

ORIGINAL ARTICLE

Liver enzyme profile and progression in association with thyroid autoimmunity in Graves' disease

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Abstract

Objective: To investigate the associations of Graves' disease (GD) severity, autoimmunity and longitudinal liver enzyme changes with time in a cohort with well-characterized GD.

Design: Retrospective cohort study.

Patients: Patients diagnosed with Graves' disease, treated at Royal Prince Alfred Hospital Sydney, Adult Thyroid Clinic from 2000 to 2012 inclusive.

Measurements: Inclusion criteria were patients with a complete set of TSH, FT4, FT3, liver enzymes and TSH receptor antibody (TRAb) results prior to commencement of thionamide therapy.

Results: Of the 146 patients who had complete results, 69 (47%) had at least one abnormal liver enzyme. Gamma glutamyltransferase (GGT) was most frequently abnormal (74%), followed by alanine aminotransferase (ALT) (57%), alkaline phosphatase (ALP) (39%) and then aspartate aminotransferase (AST) (29%). Subsequent to thyroid function normalization, 78% of the liver enzymes were normalized, 10% were persistently abnormal and 12% were lost to follow-up. Circulating TRAb, FT3 and FT4 results were categorized into mild, moderate and severe elevations. At univariate regression analyses, TRAb, FT3 and FT4 levels were each significantly associated with abnormal liver enzyme profile. Multivariate regression including TRAb, FT3 and FT4 as independent variables demonstrated FT3 and FT4 were more strongly associated with abnormal liver profile than TRAb. However, the initial FT3 and FT4 levels were not associated with abnormal liver profile in the subgroup with persistently abnormal liver profile.

Conclusion: Graves' disease is commonly associated with abnormal liver enzymes, and most commonly with abnormal levels of GGT, and that an abnormal liver enzyme profile is more directly linked to the degree of thyrotoxicosis than levels of TRAb.

KEYWORDS

Graves' disease, liver enzyme, thyroid hormone, thyrotoxicosis, TSH receptor antibody

1 | INTRODUCTION

Abnormal liver enzyme levels are commonly detected at the onset of Graves' disease (GD), with the reported prevalence ranging from 37% to 78% during the acute thyrotoxic phase of the disease.¹⁻⁵ Most of the studies have described alkaline phosphatase (ALP) as the most common liver enzyme elevated, in up to nearly two-thirds of studied cases.^{1,3-11} The degree of thyrotoxicosis, age, sex and ethnicity have all been reported to be associated with liver enzyme abnormalities during the acute hyperthyroid state.^{2,8,10,12} However, conflicting findings disputing the significance of thyroid hormone levels and liver function abnormality have been reported in similarly large studies.^{1,7} Although Graves' disease is probably the most common cause of overt hyperthyroidism, most of the published studies examining liver enzymes have not differentiated the cause of hyperthyroidism. To date, the thyrotropin receptor antibody (TRAb), which includes the stimulating agent of TSH receptor and thyroid hormone production,¹³ has also been linked to biochemical liver function abnormalities, in the Chinese population only.^{2,3,12} Furthermore, there is very limited data on longitudinal liver enzyme profiles after normalization of thyroid function in patients with Graves' disease. Given that background, the aim of this study was to investigate the acute presenting patterns and factors associated with liver enzyme abnormalities in a population with well characterised Graves' disease, as well as the subsequent liver enzyme changes following treatment, in a mixed ethnic cohort.

2 | MATERIALS AND METHODS

An audit of the Royal Prince Alfred Hospital Adult Thyroid Clinic, Sydney, Australia, database from 2000 to 2012 inclusive was undertaken to determine the liver enzyme profiles in patients with GD at

baseline and after therapy. All patients aged 18 years or over with complete medical records, plus a blood TSH level below the lower limit of the normal laboratory reference range with an elevated free T3 and/or free T4 above the normal reference range at the time of GD diagnosis were included. Graves' disease was confirmed by an elevated TSH receptor antibody (TRAb) (>1.0 U/L) in serum at the time of diagnosis.¹³ The TRAb measure was performed on either the B-R-A-H-M-S TRAK HUMAN RIA or the Roche Elecsys Anti-TSHR assay. Patients were categorized into one of seven ethnicity groups based on the self-reported heritage (adapted from Alharbi et al¹⁴).

The liver enzymes, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP and gamma glutamyltransferase (GGT), prior to commencement of anti-thyroid medications, were tested on a standard biochemical autoanalyser platform. An abnormal liver profile was defined as one or more liver enzyme abnormality, outside the laboratory reported normal assay range, being present. A repeat liver enzyme profile of the same enzymes performed after patients achieved biochemical euthyroidism (defined as free T3 and free T4 in the normal range as well as blood TSH measure within the normal reference range), was included for analysis. We included any patients with no reported known history of active liver disease or being on hepatotoxic medications. The cohort included one patient with a history of chronic hepatitis B. This patient had an abnormal liver enzyme profile on initial presentation and was not receiving antiviral therapy; the liver enzyme abnormality resolved when thyroid hormone normalized. One patient only was excluded from the study as having hepatitis C receiving interferon alpha treatment. There was no history of alcohol dependence or heavy alcohol usage in any patients in the cohort.

Considering the non-linear reading of TRAb, FT3 and FT4 results at high levels, the TRAb level was categorized into mild, moderate and severe elevations, as TRAb ≤ 10 IU/L, TRAb = 10.1-20 and TRAb > 20,

TABLE 1 Characteristics of patients and liver enzyme results at the diagnosis of Graves' disease (GD)

	Total cohort	Normal liver function test (LFT)	Abnormal LFT	Statistical test between normal vs abnormal LFT
Number of patients	146	77	69	
Gender—Female	119 (82%)	65 (84%)	54 (78%)	<i>P</i> = 0.40
Mean age at GD diagnosis (y)	35.2	33.5	37.2	<i>P</i> = 0.06
Family history of thyroid disorder	57 (39%)	31 (40%)	26 (38%)	<i>P</i> = 0.75
Lifelong non-smoker	94 (64%)	52 (68%)	42 (61%)	<i>P</i> = 0.40
Ethnicity				
European	58 (40%)	34 (44%).	24 (35%).	<i>P</i> = 0.25
East Asian	70 (48%)	33 (43%).	37 (54%).	<i>P</i> = 0.19
South Asian	3 (2%)	2 (3%).	1 (1%).	<i>P</i> = 0.63
Middle Eastern	5 (3%)	4 (5%).	1 (1%).	<i>P</i> = 0.21
African	1 (1%)	0 (0%).	1 (1%).	<i>P</i> = 0.29
Australian Aboriginal	8 (5%)	3 (4%).	5 (7%).	<i>P</i> = 0.37
Other	1 (1%)	1 (1%).	0 (0%).	<i>P</i> = 0.34

Note: East Asian includes East Asian & South East Asian countries. South Asian includes sub-Himalayan South Asian Association for Regional Cooperation (SAARC) countries.

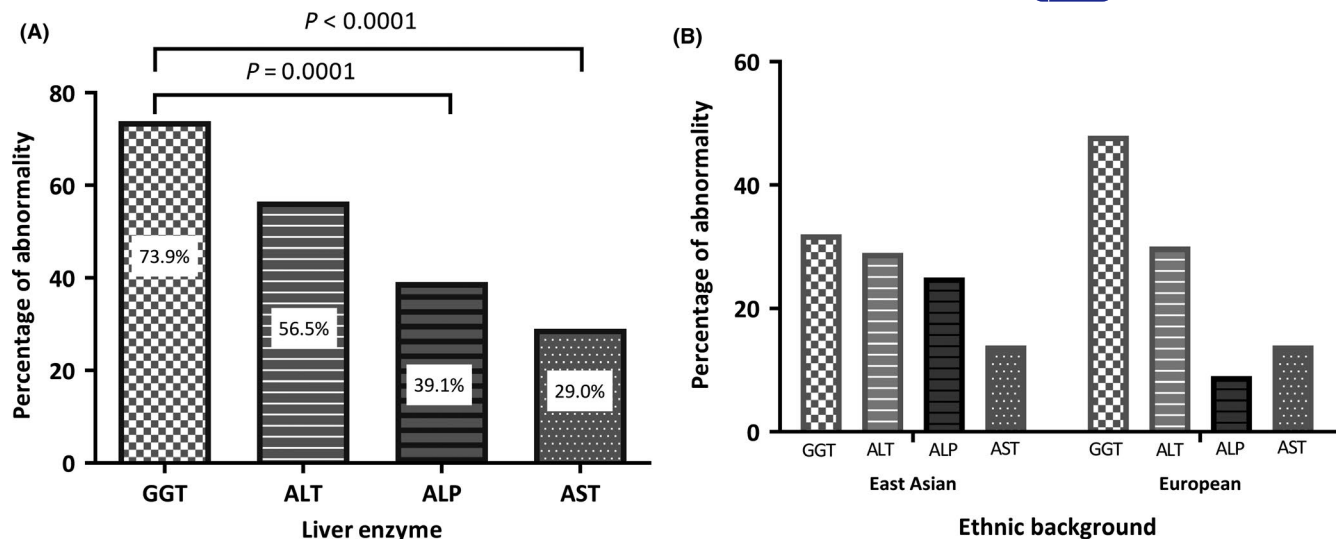


FIGURE 1 A, Distribution of liver enzyme abnormalities at diagnosis. B, Abnormal liver enzyme patterns: East Asian vs European background

respectively. FT3 was categorized by multiples of the upper limit of normal (ULN), as FT3 $\leq 2.5 \times$ ULN, FT3 at $2.51-5 \times$ ULN, and FT3 $> 5 \times$ ULN, and FT4 by $\leq 2 \times$ ULN, FT4 at $2.1-3 \times$ ULN, and FT4 $> 3 \times$ ULN.

Chi-square tests were used to analyse between-group differences, and logistic regression was performed to analyse the correlation between potential risk factors and abnormal liver enzyme profiles. Statistical analyses were performed on IBM® SPSS® Statistics Version 24 and GRAPHPAD® Prism 7. *P* values of <0.05 were considered statistically significant.

3 | RESULTS

There were 146 patients diagnosed with Graves' disease with a complete medical record and blood tests as described, between the years 2000 and 2012 (Table 1). Eighty-two per cent of the cohort were female, with mean age \pm SD for GD diagnosis of 35.2 ± 11.5 years, and median 33 years. Thirty-nine per cent of the entire cohort had a family history of thyroid disorder and 64% were lifelong non-smokers. The predominant ethnic background was East Asian (48%), followed by European (40%). Apart from a trend towards significance ($P = 0.06$) for mean age of GD diagnosis between patients with normal and abnormal liver function results, there were no other patient clinical characteristics associated with an abnormal liver enzyme profile (Table 1). Overall, 75% of patients received carbimazole and 25% received PTU.

Among the 146 patients, 69 (47%) had at least one abnormal liver enzyme. Among the liver enzymes, the GGT was most frequent abnormality, in 74% of patients, followed by ALT (56.5%), ALP (39.1%) and AST (29.0%; Figure 1A). In individuals with East Asian background, GGT and ALP abnormality were found in 32% and 25% of the liver enzyme abnormalities, whereas 48% and 9% of those liver enzyme abnormalities, respectively, were noted among the European descendants (Figure 1B).

By logistic regression analyses, severely elevated TRAb (>20 IU/L) was significantly associated with the presence of one or more liver enzyme abnormality ($P = 0.008$; Table 2). Free T3 and free T4 were also independently associated with the presence of abnormal liver enzymes. Both severely and moderately elevated FT3 were significantly associated with at least one abnormal liver enzyme (OR = 7.32, $P < 0.001$ and OR 8.57, $P < 0.001$ respectively; Table 2). Having moderately elevated FT4 was significantly associated with an abnormal liver enzyme profile (Odds Ratio 2.65, $P = 0.01$), whereas severely elevated FT4 carried a much greater odds ratio, of 10.9 ($P < 0.001$; Table 2). However, neither TRAb, nor FT4 or FT3 was associated with any specific individual liver enzyme elevation.

When combining the thyroid hormones (FT3 and FT4) and TSH receptor antibody (TRAb) results in a multivariable analysis, the TRAb level was no longer associated with abnormal liver enzymes (Table 3). In contrast, moderately elevated FT3 ($P = 0.002$) and severely elevated FT3 ($P = 0.02$), as well as severely elevated FT4 ($P = 0.01$), remained significantly associated with the presence of any liver enzyme abnormality. By multivariate logistic regression analysis including patient gender, age of diagnosis, family history of GD, smoking status and ethnicity, the relationship between TRAb and liver enzymes remained non-significant.

When patients attended follow-up and were found to be biochemically euthyroid, only $n = 7$ patients continued to have a persistently mild abnormal liver enzyme profile as: GGT (5/7), ALT (1/7), ALP (5/7) and AST (0/7) (Figure 2). None developed new-onset liver enzyme abnormalities that were not present at GD diagnosis.

4 | DISCUSSION

Liver enzyme abnormalities are a recognized as part of the spectrum of the acute hyperthyroid presentation. Although Graves' disease is

	Total = 69	Odds ratio (OR)	P value
TSH receptor antibody (TRAb) association with any liver enzyme elevation			
TRAb elevation			
Mild (TRAb \leq 10 IU/L)	23 (33.3%)	1	
Moderate (TRAb = 10.1-20 IU/L)	18 (26.1%)	1.9 (0.85-4.37)	0.116
Severe (TRAb > 20 IU/L)	28 (40.6%)	3.0 (1.33-6.92)	0.008
FT3 association with any liver enzyme elevation			
FT3 elevation			
Mild (FT3 \leq 2.5 \times ULN)	7 (10.1%)	1	
Moderate (2.5 \times ULN < FT3 \leq 5 \times ULN)	37 (53.6%)	7.32 (2.82-19.0)	<0.001
Severe (FT3 > 5 \times ULN)	25 (36.2%)	8.57 (3.05-24.1)	<0.001
FT4 association with any liver enzyme elevation			
FT4 elevation			
Mild (FT4 \leq 2 \times ULN)	21 (30.4%)	1	
Moderate (2 \times ULN < FT4 \leq 3 \times ULN)	29 (42%)	2.65 (1.26-5.56)	0.01
Severe (FT4 > 3 \times ULN)	19 (45.2%)	10.9 (3.29-35.8)	<0.001

TABLE 2 TSH receptor antibody (TRAb)/FT4/FT3 association with abnormal liver enzyme profile

TABLE 3 Multivariate logistic regression of abnormal liver function risk factors

Study variables	Odds ratio	P value
FT3		
Mild (FT3 \leq 2.5 \times ULN)	1	
Moderate (FT3 = 2.51-5 \times ULN)	5.23 (1.87-14.6)	0.002
Severe (FT3 > 5 \times ULN)	4.39 (1.27-15.2)	0.02
FT4		
Mild (FT4 \leq 2 \times ULN)	1	
Moderate (FT4 = 2.1-3 \times ULN)	1.45 (0.61-3.48)	0.4
Severe (FT4 > 3 \times ULN)	5.57 (1.52-20.5)	0.01
TRAb		
Mild (TRAb \leq 10 IU/L)	1	
Moderate (TRAb = 10.1-20 IU/L)	1.02 (0.40-2.64)	0.96
Severe (TRAb > 20 IU/L)	1.58 (0.63-4.01)	0.33

the most common cause of hyperthyroidism, many published studies have reported data combining all hyperthyroid diagnoses (Table 4). In this Graves' disease-specific cohort, we found 47% of patients presented with at least one abnormal liver enzyme. The frequency approximates data reported in the other GD-specific studies, where 35%-70% of study participants had at least one liver enzyme abnormality.^{2,3,12} Among the $n = 69$ patients with any liver enzyme abnormality in the current series, 74% had a GGT abnormality, followed by ALT (56.5%), ALP (39.1%) and AST (29%; Figure 1A). The distribution of liver enzyme abnormalities in this cohort was notably different from other previously reported GD-specific studies and other hyperthyroid studies (Table 4). Most studies reported ALP as the most commonly elevated liver enzyme. In our study, among individuals with East Asian background, GGT and ALP abnormalities were found in 32% and 25% of the liver enzyme abnormalities, whereas 48% and 9% of those liver enzyme abnormalities, respectively, were noted among the European descendants (Figure 1B). The

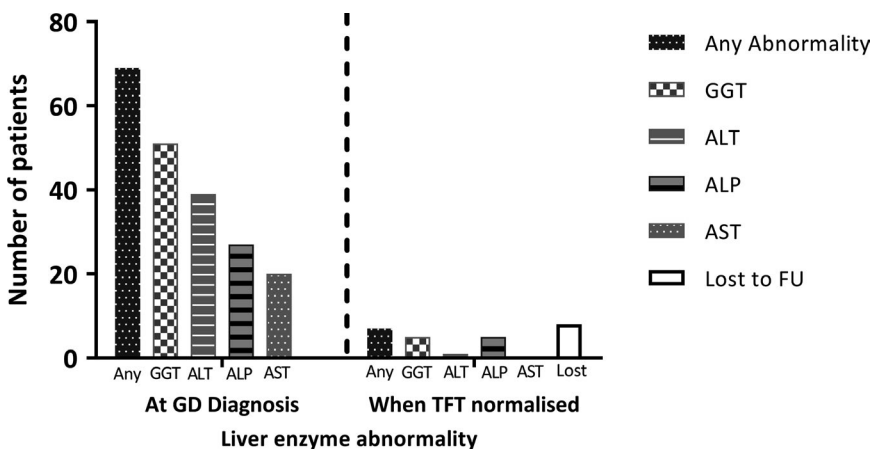


FIGURE 2 Liver enzyme longitudinal data

TABLE 4 Liver enzyme abnormality profiles in studies of Graves' disease (GD) specifically and all hyperthyroid patients

Liver enzyme abnormality in GD-specific studies									
Author and reference	Niculescu ¹⁸	Zhang ¹²	Li ²	He ³	Sarinnapakorn ⁴	Kubota ¹	Biscoveanu ⁵	Published year	
Sample size (n)	59	289	1070	236	112	30	30	2000	
Location	Romania	China	China	China	Thailand	Japan	US		
Abnormal LFT	35.6%	70.9%	66.3%	77.9%	No composite	76.7%	37%		
AST		32.2%		42.5		6.6%	17%		
ALT		52.7%		63.6		26.7%	26%		
ALP		45.9%		66.3		60%	33%		
GGT		38.5%		36.1		26.7%	24%		
Liver enzyme abnormality profiles in all hyperthyroid studies									
Author and reference	Lin ¹⁰	Niculescu ¹⁸	Gurlek ¹⁹	Huang ⁷	Fong ²⁰	Azizi ²¹	Thompson ⁸	Ashkar ¹¹	Perlin ⁹
Published year	2017	2016	1997	1994	1992	1982	1978	1971	1970
Sample size (n)	811 (TSH ≤ 0.02)	77	43	95	43	16	85	570	9
Location	US	Romania	Turkey	Taiwan	US	Iran	US	US	US
Abnormal LFT	45%	32.5%	60.5%	75.8%	100%		76%	15%	100%
AST	13%	20.7%	14%	27.4%			24%	6%	22%
ALT	13%	27.7%	23.3%	36.8%	67%		26%		
ALP	35%	44.2%	44.2%	64.2%	≥50%	50%	67%	9.6%	56%
GGT	2%		14%	16.8%		62%			

AST and ALT distributions, however, were similar between these two ethnic subgroups. Interestingly, there appears to be an ethnic difference between cases of GD with a liver enzyme abnormality. Two large studies in China with over 200 participants with GD^{3,12} demonstrated ALT and ALP as the most frequently detected liver enzyme abnormalities, compared with ALP predominantly in other studies.^{1,4,5} The cause for this difference is unclear and as liver and bone ALP isoenzymes were not differentiated in those studies, and it is unclear whether the ALP elevations reported were contributed to by bone-derived ALP.

Our study did not specifically exclude patients with potential liver function abnormalities related to hepatitis history, alcohol use or iatrogenic causes; however, the longitudinal data demonstrate that when patients achieved a hormonal euthyroid state, only 11% of individuals with initial liver enzyme abnormalities had any persistent abnormality, which was predominantly in the ALP and GGT. This longitudinal data provide evidence that the abnormal liver enzyme profile at acute hyperthyroid presentation is likely due to the hyperthyroid state, and the persistent cholestatic liver enzyme abnormality, albeit in a minority of cases, may in some cases be related to ongoing use of thionamides, as observed by other studies,^{4,7} even though the enzyme abnormalities in the current series were present before thionamides had been commenced, or possibly in the case of ALP may be bone-derived.

The univariate analysis identified FT3, FT4 and TRAb as three independent risk factors associated with a liver enzyme abnormality at diagnosis of GD (Table 2) whereas the multivariate logistic regression analysis of FT3, FT4 and TRAb demonstrated the elevation in liver enzymes was associated more strongly with FT3 and FT4 than TRAb (Table 3). In contrast, the multivariate analysis in the largest GD-specific study concluded that only FT4 and TRAb are strongly associated with hepatic dysfunction.¹² The average FT4 level reported by Zhang was 85.7 pmol/L (normal range: 12-22 pmol/L), which is approximately twice the average FT4 level in our cohort with similar reference range. At high FT4 and FT3 levels, many commercial immunoassays do not follow a linear correlation and this may not be addressed by logistic transformation of the data,^{15,16} hence our rationale to categorize TRAb, FT3, FT4 elevation in our analysis. In addition, FT3 and FT4 levels were to some degree independently correlated with the serum TRAb level (Table S1), leading to a partial collinear effect in the multivariable analysis. Although commercial TRAb assays are sensitive and specific,¹⁷ they also detect neutral and blocking TRAb. A thyroid stimulating immunoglobulin (TSI) assay, if it were accessible, may have better reflected the association of the pathogenic antibody with a liver enzyme abnormality.

Strengths of the current research are that GD was carefully defined in the cohort studied, liver enzymes were measured before any treatment of the hyperthyroidism, and follow-up liver enzymes were documented as GD was treated. Relative study weaknesses include the retrospective nature of the cohort limiting total patient numbers with complete data and no ALP isoenzyme measures, some loss to follow-up of patients and the absence of TSI measures in preference or in addition to the clinical TRAb measure. Despite these

shortcomings, we believe that the work adds valuable information about liver enzyme frequency and sub-type, and resolution in GD, which aids clinical interpretation in patients with GD and liver enzyme abnormalities.

In conclusion, our data identified the liver enzyme abnormality patterns and the normalization of liver enzymes in treated Graves' disease, and that the enzyme abnormality most commonly present was GGT. The elevation in liver enzymes was associated more strongly with FT3 and FT4 than TRAb. With the observation that liver enzyme abnormalities are common in untreated GD and that they may secondarily be affected by thionamide therapy in GD, we agree with the ATA 2016 guideline comment that baseline liver function enzyme tests should be considered before initiation of anti-thyroid medication.¹³ In addition, we assert that patients should be assured that liver enzyme abnormalities at diagnosis will most likely settle in time, with appropriate medical therapy as the patient becomes biochemically euthyroid.

CONFLICT OF INTEREST

The authors do not have conflict of interest to report related to this manuscript.

AUTHOR CONTRIBUTION

A.H. contributed to study conception, data collection, analysis and interpretation of data, and drafted the outline of the manuscript. S.T. contributed to study conception, analysis and interpretation of data and critical review of manuscript. E.C. contributed to study conception, interpretation of data and critical review of manuscript. S.A., S.M. and P.W. contributed to the interpretation of data and critical review of manuscript.

ETHICAL APPROVAL

The study was approved by the Sydney Local Health District – RPAH, Human Research Ethics Committee.

DATA ACCESSIBILITY

The data that support the findings of this study are available on reasonable request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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