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Clinical significance of hepatic function in Graves disease with type 2 diabetic mellitus

A single-center retrospective cross-sectional study in Taiwan

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Abstract

Graves disease (GD) and type 2 diabetes mellitus (T2DM) both impair liver function; we therefore explored the possibility of a relationship among diabetic control, thyroid function, and liver function.

This retrospective, cross-sectional study compared serum liver function biomarkers of primary GD patients in a single center between 2016 and 2020, derived from clinical databases, and clarified the correlation of liver function in GD patients with or without T2DM. Furthermore, the diabetes mellitus group was divided into glycated hemoglobin A1C (HbA1C) <6.5% group and ≥6.5% group to further analyze the effect by disease control in patients. Statistical differences between groups were assessed using independent *t* tests to clarify the association of serum biomarkers between GD with T2DM. Pearson test was applied to assess within-group statistical correlation of serum biomarkers. The correlation of factors in each group was demonstrated by using the Kendall tau-b method and stepwise regression analysis.

A total of 77 patients were included in the study. In the study population, glutamate pyruvate transaminase (GPT) was significantly correlated with thyroid-stimulating hormone, and HbA1C was significantly correlated with alkaline phosphatase (ALK-P), glutamate oxaloacetate transaminase (GOT), and GPT. An examination of GOT, GPT, free thyroxine (FT4), and HbA1C levels revealed a significant difference between the non-T2DM and T2DM groups. GPT also exhibited a significant correlation with triiodothyronine in the T2DM group. The T2DM group was further divided into groups: HbA1C <6.5% and ≥6.5%. The results demonstrated that ALK-P, GOT, GPT, and FT4 levels were significantly different between the groups. A significant correlation between ALK-P and thyroid-stimulating hormone and between GOT and FT4 was also identified in the HbA1C <6.5% group.

Our single-center study revealed that diabetes affects liver function in patients with GD. For patients with T2DM, when liver function becomes impaired, thyroid function control deteriorates. GPT was correlated with triiodothyronine but not with FT4, which indicated the impairment of deiodination in the liver. This phenomenon was not observed in the non-T2DM population. The early detection of abnormal liver function in patients with GD and T2DM may help limit the development of comorbidities and improve disease management.

Abbreviations: ALK-P = alkaline phosphatase, FT4 = free thyroxine, GD = Graves disease, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, ICD-10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification, T2DM = type 2 diabetes mellitus, T3 = triiodothyronine, T4 = thyroxine, TRAb = thyrotrophin receptor antibody, TSH = thyroid-stimulating hormone.

Keywords: Graves disease, HbA1C, hepatic function, T2DM

Y-WL and Y-YL contributed equally to this work.

This study was performed in accordance with the Declaration of Helsinki and was approved by The Taipei Medical University Hospital (TMUH) Institutional Review Board for Clinical Research approved this study (No. N202104091). It was conducted in accordance with the Declaration of Helsinki. As this was a retrospective study and all patient information was deidentified before analysis.

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The deidentified statistical datas are from the Clinical Data Center, Office of Data Science, Taipei Medical University, Taiwan.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All the authors declare that they have no conflict of interest with any organization that sponsored the research.

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1. Introduction

Graves disease (GD) is a common disease in clinical practice, with an annual incidence of 20 to 50 cases per 100,000 persons.[1] The lifetime risk is 3% for women and 0.5% for men. GD can affect multiple organ systems, including the hepatic, metabolic, cardiovascular, and gastrointestinal systems. Relevant analyses have revealed that hepatic dysfunction is related to thyrotoxicosis and hyperthyroidism.[2,3] Physiologically, thyroid hormones are glucuronidated and sulfated within the liver and subsequently excreted into bile. Liver damage in hyperthyroidism normally occurs due to the effects of excessive thyroid hormones, antithyroid drug–related liver injury, and the presence of concomitant liver disease.

According to Taiwan's National Health Insurance Research Database, the prevalence of diabetes mellitus (DM) has steadily increased, accounting for 6% of people aged 20 to 75 years in Taiwan in 2014. In the DM population, type 2 DM (T2DM) accounts for 94% of cases.[4] DM-related complications may cause organ dysfunction, leading to conditions such as cardiovascular disease, cerebrovascular disease, end-stage renal disease, retinopathy, and peripheral neuropathy. Additionally, DM has been reported to occur in a considerable proportion of patients with hyperthyroidism.[5] Regarding autoimmune system dysfunction, most reports relate to GD and type 1 DM. However, a deep relationship has been identified between T2DM and GD.

T2DM is reported to be the most common cause of liver diseases. The liver plays a key role in glucose homeostasis and insulin resistance in T2DM. The prevalence of diabetes in cirrhosis ranges from 12.3% to 57%, depending on the study.[6] Studies have indicated that patients with GD develop abnormal glucose homeostasis and insulin resistance[7,8] because thyroid hormones increase insulin secretion, gluconeogenesis, and the intestinal absorption of glucose. T2DM and GD both impair liver function; we therefore explored whether the coexistence of these diseases would have a synergetic effect on liver function to demonstrate the relationship among diabetic control, thyroid function, and liver function.

In this study, we collected data from patients with GD treated at a single center between 2016 and 2020 to analyze the comorbidities and liver and thyroid function test results. We aimed to evaluate the role of liver function in the coexistence of GD and T2DM.

2. Methods

2.1. Patients

The data on 193 patients who had received a diagnosis of primary GD and who were treated at the Taipei Medical University Hospital between January 2016 and December 2020 were analyzed retrospectively. The diagnosis was based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code E05.00. The data derived from the Taipei Medical University Clinical Research Database were pseudo-anonymized. The requirement for patient consent was waived by the Taipei Medical University Clinical Research Database and the Institutional Review Board of Taipei Medical University (TMU-JIRB-N202104091). No additional records regarding the patients were obtained.

Patients were included in the study who had received a diagnosis of primary GD and had received continuous treatment between January 2016 and December 2020. Women who were pregnant, those under 20 years, and patients with neoplasms (ICD-10-CM C00-D49), cardiac disease (ICD-10-CM I00-I99), chronic hepatitis or liver disease (ICD-10-CM K70-K77), or nonprimary GD were excluded from the study. To exclude the alcohol-related disease, we confirmed the patients who include in this study without alcohol-related diagnosis (*ICD-10-CM* F01-F99; K29.2; K85.2; K86.0). Finally, 77 patients were included in the study. We separated them into DM group and non-DM group and used a between-group and within-group comparison to clarify the association of serum biomarkers between GD with T2DM. Furthermore, The DM group was divided into glycated hemoglobin A1c (HbA1C) <6.5% group and ≥6.5% group.

2.2. Statistical analysis

All statistical analyses were performed using SPSS 22.0 for Windows (IBM, Armonk, NY). Normally distributed continuous variables are expressed as mean and standard deviation, and statistical differences between the groups were assessed using independent sample *t* tests. $P < .05$ was considered significant.

Descriptive statistics were used to summarize the demographic data. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as the number of patients and percentage (%). The Pearson test was applied to assess within-group statistical correlation of serum biomarkers. The Kendall tau-b method was used to assess the strength and direction of the association between 2 measured variables.[9,10] As a follow-up procedure, a stepwise regression analysis was performed to further evaluate the association of the biomarkers of serum which showed significant correlation, and $P < .05$ was considered significant.

3. Results

3.1. Study population characteristics

The patient selection flowchart is presented in Figure 1, and the baseline characteristics of the patients are summarized in Table 1. Among the 77 patients with primary GD, 44 (57%) had been diagnosed as T2DM before receiving the diagnosis of primary GD, 27 (35%) were men and 50 (65%) were women; the male-to-female ratio was 0.54. Ages ranged from 27 to 86 years, and the mean age was (63 ± 19) years.

In study subjects, 68 patients had received the Methimazole therapy, and 10 patients had received the propylthiouracil therapy. Among the study subjects, some were given antihyperlipidemic agents' treatment with atorvastatin (12 patients) and rosuvastatin (5 patients). However, there are no significant differences noted in the level of serum total cholesterol ($P = .573$), triglycerides ($P = .94$), low-density lipoprotein ($P = .671$), and high-density lipoprotein ($P = .937$) in both non-DM and DM groups.

In the liver function test, there was no significant difference in alkaline phosphatase (ALK-P), but the level of glutamate oxaloacetate transaminase (GOT) ($P = .02$) and glutamate pyruvate transaminase (GPT) ($P = .04$) showed significant difference in non-DM and DM groups. For thyroid function, only the free thyroxine (FT4) ($P = .02$) level in the 2 groups showed significant difference, while triiodothyronine (T3) and thyroid stimulating hormone (TSH) levels showed no difference. The blood test for HbA1C showed significant difference within the 2 groups ($P = .02$).

To establish the role of hepatic function in patients with GD and T2DM, we used a between-group and within-group comparison to clarify the factors involved in the association between hepatic function and GD with T2DM. The study design is presented in Figure 2.

3.2. Association between factors in the study population

The correlation coefficients for the association between factors in the study population are presented in Table 2. The results revealed that GPT was significantly correlated with TSH (−0.195, $P = .033$). In addition, HbA1C was significantly correlated with alkaline phosphatase (ALK-P; 0.442, $P = .001$), GOT (0.319, $P = .006$), and GPT (0.355, $P = .001$). However, no significant correlation was identified between the thyroid function factors (T3, FT4, and TSH) and HbA1C.

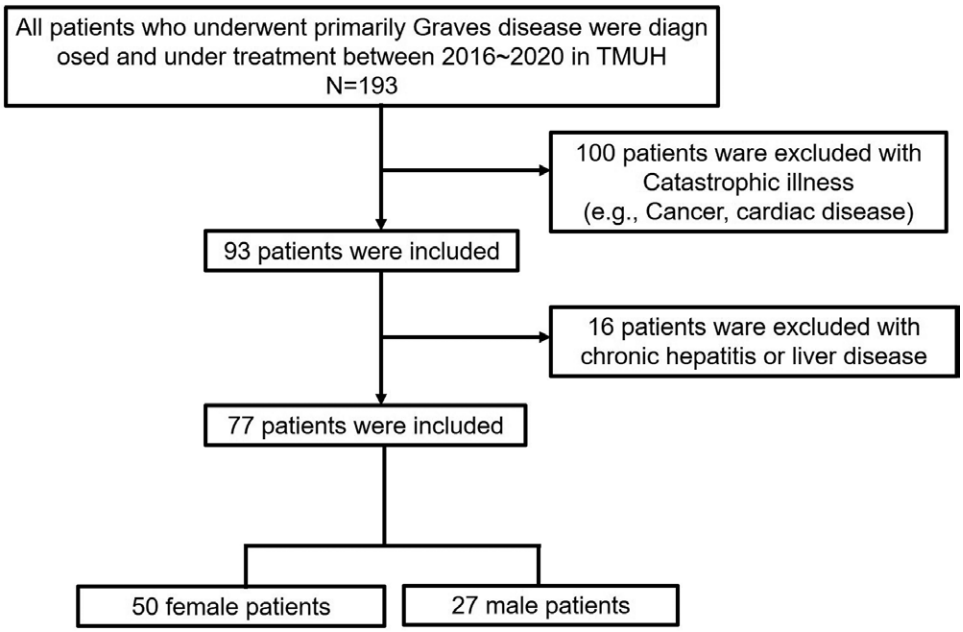

Figure 1. Flow chart showing the patient inclusion in the study.

Table 1

Baseline characteristics of the study subjects.

N	Total (N = 77)	Non-DM (N = 33)	DM (N = 44)	*P* value
Gender, female, (%)	50 (68)	20 (60)	30 (68)	.571
Age, mean (SD)	63 (19)	60 (19)	65 (17)	.263
Medication duration, month (SD)	38.6 (12.1)	39.3 (11.8)	38.08 (12.3)	.662
Antithyroid agents, N (%)				
Methimazole	67 (88)	31 (93.9)	36 (81.2)	.222
Propylthiouracil	10 (12)	2 (6)	8 (18.2)	.182
Antihyperlipidemicid agents, N (%)				
Atorvastatin	12 (16)	6 (18)	6 (14)	.344
Rosuvastatin	5 (6.5)	2 (6)	3 (7)	.913
Antihyperglycemic agents, N (%)				
Metformin	43 (57)	0 (0)	43 (97)	NA
Glimepride	9 (12)	0 (0)	9 (20)	NA
Linagliptin	3 (4)	0 (0)	3 (7)	NA
Dapagliflozin	4 (5)	0 (0)	4 (9.1)	NA
Saxagliptin and dapagliflozin	1 (1.3)	0 (0)	1 (2.3)	NA
Other medication, N (%)				
Silymarin	1 (1.3)	1 (3)	0 (0)	.2
Basic laboratory result, mean (SD)/N				
ALK-P (U/L)	105.3 (116.47)	81.5 (13.9/19)	122.3 (27.4/27)	.19
GOT (U/L)	25.47 (18.95)	21.68 (2.40/25)	28 (3.67/37)	.02*
GPT (U/L)	21 (13.02)	16.84 (2.40/26)	23.34 (1.89/46)	.04*
T3 (mg/dL)	122.72 (90.88)	1.33 (0.30/11)	1.13 (0.16/25)	.57
FT4 (ng/dL)	2.24 (2.06)	1.65 (0.14/20)	2.95 (0.41/41)	.02*
TSH (μIU/mL)	1.13 (1.69)	1.78 (0.75/25)	1.1 (0.23/41)	.28
HbA1C (%)	6.5 (1.4)	5.56 (0.41/12)	6.53 (1.41/43)	.02*
Total cholesterol (mg/dL)	166.6 (28.7)	169.0 (36.9/29)	165.0 (22.57/44)	.573
Tg (mg/dL)	181.0 (136.3)	175.0 (130.0/27)	172.6 (129.8/44)	.94
HDL (mg/dL)	56.0 (18)	55.7 (15.9/27)	56.1 (19.27/44)	.937
LDL (mg/dL)	97.7 (27.2)	95.9 (28.3/27)	98.75 (26.8/44)	.671

ALK-P = alkaline phosphatase, DM = diabetes mellitus, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NA = not available, T_3 = triiodothyronine, Tg = triglycerides, TSH = thyroid-stimulating hormone.
*$P < .05$.

3.3. Comparison of factors in the study population with T2DM

The study population was classified into 2 groups: patients with T2DM (T2DM group, N = 44) and patients without (non-T2DM group, N = 33). We then compared the factors between the 2 groups. GOT ($P = .002$), GPT ($P = .004$), FT4 ($P = .002$), and HbA1C ($P < .001$) levels in the 2 groups were significantly different (Table 1 and Fig. 3). We then calculated the correlation coefficients for the factors; no significant differences were

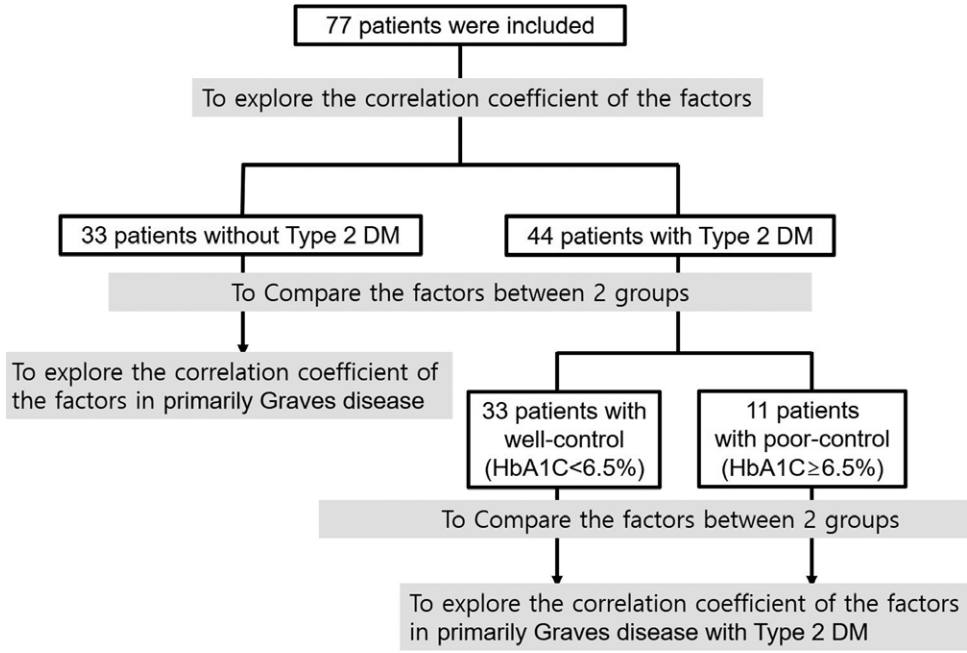

Figure 2. The study design.

Table 2

The correlation of the factors of the study population.

Relevant factors		ALK-P	GOT	GPT	T3	FT4	TSH	HbA1C
ALK-P	Coefficiency		0.266*	0.239*	−0.11	0.04	−0.10	0.442**
	P		.02	.03	.44	.73	.37	.00
GOT	Coefficiency	0.266*		0.593**	0.15	0.01	−0.12	0.319**
	P	.02		.00	.25	.94	.21	.01
GPT	Coefficiency	0.239*	0.593**		0.21	0.15	−0.195*	0.355**
	P	.03	.00		.09	.10	.03	.00
T3	Coefficiency	−0.11	0.15	0.21		0.254*	−0.292*	0.15
	P	.44	.25	.09		.03	.01	.32
FT4	Coefficiency	0.04	0.01	0.15	0.254*		−0.405**	0.10
	P	.73	.94	.10	.03		.00	.36
TSH	Coefficiency	−0.10	−0.12	−0.195*	−0.292*	−0.405**		0.00
	P	.37	.21	.03	.01	.00		.98
HbA1C	Coefficiency	0.442**	0.319**	0.355**	0.15	0.10	0.00	
	P	.00	.01	.00	.32	.36	.98	

ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, T_3 = triiodothyronine, TSH = thyroid-stimulating hormone.

*P < .05, correlation is significant at the 0.05 level (2-tailed).

**P < .01, correlation is significant at the 0.01 level (2-tailed).

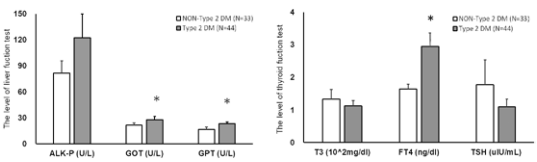

Figure 3. Compared the factors of the study subjects by T2DM. ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, T2DM = type 2 diabetes mellitus, T_3 = triiodothyronine, TSH = thyroid-stimulating hormone. *P < .05.

identified between the hepatic function factors (ALK-P, GOT, and GPT) and thyroid function factors (Table 3). However, GPT was strongly correlated with T3 (0.287, P = .047) and HbA1C (0.428, P < .001) in the T2DM group (Table 4). In addition, to further confirm the association with serum GPT level and T3 levels, we used the regression analysis in non-DM group (β = .466, r^2 = .127, P = .127) (Table 5) and DM group (β = .439, r^2 = .192, P = .028) (Table 6). In DM group, the serum GPT level was significantly associated with serum T3 levels, not in non-DM group.

3.4. Association of the thyroid function factors and HbA1C in the T2DM group

To demonstrate whether the level of HbA1C, disease control of T2DM, affected the hepatic and thyroid function in patients with GD and T2DM, we separated the patients

Table 3

The correlation of the factors of the study subjects with non-DM group.

Relevant factors		ALK-P	GOT	GPT	T3	FT4	TSH	HbA1C
ALK-P	Coefficiency		0.339	0.266	−0.143	−0.078	−0.199	0.429
	P		.070	.145	.621	.713	.324	.176
GOT	Coefficiency	0.339		0.644**	0.426	−0.101	−0.040	0.198
	P	.070		.000	.125	.567	.816	.419
GPT	Coefficiency	0.266	0.644**		0.386	0.036	−0.230	−0.133
	P	.145	.000		.125	.832	.166	.570
T3	Coefficiency	−0.143	0.426	0.386		−0.341	−0.224	0.077
	P	.621	.125	.125		.176	.345	.797
FT4	Coefficiency	−0.078	−0.101	0.036	−0.341		−0.485**	−0.141
	P	.713	.567	.832	.176		.002	.600
TSH	Coefficiency	−0.199	−0.040	−0.230	−0.224	−0.485**		0.442
	P	.324	.816	.166	.345	.002		.067
HbA1C	Coefficiency	−0.111	0.147	0.150	0.071	−0.197	−0.316	
	P	.677	.532	.530	.805	.463	.448	

ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, T_3 = triiodothyronine, TSH = thyroid-stimulating hormone.

**$P < .01$, correlation is significant at the 0.01 level (2-tailed).

Table 4

The correlation of the factors of the study subjects with DM group.

Relevant factors		ALK-P	GOT	GPT	T3	FT4	TSH	HbA1C
ALK-P	Coefficiency		0.186	0.131	−0.051	0.010	0.003	0.318*
	P		.222	.353	.786	.944	.981	.042
GOT	Coefficiency	0.186		0.528**	0.123	−0.029	−0.161	0.302*
	P	.222		.000	.429	.815	.202	.022
GPT	Coefficiency	0.131	0.528**		0.287*	0.150	−0.184	0.428**
	P	.353	.000		.047	.182	.107	.000
T3	Coefficiency	−0.051	0.123	0.287*		0.394**	−0.330*	0.158
	P	.786	.429	.047		.006	.025	.309
FT4	Coefficiency	0.010	−0.029	0.150	0.394**		−0.370**	0.092
	P	.944	.815	.182	.006		.001	.457
TSH	Coefficiency	0.003	−0.161	−0.184	−0.330*	−0.370**		−0.032
	P	.981	.202	.107	.025	.001		.799
HbA1C	Coefficiency	0.318*	0.302*	0.428**	0.158	0.092	−0.032	
	P	.042	.022	.000	.309	.457	.799	

ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, T_3 = triiodothyronine, TSH = thyroid-stimulating hormone.

*$P < .05$, correlation is significant at the 0.05 level (2-tailed).

**$P < .01$, correlation is significant at the 0.01 level (2-tailed).

Table 5

The association with serum GPT level and serum T3 levels by regression analysis with non-DM group.

	Parameter estimate	r^2	Standardized coefficients (β)	*P*value
T3	9.767	0.217	.466	.127

T3 = triiodothyronine.

Table 6

The association with serum GPT level and serum T3 levels by regression analysis with DM group.

	Parameter estimate	r^2	Standardized coefficients (β)	*P*value
T3	15.705	0.192	.439	.028*

T3 = triiodothyronine.

*$P < .05$.

in the T2DM group into 2 subgroups according to their HbA1C levels. The HbA1C ≥6.5% group had 11 patients and the HbA1C <6.5% group had 33 patients. The ALK-P ($P = .01$), GOT ($P = .009$), GPT ($P = .02$), and FT4 ($P = .02$) levels were significantly different in the HbA1C ≥6.5% and HbA1C <6.5% groups (Fig. 4).

We then considered the correlation coefficients for these factors. The results indicated a significant correlation between ALK-P and TSH (−0.232, $P = .046$) and GOT and FT4 (0.435, $P = .002$) in the HbA1C <6.5% group (Table 7), but no correlations were identified in the HbA1C ≥6.5% group (Table 8).

In addition, we tried to confirm the association between the level of serum GOT and FT4, ALK-P, and TSH by regression analysis in HbA1C <6.5% of DM group and ≥6.5% of DM group. In the HbA1C <6.5% of DM group, the serum GOT level was significantly associated with serum FT4 levels ($\beta = .652$, $r^2 = .425$, $P = .02$), and the serum ALK-P level was significantly associated with TSH levels ($\beta = -.495$, $r^2 = .245$ $P = .04$) (Table 9). In the HbA1C ≥6.5% of DM group, there were no significantly association between serum GOT level and FT4 levels ($\beta = .108$, $r^2 = .012$, $P = .78$), so as the serum ALK-P and TSH levels ($\beta = .313$, $r^2 = .098$, $P = .61$) (Table 10).

4. Discussion

In a cohort study in 2020,[11] no differences were observed in the prevalence and incidence of thyroid dysfunction in

Relevant factors	HbA1C<6.5% (N=33)		HbA1C≥6.5% (N=11)		P value
	Mean	SD	Mean	SD	
Age	70.91	10.09	62.23	16.44	0.11
ALK-P (U/L)	80.70	9.88	203.25	88.10	0.01*
GOT (U/L)	21.14	1.71	45.40	12.90	0.009**
GPT (U/L)	19.60	1.90	29.72	4.43	0.02*
T3 (10^2mg/dl)	0.98	0.12	0.84	0.12	0.50
FT4 (ng/dl)	2.95	0.54	1.49	0.16	0.02*
TSH (uIU/mL)	1.13	0.34	2.37	1.43	0.26
HbA1C(%)	5.87	0.2	7.85	0.41	0.000***
Medication duration (Month)	37.7	12.9	38.6	10.8	0.839
Total cholesterol (mg/dl)	168.78	27.5	165.9	18.84	0.76
Tg (mg/dl)	177.24	127.92	147.2	123.39	0.522
HDL (mg/dl)	56.27	19.6	19.7	18.3	0.631
LDL (mg/dl)	177.24	127.9	147	123.9	0.5

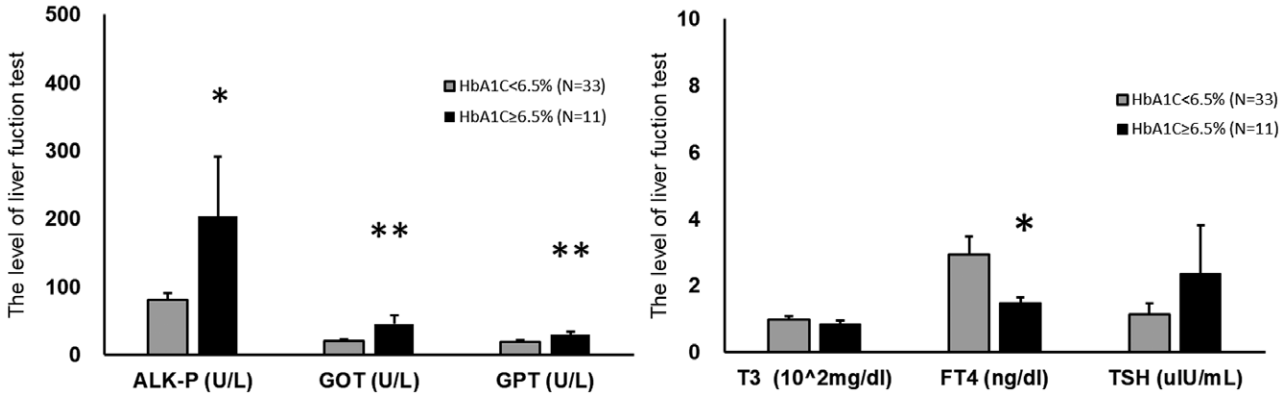

Figure 4. Compared the factors of patients by HbA1C in patients with T2DM. ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, T2DM = type 2 diabetes mellitus, T_3 = triiodothyronine, TSH = thyroid-stimulating hormone. *P < .05; **P < .01.

Table 7

The correlation of the factors of the study subjects with HbA1C <6.5% of DM group.

Relevant factors		ALK-P	GOT	GPT	T3	FT4	TSH
ALK-P	Coefficiency		0.021	−0.019	−0.100	−0.232	−0.289*
	P		.883	.921	.440	.053	.046
GOT	Coefficiency	0.021		0.057	0.187	0.435**	0.142
	P	.883		.833	.236	.002	.423
GPT	Coefficiency	−.0019	0.057		0.435	−0.029	−0.182
	P	.921	.833		.240	.881	.411
T3	Coefficiency	−0.100	0.187	0.435		0.113	−0.063
	P	.440	.236	.240		.384	.697
FT4	Coefficiency	−0.232	0.435**	−0.029	0.113		0.169
	P	.053	.002	.881	.384		.249
TSH	Coefficiency	−0.289*	0.142	−0.182	−00.063	.169	
	P	.046	.423	.411	.697	.249	

ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, T_3 = triiodothyronine, TSH = thyroid-stimulating hormone.

*P < .05, correlation is significant at the 0.05 level (2-tailed).

**P < .01, correlation is significant at the 0.01 level (2-tailed).

patients with T2DM. However, evidence suggests that Graves orbitopathy is more common and severe in patients with T2DM.[12] Moreover, body mass index and levels of anti-TSH receptor antibodies are higher in patients with T2DM than in those with type 1 DM and GD.[12] These data suggest the need for regular clinical and biochemical screening for thyroid disease as well as for T2DM. Figure 5 shows the hypothesis mechanism underlying the effect of hepatic function in Graves disease with T2DM. This cross-sectional study suggested that diabetes may affect liver function in patients with GD. Additionally, the impaired liver function may also regulate the production of thyroid hormone. Therefore, liver function should be considered monitoring in patients with both GD and T2DM.

4.1. Clinical implications of T2DM and GD coexistence

Nearly 50% of patients with GD have some degree of glucose intolerance.[13] Theoretically, increased expression of the hepatic glucose transporter type 2 gene is present in hyperthyroidism.[8]

Table 8

The correlation of the factors of the study subjects with HbA1C ≥6.5% of DM group.

	Relevant factors	ALK-P	GOT	GPT	T3	FT4	TSH
ALK-P	Coefficiency		−0.015	0.609	0.067	0.199	0.008
	P		.969	.147	.844	.557	.983
GOT	Coefficiency	−0.015		−0.308	−0.518	0.487	−0.105
	P	.969		.502	.153	.184	.822
GPT	Coefficiency	0.609	−0.308		−0.014	0.242	0.562
	P	.147	.502		.976	.602	.245
T3	Coefficiency	0.067	−0.518	−0.014		−0.053	0.596
	P	.844	.153	.976		.877	.090
FT4	Coefficiency	0.199	0.487	0.242	−0.053		−0.067
	P	.557	.184	.602	.877		.864
TSH	Coefficiency	0.008	−0.105	0.562	0.596	−0.067	
	P	.983	.822	.245	.090	.864	

ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, T_3 = triiodothyronine, TSH = thyroid-stimulating hormone.

Table 9

The association between the level of serum GOT and FT4, ALK-P, and TSH by regression analysis with HbA1C < 6.5% of DM group.

	Parameter estimate	r^2	Standardized coefficients (β)	*P* value
GOT-FT4	0.827	0.425	0.652	0.02*
ALK-P-TSH	86.932	0.245	−0.495	0.04*

ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, HbA1C = glycated hemoglobin A1C, TSH = thyroid-stimulating hormone.
*$P < .05$.

Table 10

The association between the level of serum GOT and FT4, ALK-P, and TSH by regression analysis with HbA1C ≥6.5% of DM group.

	Parameter estimate	r^2	Standardized coefficients (β)	*P* value
GOT-FT4	59.644	0.012	.108	.78
ALK-P-TSH	256.23	0.098	.313	.61

ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, HbA1C = glycated hemoglobin A1C, TSH = thyroid-stimulating hormone.

GD and hyperthyroidism have similar physiology, including increased insulin resistance, increased glucagon secretion, increased hepatic glucose production, and elevated levels of catecholamines.[14,15] Insulin resistance is the key factor connecting thyroid dysfunction and T2DM.

Excess circulating thyroid hormones in hyperthyroidism is associated with poor glycemic control. Thyroid hormones can influence multiple organs, thus hampering glucose homeostasis. They enhance gastrointestinal mobility and increase glucose absorption and gluconeogenesis in the liver. The enhanced glycogenolysis and increased hepatic glucose output induce hyperinsulinemia and glucose intolerance, causing peripheral insulin resistance.[16,17] Intracellular T3 also plays a role in insulin sensitivity.[13] T2DM is characterized by undetectable levels of insulin and hepatic insulin resistance as well as increased liver fat content, impaired insulin clearance, and increased hepatic glucose production.[18] Thus, thyroid dysfunction can aggravate T2DM, and diabetes can weaken thyroid function; the main mechanism may be related to the liver system.

4.2. Liver function in patients with GD and T2DM

In the healthy population, the thyroid gland secretes thyroxine (T4) and T3, and the conversion from T4 to T3 occurs in the extrathyroidal tissue, such as that in the liver and kidney.[19] The activation or inactivation of T4 depends on the deiodinase enzyme system. Approximately 30% to 40% of the extrathyroidal production of T3 occurs in the liver. The liver also synthesizes several plasma proteins that bind the lipophilic thyroid hormones, creating a large rapidly exchangeable pool of circulating hormones.[20] We simplified the mechanism in Figure 4.

In our study population, HbA1C was correlated with liver function but not with thyroid function. To establish whether comorbidities affect these results, we separated the patients into 2 groups, a T2DM and non-T2DM group. Notably, impaired liver function and higher levels of FT4 were identified in the T2DM group. The mean level of TSH was lower in this group, but the difference was nonsignificant. Lower TSH and higher FT4 levels in the T2DM group may indicate poorer control of thyroid function or that thyroid function is more difficult to control. Moreover, GOT and GPT levels were significantly higher in the T2DM group, and the mean ALK-P level was also higher, but the difference was nonsignificant. In the T2DM group, GPT was positively associated with T3, which was not observed in the non-T2DM group. The conversion of T4 to T3 in the liver may be impaired in liver injury (Fig. 4). In our study, this relationship was also revealed to affect the liver pathways.

4.3. Liver function and disease control in patients with T2DM

Patients with diabetes with hyperthyroidism experience deteriorating glycemic control, and thyrotoxicosis has been demonstrated to precipitate uncontrolled complications in these patients.[21] Thus, disease control may be a crucial factor in liver function. To investigate the role of diabetic control in liver function in patients with GD in depth, we divided the T2DM group into 2 groups according to their HbA1C levels. Those with HbA1C ≥6.5% were regarded as the poor-control group. Liver function parameters were significantly higher in these patients. Poor liver function can be clearly identified in patients with uncontrolled T2DM. In the HbA1C <6.5% group, the mean levels of GOT and GPT were relatively normal even in patients with T2DM. We posit that the control of T2DM can alter liver function in patients with GD.

In the within-group analysis, GOT was positively correlated with FT4 in the effective-control group. When T2DM is effectively controlled, the control of GD still influences liver

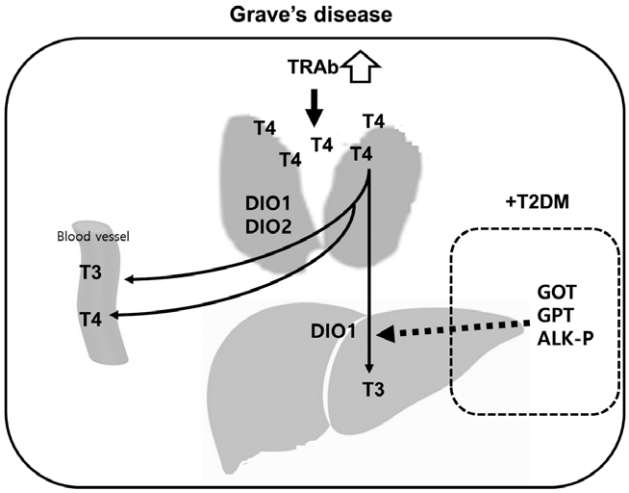

Figure 5. Hypothesis mechanism underlying the effect of hepatic function in Graves disease with T2DM. Increased TRAb would damage thyroid gland and make numerous T4 released in the vessels and the liver. The DIO1 plays the role of extrathyroidal deiodination of T4 in the liver. As diabetes affects liver function, like GOT, GPT, or ALK-P, the T3 level was affected due to possible impaired deiodination. ALK-P = alkaline phosphatase, DIO = iodothyronine deiodinases, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, T2DM = type 2 diabetes mellitus, T_3 = triiodothyronine, T_4 = thyroxine, TRAb = thyrotrophin receptor antibody.

function. In the HbA1C ≥6.5% group, no significant correlation was identified between factors. The conversion of T4 to active T3 or inactive T3 (reverse T3) may be affected by the type of deiodinase.[21] However, the mechanism is so complex that no specific factor determines the pathway for this conversion. In addition, our nonsignificant statistical results may be caused by many cofactors not considered in the present study, such as drug compliance, education, and socioeconomic status.

The coexistence of DM and thyroid diseases is common and often leads to complications, causing organ failure. GD and T2DM damage the liver individually,[2,3,6] but few studies have focused on liver injury when these diseases coexist. We posit that the 2 diseases synergistically aggravate liver injury through similar or different pathways. Although the mechanism remains uncertain, the monitoring of liver function may not only prevent liver failure but also control the coexistence of these diseases.

This study has some limitations. First, the number of cases (77 patients) enrolled in this study was relatively small, which might have led to sampling bias. Second, the patients in our study were of relatively advanced age (mean = 63 years); in epidemiology, GD is more common in younger patients. In addition, older patients are more likely to have comorbidities not included in this study, although we excluded most liver diseases. Finally, we did not analyze the medications being used by the patients with GD and T2DM. Liver function may be influenced by medication, especially in patients with GD. T2DM is also controlled through medication. Investigating liver function in patients with GD and T2DM is warranted, but the results should be interpreted with caution, with individual differences considered.

5. Conclusion

GD and T2DM are common metabolic diseases that share some clinical similarities. They not only affect metabolism but also other systems. Complications negatively affect patients and their families and can be expensive to treat. In this study, disease control was poor when these 2 diseases coexisted. The data from this single-center study revealed that diabetes has some effect on liver function in patients with GD. In patients with T2DM, thyroid function control deteriorates when liver function is impaired. GPT is correlated with T3 levels but not with FT4 levels, which indicates that the deiodination in the liver is impaired. This phenomenon was not identified in the non-T2DM population. With early detection of abnormal liver function in patients with GD and T2DM, the development of comorbidities can be limited, and disease management can be enhanced.

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