Original Article

Prevalence of T3 Toxicosis in Thai Patients with Thyrotoxicosis

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Objective: To examine the prevalence of T3 toxicosis in Thai ambulatory patients with thyrotoxicosis.

Materials and Methods: The present cross-sectional retrospective study in newly diagnosed thyrotoxicosis patients was performed at the outpatient department of Siriraj Hospital (Bangkok, Thailand) between January 2009 and December 2013. Recorded data included age, gender, current residence, duration of symptoms, etiology, and results of thyroid function tests. Patients were categorized into the T3, T4, or T3 and T4 toxicosis groups.

Results: Three hundred fourteen thyrotoxicosis patients were included. The mean age was 44.1 years, and 69% were female. The causes of thyrotoxicosis were Graves' disease (93.3%), toxic adenoma/toxic multinodular goiter (2.9%), and subacute/painless thyroiditis (3.8%). The prevalence of T3 toxicosis and T4 toxicosis was 3.5% and 10.8%, respectively. The majority of patients with T3 toxicosis were male and residing outside Bangkok. The T3 toxicosis group had significantly lower level of total T3 compared with the T3 and T4 toxicosis group.

Conclusion: The 3.5% prevalence of T3 toxicosis observed in the present study suggests free T4 and thyroid stimulating hormone as the recommended initial laboratory investigations in Thai patients with suspected thyrotoxicosis.

Keywords: Prevalence, T3 toxicosis, Ambulatory Thai patients, Thyrotoxicosis

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Thyrotoxicosis is a commonly observed endocrine disorder in routine clinical practice. The etiologies of thyrotoxicosis include 1) Graves' disease [GD], 2) autonomous thyroid hormone secretion (e.g., toxic adenoma [TA], toxic multinodular goiter [TMNG], 3) destruction of follicles with release of thyroid hormone (e.g., subacute thyroiditis, painless thyroiditis), and 4) extrathyroidal sources of thyroid hormone (e.g., thyroid hormone administration, struma ovarii)[1,2].

Most thyrotoxicosis patients have T3 and T4 toxicosis, which is defined as increased levels of both triiodothyronine (T3) and thyroxine (T4), with a suppressed level of thyroid stimulating hormone [TSH]. However, some patients have T3 toxicosis or T4 toxicosis that are defined as increased T3 level with a normal T4 level and suppressed TSH level, and increased T4 level with a normal T3 level and suppressed TSH level, respectively[2]. According to the American Thyroid Association [ATA] 2016 guideline, although TSH alone has the highest sensitivity and specificity for diagnosing thyrotoxicosis, total T3, free T4, and TSH levels should all be measured to increase diagnostic accuracy in patients with a high index of suspicion[1]. Measurement of serum thyroid hormone level with TSH helps differentiate between primary and secondary hyperthyroidism, as well as between overt and subclinical hyperthyroidism.

Previous studies from the United States reported a prevalence of T3 toxicosis of 2 to 4%[3,4]. However, the prevalence of T3 toxicosis was higher (~11% to 12.5%) in studies from areas with known iodine deficiency[5,6]. In Thailand, Snabboon et al found a prevalence of T3 toxicosis of 16.02%, and they proposed that free T3 and TSH should be the initial tests for diagnosis of hyperthyroidism in an ambulatory setting[7]. However, Munsakul et al reported a prevalence of T3 toxicosis of only 2%, and they proposed that either free T4 with TSH or T3 with TSH can be used as the initial tests for diagnosis of hyperthyroidism[8]. Given this disparity in

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initial test recommendations and prevalence rates, the aim of the present study was to estimate the prevalence of T3 toxicosis among ambulatory thyrotoxicosis patients in Thailand. This data will help guide clinicians regarding choice of initial laboratory investigations in patients with suspected thyrotoxicosis.

Materials and Methods

Study design and setting

The present cross-sectional retrospective study was performed at the outpatient department of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand between January 2009 and December 2013. Siriraj Hospital is Thailand's largest university-based national tertiary referral center. The protocol for the present study was approved by the Siriraj Institutional Review Board [SIRB] (COA No. Si194/2015).

Data collection and measurements

Newly diagnosed thyrotoxicosis patients were identified from our center's OPD database using the ICD-10 code for thyrotoxicosis (E05.90). The inclusion criteria were adults aged 18 years or older with newly diagnosed thyrotoxicosis by history, physical examination, and thyroid function tests [TFT], including TSH, T3 (total or free form), and T4 (total or free form). Patients with one or more of the following were excluded, pregnancy, secondary hyperthyroidism, and/or received contrast media or took medications that affect thyroid hormone levels, such as levothyroxine, antithyroid drugs, amiodarone, lithium, pegylated interferon, and others, within the last three months. The baseline characteristics that were recorded included age, gender, current residence, duration of symptoms, etiologies, and TFTs.

Laboratory analysis

TFTs were measured by electrochemiluminescence [ECLIA] immunoassay using an automated chemistry analyzer (Modular P800 module e170 before January 2013, and cobas 8000 module e602 after January 2013, both Roche Diagnostics, Risch-Rotkreuz, Switzerland). The normal reference ranges between January 2009 and December 2012 were 80 to 180 ng/dL for total T3, 2 to 4.4 pg/mL for free T3, 4.5 to 11.7 µg/dL for total T4, 0.9 to 1.9 ng/dL for free T4, and 0.23 to 4 µIU/mL for TSH. The normal reference ranges between January and December 2013 were 80 to 200 ng/dL for total T3, 2 to 4.4 pg/mL for free T3, 5.1 to 14.1 µg/dL for total T4, 0.93 to 1.7 ng/dL for free T4, and 0.27 to 4.2 µIU/mL for TSH. The included patients were classified into one of the three following groups:

1) T3 and T4 toxicosis: patients with elevated T3, elevated T4, and suppressed TSH

2) T3 toxicosis: patients with elevated T3, normal T4, and suppressed TSH

3) T4 toxicosis: patients with elevated T4, normal T3, and suppressed TSH

Sample size calculation and statistical analysis

The sample size for the present study was calculated using the 16.02% prevalence of T3 toxicosis reported by Hollander et al[5]. Using the estimating proportion of one group sample size calculation method with an α error of 5% and a β error of 20%, a sample size of not less than 308 participants was calculated.

Statistical analyses were performed using SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous data are reported as mean ± standard deviation [SD] or median and interquartile range [IQR], and categorical data are reported as number and percentage. One-way analysis of variance [ANOVA] or Kruskal-Wallis test was used to analyze continuous data, and Chi-square test was used to evaluate categorical data. A *p*-value smaller than 0.05 was considered statistically significant.

Results

Three hundred fourteen thyrotoxicosis patients were included. The mean age of patients was 44.1±14.4 years, and 69% were female. Median (IQR) duration of thyrotoxicosis symptoms prior to diagnosis was two (1 to 5) months. Most patients (93.3%) were diagnosed with GD.

The demographic and clinical characteristics of patients are shown in Table 1. The prevalence of T3 toxicosis was 3.5% (11 of 314 patients; 95% CI 1.76 to 6.18). The etiologies of T3 toxicosis were GD (72.7%), subacute/painless thyroiditis (18.2%), and toxic adnenoma/TMNG (9.1%). The prevalence of T4 toxicosis was 10.8% (34 of 314 patients). There were no significant differences in gender, age, or duration of symptoms prior to diagnosis among the T3 toxicosis, T4 toxicosis, and T3 and T4 toxicosis groups. The total T3 level was 1.33 times above the upper normal limit [UNL] in the T3 toxicosis group, and 2.27 times above the UNL in the T3 and T4 toxicosis group. The free T4 level was 1.28 times above the UNL in the T4 toxicosis group, and 3.1 times above the UNL in the T3 and T4 toxicosis group. More patients with either T3 toxicosis or T4 toxicosis lived outside of Bangkok than

Table 1. Characteristics of the T3 toxicosis, T4 toxicosis, and T3 and T4 toxicosis groups

Characteristics	Total (n = 314)	T3 toxicosis (n = 11)	T4 toxicosis (n = 34)	T3 and T4 toxicosis (n = 269)	*p*-value
Female, n (%)	219 (69.7)	5 (45.5)	24 (70.6)	160 (70.6)	0.20
Age (year), mean ± SD	44.1±14.4	44.8±15.6	47.2±16.5	43.7±14.1	0.41
Duration of symptoms prior to diagnosis (month), median (IQR)	2 (1 to 5)	1 (0.75 to 3)	2 (1 to 3)	2 (1 to 5)	0.14
Etiologies, n (%)					
Graves' disease	293 (93.3)	8 (72.7)	25 (73.5)	260 (96.7)	<0.001
Toxic adenoma or TMNG	9 (2.9)	1 (9.1)	4 (11.8)	4 (1.5)	<0.001
Subacute or painless thyroiditis	12 (3.8)	2 (18.2)	5 (14.7)	5 (1.9)	<0.001
Laboratory					
Total T3 (pg/mL), mean ± SD	387±166	246±66	145±26	422±151	<0.001
Free T4 (μIU/mL), mean ± SD	5.1±2.2	1.47±0.3	2.28±0.5	5.56±1.9	<0.001
Current residence, n (%)					0.03
Bangkok	162 (51.6)	4 (36.4)	11 (32.4)	147 (54.6)	
Non-Bangkok	152 (48.4)	7 (63.6)	23 (67.6)	122 (45.4)	

SD = standard deviation; IQR = interquartile range; TMNG = toxic multinodular goiter

A *p*-value <0.05 indicates statistical significance

in Bangkok. Most GD patients were female (69.3%); however, 75% of the patients diagnosed as GD with T3 toxicosis were male. There were no significant differences in age or duration of symptoms for any of the three etiologies among the T3 toxicosis, T4 toxicosis, and T3 and T4 toxicosis groups.

Discussion

T3 toxicosis might be found in patients with iodine deficiency[2]. In animal studies, when serum iodine decreased, the ratio of monoiodotyrosine to diiodotyrosine, the ratio of T3 to T4, and the intrathyroidal deiodination of T4 into T3 increased. These autoregulation mechanisms increase T3 synthesis and thyroidal T3 secretion[9,10]. Previous studies showed a high prevalence of T3 toxicosis in iodine deficiency areas[5,6]. Thailand used to have a high prevalence of iodine deficiency disorders; however, an iodine deficiency disorder elimination program has been operating in Thailand for many years[11]. Munsakul et al reported a 2% prevalence of T3 toxicosis in Thai population during 1999 to 2000. In 2000, the median urinary iodine excretion [UIE] levels in pregnant women at first antenatal care visit in Thailand were 153 μg/L[11]. Later, Snabboon et al reported a 16.02% prevalence of T3 toxicosis in Thai population during 2000 to 2002[7]. The UIE levels in pregnant women at first antenatal care visit in Thailand were 111.6 and 106.8 μg/L in the years 2001 and 2002, respectively[11]. The prevalence of T3 toxicosis in the present study was 3.5%. The study in 2016 by Sriphrapradang et al found a prevalence of T3 toxicosis of 5.6% in Thai population[12]. The low prevalence of T3 toxicosis in our study might be explained by improvement in iodine status among Thai people because of the implementation of the iodine deficiency disorder elimination program. During our study period, median UIE levels in pregnant women were 117.8, 142, 181.2, 159.4, and 146.8 μg/L during the years 2009, 2010, 2011, 2012, and 2013, respectively[11]. The World Health Organization [WHO] cut-off for iodine deficiency in pregnancy was lower than 100 μg/L prior to 2007, and has been lower than 150 μg/L since 2007[13]. Furthermore, Iodine Global Network data reported the iodine status of school-age children in 2012, and the iodine status of pregnant women in 2014 in Thailand to be adequate[14].

The other possibility of T3 toxicosis is the earliest stage of hyperthyroidism. Woeber proposed that T3 toxicosis in GD patients that live in iodine sufficient areas represents a milder form or an earlier phase in the evolution of GD rather than a distinct pathophysiology, because of the same molar ratio of free T4/free T3 between T3 toxicosis and T3 and T4 toxicosis patients[15]. T3 toxicosis was mostly found in GD (72.7%) in our study, which is similar to the findings of other studies[3,8,12]. The total T3 level was significantly lower in the T3 toxicosis group than in the T3 and T4 toxicosis group ($p<0.001$), which indicates a milder form of thyrotoxicosis. However, the duration of symptoms prior to thyrotoxicosis diagnosis was not different between groups.

The most notable limitation of the present study is that most of our patients had total T3 measured, and total T3 can be affected by alteration of thyroid hormone binding proteins. However, the ATA 2016

guideline states that assays for estimating free T3 are less widely validated and less robust than those for free T4. Therefore, measurement of total T3 is frequently preferred over free T3 in clinical practice[1].

Conclusion

The low 3.5% prevalence of T3 toxicosis observed in the present study supports the recommendation of the Endocrine Society of Thailand to measure free T4 and TSH as the initial laboratory investigations in patients with a high index of suspicion for thyrotoxicosis[16]. However, in the case of low TSH with normal free T4, Total T3 should be measured to diagnose T3 toxicosis.

What is already known on this topic?

T3 toxicosis might be found in patients with iodine deficiency, in patients in the earliest stages of hyperthyroidism caused by GD, and in patients with autonomously functioning thyroid nodules. Disparate rates of prevalence of T3 toxicosis were reported from Thailand. Munsakul et al[8] reported a 2% prevalence of T3 toxicosis between 1999 and 2000, and Snabboon et al[7] reported a 16.02% prevalence between 2000 and 2002.

What this study adds?

Between 2009 and 2013, the prevalence of T3 toxicosis was 3.5% among ambulatory Thais diagnosed with thyrotoxicosis.

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Potential conflicts of interest

The authors declare no conflict of interest.

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