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Association between Elevated Liver Enzymes and Microvascular Complications in Patients with Type 2 Diabetes: The PERSIAN Guilan Cohort Study

ABSTRACT

Objective: The present study investigated the association between increased serum levels of liver enzymes and the risk of diabetic microvascular complications among Prospective Epidemiological Research Studies in IRAN (PERSIAN) Guilan Cohort Study (PGCS) population.

Materials and methods: In this cross-sectional study, 403 patients with T2D from PGCS were included. Patients' demographic, anthropometric, and clinical characteristics were assessed using a questionnaire. Urine analysis and blood laboratory tests were conducted to assess diabetic nephropathy and serum liver enzyme levels. Fundus photometry and the Michigan Neuropathy Screening Instrument (MNSI) were used to assess retinopathy and neuropathy, respectively. All statistical analyses were performed using SPSS version 16.0, and the significant level was $p < 0.05$.

Results: Of 403 patients with diabetes, 202 (50.1%) were male, and the mean age of participants was 59.67 ± 6.33 years. No statistically significant association between the increased level of liver enzymes and developing retinopathy or neuropathy in patients with diabetes was observed ($p > 0.05$). However, increased levels of gamma-glutamyl transferase (GGT) were significantly associated with the development of diabetic nephropathy (OR = 3.42, 95% CI, 1.28–6.00, $p = 0.014$). No statistically significant association was observed between increased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) and diabetic nephropathy ($p > 0.05$).

Conclusions: The results of the study suggested increased levels of GGT as an independent risk factor for the development of nephropathy in patients with diabetes. (Clin Diabetol 2024; 13, 5: 260–267)

Keywords: diabetes mellitus, liver enzyme, retinopathy, neuropathy, nephropathy

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Introduction

Type 2 diabetes (T2D) is closely associated with development of microvascular complications. One of the most common microvascular complications of diabetes is retinopathy, which can result in irreversible blindness [1]. Increased pericyte loss, retinal capillary leakage, endothelial cell apoptosis, advanced glycation end-product accumulation, and thickening of the endothelial basement membrane occur early in diabetic retinopathy [2].

Another microvascular complication is diabetic nephropathy that is the main cause of end-stage renal disease (ESRD) globally leads to significant morbidity and mortality worldwide [1, 3]. Moreover, diabetic neuropathy consists of various clinical conditions that could involve both the autonomic and peripheral nervous systems. Diabetic peripheral neuropathy (DPN) is the most prevalent form that results in pain, gait disturbances, depressive symptoms, and reduced quality of life, in nearly one-third of patients with T2D [4].

Metabolic dysfunction-associated steatotic liver disease (MASLD) is suggested to be a risk factor for the development and progression of diabetes mellitus [5]. In addition, it has been demonstrated that MASLD increases the risk of diabetic microvascular complications such as retinopathy, neuropathy, and nephropathy [6]. MASLD commonly causes mild to moderate increases in the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as well as a slight increase in the levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). However, ALT and AST are suggested to be more specific for MASLD [7–9]. Also, controversial evidence is available on the relationship between the increased serum levels of liver enzymes, e.g., ALT, AST, ALP, and GGT, and the risk of microvascular complications of diabetes mellitus [10, 11].

A study among an Iranian population suggested an inverse association between serum levels of ALT and the risk of diabetic retinopathy [12], while another one showed that increased ALT levels are associated with the remission of diabetic nephropathy [13]. Due to the discrepancy in results of different studies on the association between elevated liver enzymes and the chance of development microvascular complications in patients with T2D, we aimed to investigate the association between increased serum levels of liver enzymes and the risk of diabetic microvascular complications among patients with T2D.

Materials and methods

Study design and patients

This cross-sectional study was conducted based on the data obtained during the Prospective Epidemiological Research Studies in IRAN (PERSIAN) Guilan Cohort Study (PGCS) [14] as a part of the PERSIAN study [15]. The overall number of participants in the PGCS is 10,520 males and females aged between 35 and 70 years from Sowme'e Sara, Guilan, Iran. In the PGCS, diabetes is defined as fasting blood sugar (FBS) >126 mg/dL, a history of diagnosis by a physician, or consuming glucose-lowering agents. Among all participants of the study, 2531 (24.1%) had diabetes. The protocol, sampling methods, laboratory measurements, and physical examinations of the PGCS are available online: https://irancohorts.ir. The systemic random sampling method was applied to select study participants. Patients with a history of chronic liver diseases, systemic diseases, autoimmune or viral hepatitis, consuming hepatotoxic or nephrotoxic agents, consuming fenofibrate, consuming alcohol, and glomerular filtration rate below 60 mL/h were excluded from the study.

Data collection and measurements

Data collection was conducted using a questionnaire consisting of participants' demographic and clinical characteristics including gender, age, habitat, marital status, educational level, wealth score index (SES), cigarette smoking, hookah smoking, body mass index (BMI), hypertension, and physical activity during a face-to-face interview.

Blood pressure (mmHg) was measured after a 10 minutes rest period twice in the right arm with participants in a seated position, back supported, and legs uncrossed in a quiet room after 10-min intervals, using Richter auscultatory mercury sphygmomanometers (MTM Munich, Germany) [15]. The mean of the 2 measurements was used in the analyses. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or a prior diagnosis of hypertension by a health professional or current use of antihypertensive drugs [14]. Anthropometric characteristics including weight (kg), height (cm), and body mass index (BMI) were measured using US National Institutes of Health protocols, and they have been previously described in detail [15].

Biochemical analysis was performed on the serum sample of participants using FBS, ALT, AST, ALP, GGT, and HbA1c evaluation kits (Parsazmun®, Iran) via a BT-1500 (Biotecnica®, Italy) auto-analyzer. Laboratory overall CV was < 5%, and all tests were performed after confirmed accuracy and precision. In randomly selected urine samples, the measure of urinary albumin excretion was performed using the urinary albumin-to-creatinine ratio. FBS levels 80–110 mg/dL, HbA1c < 5.4%, ALT levels < 30 U/L for females and < 45 IU/L for males, AST levels < 31 U/L, ALP levels < 306.0 IU/L, and GGT

levels < 50 IU/L were considered as normal range. The normal range of urinary albumin concentrations (microalbumin) was set at < 30 mg/d [14, 15].

Microvascular complications

Diabetic retinopathy was assessed by a trained optometrist and defined as the presence of exudation, neovascularization, micro hemangioma, or retinal hemorrhage in the fundus photography (non-mydriatic retinal camera, TRC-NW400, Topcon). Patients with an albumin/creatinine ratio higher than 30 mg/g in a spot urine sample were considered to have diabetic nephropathy [16]. Diabetic neuropathy was diagnosed using the Michigan Neuropathy Screening Instrument (MNSI) during a face-to-face interview. This questionnaire consists of 2 separate assessments: a 15-item self-administered questionnaire that is scored by summing abnormal responses and an examination of the lower extremity, which includes inspection and assessment of ankle reflexes and vibratory sensation and is scored by assigning points for abnormal findings. Patients who received high scores on the questionnaire as well as those who had absent/reduced ankle reflexes, absent/reduced vibration sense, and absent/reduced sensation to the monofilament test were all considered to have developed diabetic neuropathy. Also, patients who scored greater than 2 out of 10 points on the clinical portion of the MNSI were considered neuropathic [17].

Statistical analysis

The sample size was calculated according to the rule of thumb for a logistic regression analysis recommended by Peduzzi et al. [18], whereby 10 events per independent variable were considered for analysis (i.e., n = 10 k/p, where k is the number of independent variables and p is the smallest proportion of positive or negative cases in the population). With a prevalence of 41.9 for nephropathy [19] and 14 independent variables, at least 314 subjects would be necessary for the study. The continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range) and categorical variables as numbers (percentage). The normality of the data was assessed using the Kolmogorov-Smirnov test and descriptive analysis. The Mann-Whitney U test was applied to compare the levels of ALT, AST, ALP, and GGT between the groups of patients who developed or did not develop diabetic microvascular complications. The relationship between increased liver enzymes and diabetic microvascular complications was assessed using the chi-square test. Also, simple and multiple logistic regression was used to identify the relationship between increased levels of liver enzymes and microvascular complications of diabetes. Results are represented as crude and adjusted odds ratios (OR). All statistical analyses were performed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA), and P < 0.05 was considered statistically significant.

Results

A total of 403 patients with T2D with a mean age of 59.67 ± 6.33 years were included in the study. Among all the participants, 203 (50.4%) were aged between 55 and 65 years, and 202 (50.1%) were male. The medians of ALT, AST, ALP, and GGT among the studied population were 18.0 (IQR: 13.0–25.0), 17.0 (IQR: 14.0–22.0), 209.0 (IQR: 177.0–246.0), and 24.0 (IQR: 18.0–32.5), respectively. The demographic characteristics of the patients are represented in Table 1. The overall frequency of microvascular complications of diabetes among participants was 75.5% (305 out of 403). Among them, diabetic retinopathy (n = 267, 66.3%) followed by neuropathy (n = 134, 33.3%) and nephropathy (n = 26, 6.5%) were the most prevalent (Tab. 2).

There was a significant difference between the levels of AST in patients with diabetes with or without retinopathy (p = 0.039). There was no significant relationship between the level of ALT, ALP, and GGT and developing retinopathy in patients with diabetes (p = 0.669, 0.255, and 0.971, respectively). Also, no significant differences were found between developing neuropathy and levels of ALT, AST, ALP, and GGT (p = 0.679, 0.281, 0.230, and 0.301, respectively) in patients with diabetes. There was a significant relationship between the levels of GGT and nephropathy in patients with diabetes (p = 0.003). However, this relationship was not detected with the levels of ALT, AST, and ALP (p = 0.109, 0.844, and 0.351, respectively) (Tab. 3).

Further analysis using multiple logistic regression found no significant association between the increased level of liver enzymes and developing retinopathy or neuropathy in patients with diabetes. However, increased levels of GGT were significantly associated with the development of diabetic nephropathy (OR = 3.42, 95% CI, 1.28–6.00, p = 0.014). This significant association was not detected between increased levels of ALT, AST, or ALP and diabetic nephropathy (Tab. 4).

Discussion

Overall, our results showed that most of the patients with diabetes suffered from at least one of the microvascular complications of the disease. The most prevalent microvascular complication was diabetic retinopathy followed by neuropathy and nephropathy. In addition, our findings showed a significant asso-

Table 1. Demographic Characteristics of the Patients

Variables	n (%)	Mean (SD) or median (IQR)
Age [y]		**59.67 (6.33)**
< 55	98 (24.3)	
55–65	203 (50.4)	
≥ 65	102 (25.3)	
Male sex	202 (50.1)	
Marital status		
Married	377 (93.5)	
Widowed	26 (6.5)	
Habitat		
Urban	137 (34.0)	
Rural	266 (66.0)	
Education [y]		7.14 (4.61)
Illiterate	51 (12.7)	
1–5 years	124 (30.8)	
6–12 years	191 (47.4)	
University	37 (9.2)	
Wealth score		
Tertile 1 (poor)	134 (33.3)	
Tertile 2 (intermediate)	135 (33.5)	
Tertile 3 (rich)	134 (33.3)	
BMI [kg/m]		28.95 (5.19)
Normal	87 (21.6)	
Overweight	170 (42.2)	
Obese	146 (36.2)	
Physical activity	39.34 7.73	39.34 (7.73)
Tertile 1 (low)	134 (33.3)	
Tertile 2 (intermediate)	135 (33.5)	
Tertile 3 (high)	134 (33.3)	
Smoking	96 (23.8)	
Hookah	50 (12.4)	
Substance use	20 (5.0)	
Alcohol	42 (10.4)	
Hypertension	243 (60.3)	
Liver enzymes [IU/L]		
ALT		18.0 (13.0–25.0)
AST		17.0 (14.0–22.0)
ALP		209.0 (177.0–246.0)
GGT		24.0 (18.0–32.5)

ALP — alkaline phosphatase; ALT — alanine aminotransferase; AST — aspartate aminotransferase; BMI — body mass index; GGT — gamma-glutamyl transferase; IQR — interquartile range; SD — standard deviation

ciation between increased GGT levels and developing nephropathy in patients with diabetes. In contrast, no significant association was found between the level of liver enzymes, including ALT, AST, ALP, or GGT, and diabetic neuropathy or retinopathy.

Our analysis suggested retinopathy, neuropathy, and nephropathy as the most prevalent microvascular complications of diabetes. Based on our results, the frequency of retinopathy (66.3%) was much higher than the frequency of neuropathy (33.3%) and nephropathy (6.5%) in patients with diabetes. A meta-analysis of the Iranian population suggested nephropathy as the most prevalent microvascular complication of diabetes, followed by neuropathy and retinopathy [20]. Also, the frequency of retinopathy in our study was much higher than in global reports [21]. A meta-analysis found a prevalence of 30.6% for diabetic nephropathy among Iranian patients with diabetes. This prevalence ranged from 14.4% to 57.3% in different provinces around the country [22]. Moreover, Mohammadi et al. [23] found a prevalence of 37.8% for retinopathy among patients with diabetes in Iran. There was a wide variation in this number between different provinces. This prevalence was estimated to be 56.5% for diabetic neuropathy, and it decreased significantly over the period between 2003 to 2017 [24]. These variations in the prevalence of different microvascular complications of diabetes could be attributed to the differences in demographic and genetic factors as well as applied screening methods and the date of the study.

Our findings showed no significant association between increased serum levels of ALP and liver enzymes (ALT, AST, and GGT) and the risk of retinopathy in patients with diabetes. In line with this finding, Bulum et al. [25] found no significant difference between the level of liver enzymes in patients with diabetes with or without retinopathy. Also, meta-analyses suggested no significant correlation between diabetic retinopathy and non-alcoholic fatty liver disease as a main cause of increased levels of liver enzymes [26]. In contrast, a recent study on an Iranian population found an inverse but poor (OR = 0.998) association between the level of AST and ALT and the risk of diabetic retinopathy [10]. Afarideh et al. [12] found that

Table 2. Prevalence of Microvascular Complications of Diabetes Among the Studied Population

Microvascular complications	Males (n = 202)		Females (n = 201)		Total (n = 403)	
	n	Prevalence (%)	n	Prevalence (%)	n	Prevalence (%)
Diabetic neuropathy	47	23.3	87	43.3	134	33.3
Diabetic nephropathy	12	5.9	14	7.0	26	6.5
Diabetic retinopathy	125	61.9	142	70.6	267	66.3
Microvascular	139	68.8	166	82.6	305	75.7

Table 3. Level of ALT, AST, ALP, and GGT in patients with diabetes with or without neuropathy, nephropathy, or retinopathy

Variables	Without microvascular complication	With microvascular complication	P-value
Diabetic retinopathy	**n = 136**	**n = 267**	
ALT (IU/L)	18.0 (13.0–25.8)	18.0 (13.0–24.0)	0.669
AST	18.0 (15.0–22.8)	17.0 (14.0–21.0)	0.039
ALP	199.5 (174.2–244.0)	211.0 (178.0–247.0)	0.255
GGT	24.0 (18.2–34.7)	24.0 (18.0–32.0)	0.971
Diabetic neuropathy	n = 269	n = 134	
ALT (IU/L)	18.0 (13.0–25.0)	18.0 (13.0–24.2)	0.679
AST	17.0 (13.8–22.0)	17.0 (13.8–20.2)	0.281
ALP	206.0 (176.5–241.5)	213.5 (178.8–252.0)	0.230
GGT	23.5 (18.0–32.0)	24.8 (18.2–36.2)	0.301
Diabetic nephropathy	n = 378	n = 26	
ALT (IU/L)	18.0 (13.0–24.0)	20.5 (14.0–29.2)	0.109
AST	17.0 (14.0–22.0)	15.5 (14.0–22.5)	0.844
ALP	208.0 (176.0–245.0)	215.5 (185.0–262.0)	0.351
GGT	23.0 (18.0–32.0)	28.2 (24.7–43.4)	0.003

Values are presented as median (interquartile range); P-values are based on the Mann-Whitney test
ALP —— alkaline phosphatase; ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGT — gamma-glutamyl transferase

retinopathy is associated with decreased levels of ALT and increased levels of ALP in patients with diabetes. However, they couldn't find a significant difference between the odds of diabetic retinopathy among different quartiles of ALT levels.

The recent study did not find any significant relationship between the level of ALT, AST, ALP, or GGT and the risk of diabetic neuropathy. In line with these findings, Afarideh et al. [12] found no significant difference regarding the levels of liver enzymes between patients with diabetes with or without neuropathy. Moreover, a recent prospective study found that increased levels of ALP but not ALT, AST, or GGT are associated with the risk of developing neuropathy in patients with diabetes [10]. In contrast, meta-analyses suggested that MASLD [27] as well as higher liver fibrosis indices [28] are associated with a higher risk of diabetic neuropathy. This controversy could be clarified by determining the exact etiologies of increased liver enzymes in the studied population. The main reasons for the increased liver enzymes among the participants of the study may be etiologies other than MASLD.

The results of the recent study suggest a positive association between increased levels of GGT but not ALT, AST, or ALP with the risk of developing nephropathy in patients with diabetes. In line with this finding, Deravi et al. [10] showed that higher levels of GGT and ALP are accompanied by an increased risk of diabetic nephropathy. They found no significant relationship between the levels of AST or ALT and the risk of diabetic nephropathy. Another case-control study showed no significant association between increased levels of ALP but not ALT, AST, or GGT and developing nephropathy in patients with diabetes. A recent cross-sectional study suggested increased serum levels of GGT as an independent risk factor for developing nephropathy among patients with T2D [29]. A positive association has been shown between GGT levels and insulin resistance [30]. In addition, GGT plays a key role in the production of free radical species through its interaction with iron, and it has been suggested to be a reliable and sensitive biomarker of oxidative stress [31]. Moreover, GGT is considered a potential predictor of inflammatory markers, like C–C-reactive protein, fibrinogen, and F2-isoprostanes [32]. Oxidative stress is one of the main pathophysiological mechanisms responsible for the progression of kidney injury [33], and it is also the forerunner of renal fibrosis [34], which may contribute to the relationship between serum GGT level and the incidence of chronic kidney disease (CKD). Insulin resistance, inflammation, and increased oxidative stress contribute to hypertension, CVD, diabetes, obesity, and high serum lipids. Based on these findings, insulin resistance, inflammation,

Table 4. Relationship Between Increased Serum Level of Liver Enzymes and Diabetic Neuropathy, Nephropathy, or Retinopathy

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Diabetic retinopathy						
Increased ALT	1.00 (0.61 – 1.65)	0.993	1.03 (0.62 – 1.71)	0.901	1.05 (0.63 – 1.77)	0.849
Increased AST	1.23 (0.43 – 3.57)	0.700	1.30 (0.44 – 3.78)	0.636	1.33 (0.43 – 4.06)	0.620
Increased ALP	1.37 (0.59 – 3.17)	0.468	1.24 (0.53 – 2.91)	0.626	1.19 (0.50 – 2.86)	0.689
Increased GGT	1.18 (0.66 – 2.212)	0.575	1.10 (0.60 – 2.00)	0.767	1.13 (0.60 – 2.12)	0.697
Increased liver enzyme	1.28 (0.82 – 2.01)	0.274	1.26 (0.80 – 1.98)	0.317	1.27 (0.80 – 2.02)	0.307
Diabetic neuropathy						
Increased ALT	1.17 (0.71 – 1.91)	0.540	1.18 (0.71 – 1.97)	0.517	1.39 (0.82 – 2.36)	0.221
Increased AST	1.10 (0.40 – 3.04)	0.855	1.21 (0.43 – 3.44)	0.719	1.37 (0.46 – 4.11)	0.570
Increased ALP	0.75 (0.32 – 1.74)	0.503	0.65 (0.27 – 1.55)	0.327	0.63 (0.26 – 1.55)	0.315
Increased GGT	1.44 (0.82 – 2.51)	0.200	1.15 (0.64 – 2.06)	0.635	1.21 (0.66 – 2.24)	0.536
Increased liver enzyme	1.09 (0.71 – 1.70)	0.690	1.02 (0.65 – 1.60)	0.941	1.10 (0.69 – 1.75)	0.701
Diabetic nephropathy						
Increased ALT	1.62 (0.68 – 3.87)	0.274	1.62 (0.68 – 3.88)	0.280	1.66 (0.68 – 4.06)	0.262
Increased AST	0.90 (0.11 – 7.08)	0.922	0.91 (0.12 – 7.19)	0.932	1.27 (0.75 – 8.60)	0.826
Increased ALP	2.56 (0.82 – 8.00)	0.106	2.65 (0.82 – 8.52)	0.102	2.54 (0.75 – 8.60)	0.133
Increased GGT	2.66 (1.10 – 6.42)	0.030	2.69 (1.07 – 6.75)	0.035	3.42 (1.28 – 9.10)	0.014
Increased liver enzyme	2.53 (1.14 – 5.64)	0.023	2.51 (1.12 – 5.60)	0.025	2.64 (1.16 – 6.00)	0.020

ALP — alkaline phosphatase; ALT — alanine aminotransferase; AST — aspartate aminotransferase; BMI — body mass index; CI — confidence interval; GGT — gamma-glutamyl transferase; OR — odds ratio
Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, marital status, habitat, educational level, wealth score, BMI, level of physical activity, smoking, hookah, substance misuse, alcohol, and hypertension

and oxidative stress may serve as a link between GGT levels and several risk factors of CKD, including hypertension, high BMI level, and high serum lipids level. In addition, previous studies suggested that Serum GGT levels have an inverse relationship with endothelial function [35]. Also, greater endothelial dysfunction is shown to be related to decreased GFR [36]. It is noteworthy that the decreased renal excretion of GGT secondary to the reduced renal function may increase the serum GGT levels.

Several studies showed a positive relationship between increased serum GGT and the risk of CKD [37]. Clinical and experimental studies showed the involvement of GGT in the pathogenesis of many disease conditions like cardiovascular diseases, lung inflammation, atherosclerosis, cancer, and neuroinflammation, because of its role in the origination of prooxidant reactions [38]. In addition, the interaction of GGT and iron is shown to be an important source of free radical species generation [39]. Also, increased GGT levels are suggested to be associated with increased levels of inflammatory markers such as C-reactive protein, fibrinogen, and F2-isoprostanes [32]. Evidence speculated that oxidative stress, insulin resistance, and inflammation could be the link between GGT and several risk factors of CKD such as diabetes, hypertension, and high BMI level [40].

The present study has several limitations that should be noted. First, the sample was drawn from a single center and included only adults older than 35 years; thus, the generalizability of the results may be limited. Second, because of the cross-sectional nature of the present study, it is not possible to infer causality between study variables.

In summary, our study found that increased levels of GGT are an independent risk factor for the development of nephropathy in patients with diabetes. However, no significant relationship was found between the levels of ALT, AST, or ALP and any microvascular complication in patients with diabetes. Further research is needed to elucidate the exact relationship between the level of liver enzymes and the risk of microvascular complications of diabetes. Also, future studies could identify the nature of the relationship between the increased levels of GGT and kidney damage in diabetes.

Article information

Availability of data and materials

The study protocol and the datasets analyzed are available from the corresponding author upon request.

Ethics approval and consent to participate

This study was approved by the ethics committees of the Guilan University of Medical Sciences [IR.GUMS.REC.1400.228]. Informed consent was obtained from participants, a parent, and/or legal guardians.

Authors' contributions

F.MGH, Z.AR, and F.J. participated in the research design. B.F., S.M., A.A., Y.A., and Y.HS participated in writing the first draft. F.J., Z.AR, and S.M. participated in the performance of the research and analytic tools. S.M. and F.J. participated in data analysis. All authors reviewed and confirmed the final manuscript.

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Conflict of interest

The authors declare no conflict of interest. This study was extracted from MD thesis.

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