27)	585(24.6)	528(25.2)	
Q3(22–29)	2516(24.2)	639(26.7)	567(27.1)	
Q4(≥ 30)	2239(21.5)	659(27.7)	631(30.2)	
GGT(IU/L)				< 0.001
Q1(≤ 14)	3079(29.6)	488(20.5)	289(13.8)	
Q2(15–20)	3001(28.9)	614(25.8)	445(21.3)	
Q3(21–29)	2197(21.1)	625(26.2)	599(28.6)	
Q4(≥ 30)	2114(20.3)	655(27.5)	759(36.3)	
ALP(IU/L)				< 0.001
Q1(≤ 149	2894(27.9)	473(19.9)	371(17.7)	
Q2 (150–181)	2703(26)	577(24.2)	423(20.2)	
Q3(182–200)	2530(24.3)	612(25.7)	555(26.5)	
Q4(≥ 221)	2264(21.8)	720(30.2)	743(35.5)	

**P*: Kruskal–Wallis

a There is a significant difference between non–diabetes and prediabetes groups (*P*=0.001); b There is a significant difference between pre–diabetes and diabetes groups (*P*=0.007). c A significant difference exists among all groups (*P*<0.05)

normal participants [33]. Some others also showed a higher serum ALT level in prediabetic subjects [19, 34]. Gao et al. demonstrated that ALT and GGT concentrations were positively associated with insulin resistance and closely related to prediabetes [35]. Since most of the previous works investigated the association between hepatic enzymes and diabetes incidence, increased ALP and AST levels have mainly been shown in subjects with T2DM [15]. This is while prediabetes is reversible and must be detected early to prevent the incidence of diabetes.

In accordance with this study's findings, Chen et al. reported that elevated ALT, AST, GGT, and ALP were significantly associated with an increased risk of diabetes [18]. They suggest that ALT, AST, GGT, and ALP are independent predictors for incident diabetes in men and women after controlling other liver-related factors [18]. Li et al. also linked the highest quartiles of ALT and AST levels with a significantly higher risk of T2DM development after adjustment for potential confounders [36]. In addition, the prevalence of diabetes was reported to be high in patients with liver diseases, including cirrhosis [37] and hepatitis C [38], who tend to have elevated levels of hepatic enzymes.

As an enzyme primarily found in liver and kidney cells, the blood concentration of ALT is typically low, but liver damage causes its release into the blood and increases its serum levels [35]. Regarding ALP, it is usually elevated in patients with bone diseases or renal hyperfiltration [39], both of which have been associated with diabetes [40]. In particular, renal hyperfiltration has been observed in patients with newly diagnosed T2DM [41]. ALP is a potent marker of insulin resistance development in diabetic patients [42]. Experimental studies revealed that ALP, via the stimulation of extracellular glutathione transport, fulfills a vital role in antioxidant defense in most types of cells [15]. In other words, increased oxidative stress in

Table 3 Association between liver enzymes and prediabetes stratified by gender

	Pre-Diabetes		
	Crude model OR (95%CI)	**Adjusted model 1 OR (95%CI)**	**Adjusted model 2 OR (95%CI)**
AST			
Quartile 1	Reference		
Quartile 2	1.12(0.99–1.27)	1.05 (0.93–1.22)	1.02(0.89–1.16)
Quartile 3	1.18(1.04–1.33)	1.10(0.97–1.25)	1.06(0.93–1.20)
Quartile 4	1.27(1.12–1.44)	1.26(1.11–1.43)	1.18(1.04–1.35)
ALT			
Quartile 1	Reference		
Quartile 2	1.17(1.02–1.33)	1.09(0.95–1.25)	1.05(0.91–1.20)
Quartile 3	1.42(1.25–1.61)	1.39(1.22–1.59)	1.29(1.13–1.47)
Quartile 4	1.65(1.45–1.88)	1.83(1.60–2.09)	1.61(1.40–1.85)
GGT			
Quartile 1	Reference		
Quartile 2	1.29(1.13–1.46)	1.27(1.11–1.45)	1.22(1.07–1.39)
Quartile 3	1.79(1.57–2.04)	1.82(1.59–2.09)	1.69(1.47–1.94)
Quartile 4	1.95(1.71–2.22)	2.01(1.76–2.31)	1.85(1.61–2.13)
ALP			
Quartile 1	Reference		
Quartile 2	1.30(1.14–1.49)	1.22(1.06–1.39)	1.20(1.05–1.38)
Quartile 3	1.48(1.29–1.68)	1.31(1.15–1.50)	1.28(1.12–1.46)
Quartile 4	1.94(1.71–2.21)	1.65(1.45–1.89)	1.60(1.40–1.83)
Gender			
Male			
AST			
Quartile 1	Reference		
Quartile 2	1.03(0.83–1.27)	1.05(0.84–1.30)	0.96(0.77–1.20)
Quartile 3	1.09(0.90–1.33)	1.14(0.93–1.39)	1.01(0.82–1.24)
Quartile 4	1.18(0.97–1.44)	1.29(1.06–1.57)	1.12(0.91–1.37)
ALT			
Quartile 1	Reference		
Quartile 2	0.92(0.72–1.18)	0.94(0.73–1.19)	0.88(0.68–1.12)
Quartile 3	1.29(1.03–1.61)	1.40(1.11–1.76)	1.19(0.94–1.51)
Quartile 4	1.53(1.23–1.89)	1.86(1.49–2.32)	1.49(1.18–1.88)
GGT			
Quartile 1	Reference		
Quartile 2	1.34(1.04–1.73)	1.35(1.05–1.74)	1.28(0.99–1.66)
Quartile 3	1.84(1.44–2.34)	1.88(1.48–2.40)	1.72(1.34–2.21)
Quartile 4	2.0(1.58–2.53)	2.09(1.64–2.65)	1.84(1.43–2.36)
ALP			
Quartile 1	Reference		
Quartile 2	1.14(0.94–1.39)	1.13(0.93–1.38)	1.15(0.94–1.41)
Quartile 3	1.23(1.01–1.49)	1.22(1.00-1.49)	1.24(1.02–1.51)
Quartile 4	1.43(1.17–1.74)	1.41(1.16–1.73)	1.44(1.17–1.76)
Female			
AST			
Quartile 1	Reference		
Quartile 2	1.18(1.01–1.39)	1.05(0.89–1.23)	1.03(0.88–1.22)
Quartile 3	1.25(1.06–1.47)	1.05(0.89–1.24)	1.05(0.89–1.24)
Quartile 4	1.39(1.16–1.66)	1.17(0.98–1.41)	1.17(0.97–1.41)
ALT			
Quartile 1	Reference		
Quartile 2	1.33(1.13–1.55)	1.17(1.0-1.37)	1.14(0.97–1.34)
Quartile 3	1.54(1.31–1.82)	1.35(1.14–1.59)	1.30(1.09–1.54)

Table 3 (continued)

	Pre-Diabetes		
	Crude model OR (95%CI)	**Adjusted model 1 OR (95%CI)**	**Adjusted model 2 OR (95%CI)**
Quartile 4	1.86(1.54–2.24)	1.65(1.37-2.00)	1.54(1.27–1.87)
GGT			
Quartile 1	Reference		
Quartile 2	1.32(1.13–1.54)	1.22(1.04–1.43)	1.18(1.01–1.39)
Quartile 3	1.98(1.66–2.34)	1.79(1.51–2.13)	1.66(1.39–1.98)
Quartile 4	2.27(1.90–2.71)	1.95(1.62–2.34)	1.84(1.53–2.21)
ALP			
Quartile 1	Reference		
Quartile 2	1.42(1.19–1.70)	1.26(1.05–1.51)	1.23(1.02–1.48)
Quartile 3	1.69(1.42–2.03)	1.35(1.12–1.62)	1.28(1.07–1.55)
Quartile 4	2.43(2.05–2.89)	1.80(1.50–2.15)	1.70(1.42–2.04)

Model1: adjusted for age and gender (if appropriate); Model2: adjusted for age, gender, BMI, WSI, physical activity level, smoking status

T2DM patients leads to increased ALP activity, consequently increasing serum ALP levels [15].

The significant association of ALT and GGT with diabetes odds found in the present study aligns with the role of liver diseases and liver injury in the development of diabetes. As a site of glycogen synthesis, gluconeogenesis, and insulin degradation, the liver plays an essential role in plasma glucose homeostasis [43]. On the other hand, changes in hepatic enzymes have been reported in diabetic patients, with diabetes being associated with liver diseases like non-alcoholic fatty liver disease (NAFLD). Patients with NAFLD have elevated serum ALT, AST, and GGT levels [44]. Therefore, these hepatic enzymes were used as markers of liver fat accumulation to predict incident diabetes before direct measurements of liver fat became readily available [16, 24]. Moreover, changes in hepatic enzymes can be considered an indicator of liver dysfunction in prediabetic and diabetic patients.

The results also indicated that the increased odds of diabetes with elevated levels of hepatic enzymes were similar in both genders. Moreover, in the association with prediabetes, a similar pattern was observed among men and women, except for AST levels, which were associated with high odds of prediabetes in the fourth quartile in males. Previous studies also reported similar findings in men and women [18, 45]. The study by Doi et al. reported that after adjustment for some confounders, the significant association of serum GGT and ALT with ORs of future diabetes was similar in both genders, but not for AST levels. Diabetes risk increased significantly with elevating quartiles of AST levels for men but not for women [45]. However, André et al. demonstrated a significant association between ALT levels and future diabetes risk in men only [25].

Early identification and control of T2DM-related indices can be an effective strategy to prevent, control, and treat T2DM and its related complications. Our results offer potential implications for clinical practice. Since the measurements of these enzymes are well standardized and available in routine clinical practice, it has been suggested that they could be included in future diabetes prediction algorithms [24].

The present cross-sectional study, as part of a prospective cohort examination, had a relatively large sample size, meaning that the findings might be quite convincing. However, this study had some limitations. Firstly, the cross-sectional design restrains the interpretation of cause-and-effect relations. Longitudinal analysis could have provided better evidence that the enzymes predict the incidence of prediabetes and diabetes. Secondly, the participants were middle-aged and elderly Iranians; thus, the findings might not be generalizable to other populations. Finally, we measured the levels of hepatic enzymes only once and used fasting blood glucose but no other indices to identify the prediabetic and diabetic patients, which might result in some misclassification.

Conclusions

The present study demonstrated that the serum levels of ALT, AST, GGT, and ALP were significantly higher in prediabetes and diabetes fasting glucose concentrations compared with non-diabetes fasting glucose concentrations in the participants. Moreover, there was a significant association between elevated serum levels of these enzymes and an increased risk of prediabetes and diabetes. Therefore, these hepatic enzymes can be considered an easy and valuable tool in routine clinical practice for the early identification of prediabetes and diabetes in primary care settings. Nevertheless, further investigations are suggested to confirm our findings in other age groups and populations.

Table 4 Association between liver enzymes and diabetes stratified by gender

	Diabetes		
	Crude model OR (95%CI)	**Adjusted model 1 OR (95%CI)**	**Adjusted model 2 OR (95%CI)**
AST			
Quartile 1	Reference		
Quartile 2	0.76(0.67–0.88)	0.70(0.61–0.81)	0.70(0.61–0.81)
Quartile 3	0.75(0.66–0.86)	0.69(0.60–0.79)	0.69(0.60–0.79)
Quartile 4	1.06(0.93–1.20)	1.09(0.95–1.24)	1.04(0.91–1.19)
ALT			
Quartile 1	Reference		
Quartile 2	1.45(1.25–1.67)	1.32)1.13–1.53)	1.25(1.08–1.46)
Quartile 3	1.74(1.51-2.0)	1.75 (1.51–2.03)	1.56(1.34–1.82)
Quartile 4	2.17(1.89–2.50)	2.80(2.40–3.25)	2.29(1.97–2.66)
GGT			
Quartile 1	Reference		
Quartile 2	1.58(1.35–1.84)	1.54)1.31–1.81(	1.40(1.19–1.65)
Quartile 3	2.90(2.49–3.37)	3.08)2.62–3.61(	2.57(2.19–3.02)
Quartile 4	3.82(3.30–4.42)	4.36)3.72–5.10(	3.40(2.91–3.97)
ALP			
Quartile 1	Reference		
Quartile 2	1.22(1.05–1.41(	1.10)0.94–1.28)	1.09 (0.93–1.28)
Quartile 3	1.71(1.48–1.97)	1.39(1.20–1.61)	1.34(1.15–1.56)
Quartile 4	2.56(2.23–2.93)	1.92(1.66–2.21)	1.85(1.60–2.13)
Gender			
Male			
AST			
Quartile 1	Reference		
Quartile 2	0.77(0.62–0.96)	0.81(0.64–1.01)	0.74(0.58–0.94)
Quartile 3	0.62(0.50–0.77)	0.69(0.55–0.85)	0.61(0.48–0.76)
Quartile 4	0.77(0.63–0.94)	0.96(0.78–1.18)	0.78(0.63–0.97)
ALT			
Quartile 1	Reference		
Quartile 2	1.20(0.91–1.57)	1.26(0.95–1.66)	1.18(0.89–1.58)
Quartile 3	1.41(1.09–1.82)	1.69(1.30–2.21)	1.36(1.03–1.79)
Quartile 4	1.72(1.34–2.20)	2.71(2.09–3.52)	1.91(1.45–2.52)
GGT			
Quartile 1	Reference		
Quartile 2	1.23(0.90–1.68)	1.26(0.92–1.74)	1.09(0.79–1.50)
Quartile 3	2.18(1.63–2.92)	2.34(1.73–3.15)	1.79(1.32–2.43)
Quartile 4	3.19(2.41–4.23)	3.71(2.78–4.96)	2.52(1.86–3.40)
ALP			
Quartile 1	Reference		
Quartile 2	1.06(0.84–1.33)	1.07(0.84–1.35)	1.10(0.86–1.40)
Quartile 3	1.29(1.04–1.61)	1.32(1.05–1.65)	1.36(1.08–1.72)
Quartile 4	1.81(1.46–2.25)	1.79(1.44–2.24)	1.87(1.48–2.35)
Female			
AST			
Quartile 1	Reference		
Quartile 2	0.75(0.63–0.90)	0.61(0.51–0.74)	0.63(0.52–0.76)
Quartile 3	0.89(0.75–1.05)	0.68(0.57–0.81)	0.70(0.58–0.83)
Quartile 4	1.54(1.30–1.82)	1.19(1.00-1.43)	1.20(1.00-1.44)
ALT			
Quartile 1	Reference		
Quartile 2	1.61(1.36–1.91)	1.34(1.12–1.60)	1.28(1.07–1.54)

Table 4 (continued)

	Diabetes		
	Crude model OR (95%CI)	**Adjusted model 1 OR (95%CI)**	**Adjusted model 2 OR (95%CI)**
Quartile 3	2.13(1.78–2.54)	1.76(1.46–2.12)	1.68(1.39–2.03)
Quartile 4	3.24(2.69–3.90)	2.79(2.30–3.40)	2.59(2.12–3.16)
GGT			
Quartile 1	Reference		
Quartile 2	1.86(1.55–2.24)	1.63(1.35–1.97)	1.55(1.28–1.88)
Quartile 3	4.09(3.40–4.92)	3.48(2.87–4.22)	3.17(2.613.86)
Quartile 4	5.43(4.50–6.54)	4.38(3.60–5.31)	3.98(3.27–4.85)
ALP			
Quartile 1	Reference		
Quartile 2	1.35(1.11–1.64)	1.11(0.91–1.36)	1.09(0.88–1.34)
Quartile 3	2.13(1.76–2.56)	1.41(1.15–1.71)	1.33(1.09–1.62)
Quartile 4	3.27(2.74–3.90)	1.96(1.62–2.36)	1.83(1.51–2.21)

Model1: adjusted for age and gender (if applicable); Model2: adjusted for age, gender (if applicable), BMI, WSI, physical activity level, smoking status

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01871-x.

Supplementary Material 1

Acknowledgements
The authors are grateful for the financial support of the liver and gastrointestinal diseases research center, Tabriz University of Medical Sciences. The authors also are deeply indebted to all subjects who participated in this study. We appreciate the contribution by the investigators and the staff of the Azar cohort study. We thank the close collaboration of the Shabestar health center. In addition, we would like to thank the Persian cohort study staff for their technical support. We would like to appreciate the cooperation of the Clinical Research development Unit of Imam Reza General Hospital, Tabriz, Iran in conducting this research.

Author contributions
The conception or design of the work was performed by EF, SM, and SD. The acquisition, analysis, and interpretation of data was done by EF, SD, and RMG. The manuscript was drafted and substantively revised by RMG and EF. All authors have read and approved the manuscript.

Funding
This study was supported by the Liver and Gastrointestinal Diseases Research Center (Grant number 700/108 on 14 March 2016), Tabriz University of Medical Sciences. The funder had no role in the study design, data analysis, interpretation, and writing the manuscript in this study. The Iranian Ministry of Health and Medical Education has contributed to the funding used in the Persian Cohort through Grant no.700/534.

Data availability
Data are available from the corresponding authors upon reasonable request and with permission of Vice Chancellor for Research.

Declarations

Ethical approval and consent to participate
This study has been performed under the Declaration of Helsinki and has been approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethical code: IR.TBZMED.REC.1400.884). We confirm that all methods were performed following the relevant guidelines and regulations. At the time of enrollment, written informed consent to participate in the study was obtained from participants (or their legal guardians in the case of illiterate participants). The aim and steps of the study were completely explained to the participants, and then anyone who filled out the informed consent was included. They were free to leave the study at any time and for any reason.

Clinical trial number
Not applicable.

Consent to publish
Not Applicable.

Conflict of interest
The authors declare that they have no competing interests. All the authors are primarily involved in education or medical research and are not directly supported by the government.

Received: 11 September 2024 / Accepted: 6 February 2025
Published online: 14 February 2025

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