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ORIGINAL ARTICLE

Relationship between the Serum De Ritis Ratio and Diabetes Tests in Korean Adults Who Underwent Health Screening at a General Hospital in Gyeonggi-do

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경기도 일개 종합병원에서 건강검진을 받은 한국 성인의 혈청 De Ritis 비율과 당뇨 검사와의 관계

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ABSTRACT

The purpose of this study was to analyze the relationship between diabetes and liver function test results. Unlike type 2 diabetes mellitus (T2DM), hepatogenous diabetes is caused by abnormal liver function. In this study, the relationship between liver enzymes, aspartate aminotransferase (AST), alanine transaminase (ALT), and the AST/ALT ratio (De Ritis ratio), indicating liver function, and diabetes-related tests was analyzed. The results of the study showed a positive correlation between AST and glucose (r=0.14, $P<0.01$), ALT and glucose (r=0.21, $P<0.01$), AST and glycated hemoglobin (HbA1c) (r=0.15, $P<0.01$), and ALT and HbA1c (r=0.20, $P<0.01$). The De Ritis ratio showed a negative correlation with glucose (r=-0.20, $P<0.01$) and HbA1c (r=-0.14, $P<0.01$). The results of regression analysis with AST, ALT, and the De Ritis ratio as independent variables and glucose (R^2=0.05) and HbA1c (R^2=0.04) as dependent variables revealed that the independent variables had a statistically significant effect on the dependent variables. AST showed a lower correlation between blood glucose and glycated hemoglobin than ALT, and an increase in ALT caused a decrease in the De Ritis ratio. Therefore, the De Ritis ratio can be said to be meaningful in relation to diabetes-related tests.

INTRODUCTION

Diabetes mellitus (DM) is related with a spectrum of liver diseases including nonalcoholic liver disease, fatty liver disease and liver cirrhosis with their increased complications and mortality [1]. Chronic liver disease is often related with impaired glucose tolerance and diabetes [2]. Both fatty liver disease and alcohol consumption have been reported to affect incident type 2 DM (T2DM) [3]. Non-alcoholic fatty liver disease (NAFLD) is highly frequent in patients with DM and increasing evidence suggests that patients with T2DM are at an especially high risk for developing the advancing forms of NAFLD, non-alcoholic steatohepatitis and associated advanced liver fibrosis [4]. The prevalence of

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NAFLD, the hepatic manifestation of metabolic syndrome is rapidly increasing in Korean populations. NAFLD is one of the strongest risk factors of T2DM, and the presence of NAFLD in T2DM patients is associated with a worse physiological condition of diabetic complications [5]. The aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (De Ritis Ratio) has been known to be associated with insulin resistance and metabolic syndrome [6]. Therefore, the The aim of this study was to evaluate the relationship among item of the liver function test, the De Ritis Ratio etc and diabetes test in adults with health screening.

MATERIALS AND METHODS

1. Sample and setting

This study is a retrospective design, which corresponds to the IRB exemption requirements (approval number: HALLYM 2022-12-025-002) approved the study and only 699 adult (ranged from 20 to 90 years) data with health screening at Hallym University Hospital located in Pyeongchon, Gyeonggi-do, Korea for a month in October 2022.

2. Clinical chemistry data

The collected all clinical chemistry's data included total protein (T-P), albumin (Alb), total bilirubin (T-B), AST, ALT, De Ritis ratio, gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), uric acid (UA), amylase, glucose, and HbA1c. For the serum chemistry test used in the study, an automated analyzer, Beckman AU 5800 (Beckman Coulter, Brea, CA, USA) was used. Fasting blood glucose was measured using the hexokinase UV method, and AST, ALT, GGT, ALP, LDH, amylase, and UA were measured using the UV kinetic method recommended by the International Society of Clinical Chemistry (IFCC). The body mass index (BMI) was automatically calculated through Microsoft Excel (Microsoft, Redmomd, WA, USA) by dividing the subject's height squared by weight.

3. Statistical analysis

All statistical analyses were performed using SPSS Statistics version 21.0 (IBM, Armonk, NY, USA) program for windows. Data are expressed as descriptive statistics (N, mean, SD) for continuous variables. The De Ritis ratio was artificially manipulated divided into three groups defined by the following <1.0; 1.0~2.0; and >2.0 [7]. Differences between general characteristics and personal variables were tested for significance using the independent t test. In addition, the one way analysis of variance analysis was performed among DM test (glucose, HbA1c) and De Ritis ratio. Dunnett's post hoc test was performed when there was a difference between groups. In addition, Pearson's correlation t test was performed on each variable. Furthermore, the multiple regression model was used to explore the linear relationship between the De Ritis Ratio and diabetes test. All statistical significance level was presented as proportions with 95% confidence intervals (set as $P<0.05$).

RESULTS

1. General characteristics

A total of 699 participants of the mean age of the participants was 48.73±10.48 years and 48.95 ±10.58 years (N=404) were male and 48.43±10.35 years (N=295) were female. There was no statistically significant difference in age between male and female. The average height of the subjects was 167.08±8.82 cm (male: 172.52±6.25 cm, female 159.63±5.90 cm, $P<0.01$), and the average weight of the subjects was 67.69±12.87 kg (male: 74.16±10.75 kg, female: 58.84±9.94 kg, $P<0.01$ the average BMI of the subjects was 24.11±3.38 (male: 24.87±3.05, female: 23.07±3.52, $P<0.01$). Males were higher than females in terms of height, weight, and BMI, which was statistically significant (Table 1).

2. Differences by clinical chemistry data according to subjects

In the results of analysis of the subjects' clinical chemistry data, there was no statistical difference between males and females in total protein, Alb, LDH, and amylase. T-B, AST, ALT, GGT, ALP, uric acid, glucose, and HbA1c were higher in males than females and were statistically significant (P<0.01). De Ritis ratio and were higher in females than in males and were statistically significant (P<0.01) (Table 2).

3. Difference between De Ritis ratio level and diabetes-related test results by subjects

According to the level of De Ritis ratios, the glucose result showed that the De Ritis Ratio was higher than the "a (<1.0)" group (105.10±19.73 mg/dL) than the "b (1.0~2.0)" group (98.44±15.78 mg/dL), and the "a (<1.0)" group showed a higher score than "c (>2.0)" group (94.69±17.84 mg/dL) was statistically significant. The "b (1.0~2.0)" group tended to appear higher than the "c (>2.0)" group, and there was no statistical difference. The level of De Ritis ratios and HbA1c results showed that the De Ritis Ratio was higher than the "b (1.0~2.0)" group (5.57±0.58%) than the "a (<1.0)" group (5.80±0.65%), and the "a (<1.0)" group was higher than the "c (>2.0)" group (5.50±0.65%). and was statistically significant. The "b (1.0~2.0)" group tended to appear higher than the "c (>2.0)" group, and there was no statistical difference. The level of De Ritis ratio and amylase results showed that the De Ritis Ratio was lower than the "b (1.0~2.0)" group (65.74±21.59 U/L) than the "a (<1.0)" group (58.53±17.38 U/L), and the "a (<1.0)" group was lower than the "c (>2.0)" group.

Table 1. General characteristics of study

Variable	Total (N=699)	Male (N=404)	Female (N=295)	F	t
Age (yr)	48.73±10.48	48.95±10.58	48.43±10.35	0.43	0.65
Height (cm)	167.08±8.82	172.52±6.25	159.63±5.90	1.07	27.58**
Weight (kg)	67.69±12.87	74.16±10.75	58.84±9.94	3.00	19.19**
BMI (weight/height^2)	24.11±3.38	24.87±3.05	23.07±3.52	8.05	7.19**

Data are presented as mean±SD.
Abbreviation: BMI, body mass index.
**P<0.01 by independent t-test.

Table 2. Differences by clinical chemistry data according to subjects

Item	Total (N=699)	Male (N=404)	Female (N=295)	F	t
T-P (g/dL)	7.43±0.39	7.43±0.39	7.42±0.39	0.17	0.50
Alb (g/dL)	4.71±0.23	4.75±0.23	4.66±0.22	0.69	5.31
T-B (mg/dL)	0.62±0.30	0.68±0.31	0.55±0.27	5.54*	6.10**
AST (U/L)	27.07±13.19	28.93±13.74	24.53±11.95	7.09**	4.52**
ALT (U/L)	22.83±17.48	26.26±17.91	18.14±15.71	9.17**	6.36**
AST/ALT ratio (De Ritis ratio)	1.42±0.51	1.28±0.49	1.61±0.49	0.88	-8.90**
GGT (U/L)	33.74±50.61	42.70±60.20	21.46±29.16	22.25**	6.17**
ALP (U/L)	63.53±17.99	65.34±17.42	61.04±18.49	3.70	3.14**
LDH (U/L)	164.92±27.40	165.74±27.87	163.80±26.76	0.00	-0.49
UA (mg/dL)	5.68±1.43	6.36±1.30	4.76±1.02	16.06**	18.31**
Amylase (U/L)	64.10±20.82	63.30±20.78	65.20±20.87	0.03	-1.19
Glucose (mg/dL)	99.57±17.24	102.94±19.23	94.96±12.66	21.70**	6.60**
HbA1c (%)	5.61±0.62	5.68±0.69	5.52±0.47	14.73**	3.51**

Data are presented as mean±SD.
Abbreviations: T-P, total protein; Alb, albumin; T-B, total bilirubin; AST, aspartate aminotransferase; ALT, alanin aminotransferase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; UA, uric acid.
*P<0.05, **P<0.01 by independent t-test.

Table 3. Difference between AST/ALT ratio (De Ritis ratio) level and diabetes-related test results by subjects

Variables	De Ritis ratio (N=699)			Dunnett T3 (F)
	"a (<1.0)" group (N=159)	"b (1.0~2.0)" group (N=469)	"c (>2.0)" group (N=71)	
Glucose	105.10±19.73	98.44±15.78	94.69±17.84	a>b**,c** (12.44**)
HbA1c	5.80±0.65	5.57±0.58	5.50±0.65	a>b**,c** (10.16**)
Amylase	58.53±17.38	65.74±21.59	65.82±20.83	a<b**,c** (7.52**)

Data are presented as mean±SD.
Abbreviations: See Table 2.
**P<0.01 by one way ANOVA test.

Table 4. Correlation analysis between diabetes-related test results and liver function test results

Variables	Amylase (U/L)	Glucose (mg/dL)	HbA1c (%)
T-P (g/dL)	-0.022	0.088*	0.086*
Alb (g/dL)	-0.009	0.103**	0.092*
T-B (mg/dL)	-0.070	0.014	-0.092*
AST (U/L)	-0.086*	0.135**	0.148**
ALT (U/L)	-0.123**	0.206**	0.203**
AST/ALT ratio (De Ritis ratio)	0.145**	-0.202**	-0.144**
GGT (U/L)	-0.145**	0.118**	0.060
ALP (U/L)	-0.049	0.070	0.073
LDH (U/L)	0.051	0.055	0.085*
UA (mg/dL)	-0.133**	0.144**	0.074*

Abbreviations: See Table 2.
*P<0.05, **P<0.01 by Pearson's correlation t test.

(65.82±20.83 U/L), and was statistically significant. The "b (1.0~2.0)" group tended to appear lower than the "c (>2.0)" group, and there was no statistical difference (Table 3).

4. Correlation analysis between diabetes-related test results and liver function test results

AST (r=-0.086, P<0.05), ALT (r=-0.123, P<0.01), GGT (r=-0.145, P<0.01), UA (r=-0.133, P<0.01) and amylase were all statistically significant with negative correlations. Conversely, the amylase and De Ritis ratio were positively related and statistically significant (r=0.145, P<0.01). In addition, amylase and T-P, Alb, T-B and ALP showed a negative trend relationship, and amylase and LDH showed a positive trend relationship. T-P (r=0.088, P<0.05), Alb (r=0.103, P<0.01), AST (r=0.135, P<0.01), ALT (r=0.206, P<0.01), GGT (r=0.118, P<0.01), UA (r=0.144, P<0.01) and glucose were all statistically significant with positively correlations. Conversely, the glucose and De Ritis ratio were negatively related and statistically significant (r=-0.202, P<0.01). In addition, glucose and T-B, ALP, LDH showed a positive trend relationship. T-P (r=0.086, P<0.05), Alb (r=0.092, P<0.05), AST (r=0.148, P<0.01), ALT (r=0.203, P<0.01), LDH (r=0.085, P<0.05), UA (r=0.074, P<0.05) and HbA1c were all statistically significant with positively correlations. Conversely, the HbA1c and De Ritis ratio (r=-0.144, P<0.01), T-B (r=-0.092, P<0.05) were negatively related and statistically significant. In addition, HbA1c, GGT, and ALP showed a positive trend relationship (Table 4).

5. Regression analysis of De Ritis ratio with diabetes-related tests

As a result of regression analysis with AST, ALT, and De Ritis ratio as independent variables and diabetes-related tests glucose, HbA1c and amylase as dependent variables, it was found that AST, ALT, and De Ritis ratio had a statistically significant effect on glucose (R^2=0.05), HbA1c (R^2=0.04) and amylase (R^2=0.02). (Table 5).

DISCUSSION

The liver function tests typically include alanine transaminase and aspartate transaminase, alkaline phosphatase, gamma-glutamyl transferase, serum bilirubin, prothrombin time, the international normalized ratio, total protein and albumin [8]. The prevalence of diabetes mellitus in cirrhotic patients is much higher than that

Table 5. Regression analysis of AST/ALT ratio (De Ritis ratio) with diabetes-related tests

Dependent variables	Independent variables	B	Beta	SE	*t*	F/R/R2/D-W
Glucose (mg/dL)	Constant	102.80				12.92**/0.23/0.05/2.01
Glucose (mg/dL)	AST (U/L)	0.04	0.03	0.10	0.40	12.92**/0.23/0.05/2.01
Glucose (mg/dL)	ALT (U/L)	0.98	0.10	0.09	1.04	12.92**/0.23/0.05/2.01
Glucose (mg/dL)	De Ritis ratio	−4.65	−0.14	1.94	−2.40*	12.92**/0.23/0.05/2.01
HbA1c (%)	Constant	5.53				10.19**/0.21/0.04/2.02
HbA1c (%)	AST (U/L)	0.00	−0.02	0.00	−0.20	10.19**/0.21/0.04/2.02
HbA1c (%)	ALT (U/L)	0.01	0.20	0.00	2.05*	10.19**/0.21/0.04/2.02
HbA1c (%)	De Ritis ratio	−0.04	−0.03	0.07	−0.54	10.19**/0.21/0.04/2.02
Amylase (U/L)	Constant	58.13				5.96**/0.16/0.02/1.99
Amylase (U/L)	AST (U/L)	−0.15	−0.01	0.13	−1.12	5.96**/0.16/0.02/1.99
Amylase (U/L)	ALT (U/L)	0.05	0.04	0.12	0.43	5.96**/0.16/0.02/1.99
Amylase (U/L)	De Ritis ratio	6.21	0.15	2.38	2.61**	5.96**/0.16/0.02/1.99

Abbreviations: See Table 2; SE, standard error; D-W, Durbin-Watson.
**P<0.01 by regression analysis.

in the general population and the association between chronic liver disease and diabetes mellitus is known since long [9]. However, there are not many studies on the relationship between De Ritis Ratio and diabetes. The term hepatogenous diabetes (HD) was first used by Megyesi et al. [10] in the 1960's.

HD is directly caused by loss of liver function, implying that it develops after cirrhosis onset. Moreover, patients with HD usually present with almost normal fasting glucose and HbA1c levels [11]. Therefore, the purpose of this study was to analyze the relationship between liver function tests, blood glucose, and glycated hemoglobin in adults who had undergone health checkups based on these previous studies. The level of De Ritis ratio and HbA1c results showed that the De Ritis ratio was higher than the "b (1.0~2.0)" group (5.57±0.58%) than the "a (<1.0)" group (5.80±0.65%), and the "a (<1.0)" group was higher than the "c (>2.0)" group (5.50±0.65%) and was statistically significant. The "b (1.0~2.0)" group tended to appear higher than the "c (>2.0)" group, and there was no statistical difference. The level of De Ritis ratio and amylase results showed that the De Ritis Ratio was lower than the "b (1.0~2.0)" group (65.74±21.59 U/L) than the "a (<1.0)" group (58.53±17.38 U/L), and the "a (<1.0)" group was lower than the "c (>2.0)" group. (65.82±20.83 U/L), and was statistically significant. The "b (1.0~2.0)" group tended to appear lower than the "c (>2.0)" group, and there was no statistical difference (Table 3). In addition, the glucose and De Ritis ratio were negatively related and statistically significant (r=0.00, P<0.01). These results can be explained in the same contents as the results of previous studies below, De Ritis ratio of ≥1.5 suggests intrahepatic cholestasis while values ≤1.5 suggest an extrahepatic process [12] and De Ritis ratio was negatively associated with blood glucose levels [13, 14]. Low HbA1c values were associated with liver enzymes and liver disease may partially explain the association of HbA1c with mortality and other long-term outcomes [15]. In this study, the glucose levels according to the 3 groups of De Ritis ratio, the HbA1c result showed that the De Ritis Ratio was higher than the "a (<1.0)" group (5.80±0.65%) than the "b (1.0~2.0)" group (5.57±0.58%), and the "a (<1.0)" group showed a higher score than "c (>2.0)" group (5.50±0.65%) was statistically significant. However, the "b (1.0~2.0)" group tended to appear higher than the "c (>2.0)" group, and there was no statistical difference. In a similar study, ALT showed significant positive correlation with fasting glucose, post prandial glucose, HbA1c at P<0.05 [16].

In 1957, Italian pathologist Fernando De Ritis first described it as an enzyme for viral hepatitis between AST and ALT in the diagnosis of viral hepatitis, where ALT is usually higher than AST. Also, a clinical descrip-

tion of the rate of De Ritis is provided and also, a clinical description of the rate of De Ritis is provided [7]. Therefore, there are studies that insist on redefining the distinction between T2DM and hepatic diabetes [11]. Specifically, elevated ALT leads to insulin resistance. Insulin resistance plays an important role in the development of diabetes, as increased insulin resistance can result in insulin not working enough, resulting in high blood sugar levels. As for the cause of insulin resistance due to elevated ALT, studies have shown that ALT produces substances that promote oxidative stress, and oxidative stress can negatively affect insulin signaling. The other is that elevated ALT causes liver dysfunction, resulting in insulin resistance as the liver does not produce enough of the substances needed to metabolize insulin [17]. An interesting fact in this study is that amylase showed a negative correlation between blood glucose and HbA1c which was also found in other studies [18]. In summary, routinely measured diabetes-related tests such as blood glucose (R^2=0.05), HbA1c (R^2=0.04), and amylase (R^2=0.02) are significantly associated with liver enzymic biomarkers functions such as AST, ALT, and De Ritis ratio among adults.

요 약

본 연구의 목적은 당뇨 검사결과와 간기능검사와의 관계연구이다. 간성당뇨는 제2형 당뇨와는 다르게 간기능 이상으로 기인하는 것이다. 본 연구에서 간기능 검사의 주요 효소검사인 아스파르트산 아미노전이효소(aspartate aminotransferase, AST), 알라닌 아미노전이효소(alanine aminotransferase, ALT) 그리고 AST/ALT ratio (De Ritis ratio)와 당뇨관련 검사와의 관계를 주로 확인하였다. 연구 결과 AST와 글루코스(glucose) (r=0.14, P<0.01); ALT 및 글루코스(r=0.21, P<0.01); AST 및 당화혈색소(HbAlc) (r=0.15, P<0.01); ALT와 HbAlc (r=0.20, P<0.01), 모든 변수는 양의 상관관계를 나타났으며, De Ritis ratio는 글루코스 (r=−0.20, P<0.01)와 당화혈색소 (r=−0.14, P<0.01)와 음의 상관관계를 보였다. AST와 ALT 그리고 De Ritis ratio 를 독립변수로 하고 글루코스 (R^2=0.05) 와 HbA1c (R^2=0.04) 를 종속변수로 하여 회귀분석한 결과 독립변수는 종속변수에 통계적으로 유의하게 영향을 나타내는 것으로 나타났다. AST는 ALT 보다 혈당과 당화혈색소에서 상관관계가 낮게 나타났으며, ALT가 증가하는 것은 즉, De Ritis ratio 감소의 원인이 된다. 따라서, De Ritis ratio는 당뇨관련 검사와의 관계에서 의미가 있는 것으로 볼 수 있다.

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Conflict of interest: None

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