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
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 modification, 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 synergistic 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 who 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. 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 glumatate 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.
3.3. Comparison of factors in the study population

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
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 \( \beta = .466, r^2 = .127, P = .127 \) (Table 5) and DM group \( \beta = .439, r^2 = .192, P = .028 \) (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
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 ($\beta = -0.495$, $r^2 = .245$, $P = .04$) (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
patients with T2DM. However, evidence suggests that Graves orbitopathy is more common and severe in patients with T2DM.\(^\text{[12]}\) 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.\(^\text{[12]}\) 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.\(^\text{[13]}\) Theoretically, increased expression of the hepatic glucose transporter type 2 gene is present in hyperthyroidism.\(^\text{[14]}\)
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 this group compared to 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.

### Table 8

| Relevant factors | ALK-P | GOT | GPT | T3 | FT4 | TSH |
|-----------------|-------|-----|-----|----|-----|-----|
| ALK-P Coefficiency | 0.015 | -0.015 | 0.609 | 0.067 | 0.199 | 0.008 |
| P | 0.960 | 0.147 | 0.844 | 0.557 | 0.983 |

### Table 9

| Parameter | Estimate | r | 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* |

### Table 10

| Parameter | Estimate | r | Standardized coefficients (β) | P value |
|-----------|----------|---|-------------------------------|---------|
| GOT-FT4   | 59.644   | 0.012 | .108 | .78 |
| ALK-P-TSH | 256.23   | 0.098 | .313 | .61 |

**Note:**
- ALK-P = alkaline phosphatase, FT4 = free thyroxine, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HbA1C = glycated hemoglobin A1C, T3 = triiodothyronine, TSH = thyroid-stimulating hormone.
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. 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, 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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