

RESEARCH ARTICLE

Transient Secondary Hypothyroidism and Thyroid Hormone Replacement Therapy in Pediatric Postoperative Cardiopulmonary Bypass

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Abstract: Background: To develop an understanding of current practices in the management of transient secondary hypothyroidism in pediatric postoperative cardiopulmonary bypass (CPB) patients.

Methods: Electronic survey comprising a 10-item questionnaire was sent to sixty-four high volume pediatric heart centers in the United States and United Kingdom. Survey participants included cardiologists, intensivists, cardiothoracic surgeons, and advanced practice providers. A retrospective chart review was also performed at a large regional referral center in the Midwest on subjects 0-18 years old who underwent CPB from 2005-2015. Information obtained included a unique identifier, date of birth, age, procedure performed, CPB time, date of surgery and date and type of Thyroid Function Test (TFT) ordered.

Results: 1,153 individuals from 64 congenital heart centers were contacted via email to participate in the electronic survey. In the 3-month response window, 129 completed surveys were received from cardiologists (55%), intensivists (17%), surgeons (15%), "other" (8%), and advanced practice providers (5%). This yielded a response rate of 11.2%. Of the 129 respondents, only 10 providers routinely order TFTs prior to (n=7) and after (n=1) CPB or when clinically indicated (n=2). All 10 providers order thyroid stimulating hormone test, 7 order thyroxine, and 3 order triiodothyronine. Only 1 provider routinely treats children with prophylactic thyroid hormone replacement therapy after CPB. Our retrospective review included 502 CPB events with 442 unique patients. Of the events, 20 patients received preoperative TFT testing while 11 received postoperative testing.

Conclusions: There is a general lack of uniformity in the evaluation, diagnosis, and treatment of transient secondary hypothyroidism in pediatric postoperative CPB patients.

Keywords: Cardiac function, physiology, cardiopulmonary bypass, CPB, congenital heart disease, CHD, hormones.

1. INTRODUCTION

Cardiopulmonary Bypass (CPB) is often used during surgery for the repair of complex congenital heart defects. The procedure itself can be disruptive of normal homeostatic mechanisms and cause various complications including transient secondary hypothyroidism [1, 2]. Similar to sick euthyroid syndrome (SES), transient secondary hypothyroidism causes a decrease in circulating thyroid hormone levels [3]. However, unlike SES, transient secondary hypothyroidism

has a significant effect on the hypothalamic pituitary axis causing a decrease in pituitary Thyroid Stimulating Hormone (TSH) secretion that ultimately results in decreased plasma thyroxine (T4) and triiodothyronine (T3) levels. Cardiopulmonary bypass and dopamine infusion augment the decrease in these hormones [1, 4, 5]. Trough T4 and T3 levels occur at 12-48 hours post surgery with levels beginning to return to baseline at 5-7 days postoperatively in patients without complications [6].

Thyroid hormone plays an integral role in cardiac and peripheral vascular function as it is a positive inotrope that increases heart rate through its permissive effects on β 1-adrenergic receptors [1-3]. In addition, thyroid hormone increases preload and decreases afterload, consequently in-

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creasing stroke volume resulting in increased cardiac output [7]. Thyroid levels are of particular importance in pediatric postoperative CPB patients due to their often fragile hemodynamic state.

Although the pathogenesis of postoperative secondary hypothyroidisms is not well understood, iatrogenic causes based on physiological pathways may explain the observation. The use of topical iodinated antiseptics in the perioperative period may lead to unregulated increases due to iodine absorption and consequently cause iodine-induced hypothyroidism [3]. Dopamine is often used postoperatively in CPB patients for hemodynamic support but has been shown to have an inhibitory effect on TSH secretion from the pituitary gland [1, 3-5].

Inflammatory factors peak postoperatively and may decrease thyroid hormone synthesis. In addition, concurrent altered tissue distribution of thyroid hormones and an increased demand for T4 during non-thyroidal disease may contribute to low plasma levels of T4 [1]. Holzer and colleagues propose that after significant oxidative stress, such as CPB, selenium is preferentially used for glutathione peroxidase at the expense of thyroxine 5'-deiodinase resulting in decreased T3 levels [8].

In spite of the research showing that low levels of thyroid hormones are associated with increased postoperative morbidity and mortality and patients may benefit from therapeutic replacement [2, 9, 10], there remains uncertainty and a lack of consensus on what the exact approach should be. As there is a lack of standardized guidelines or practice protocols for management of transient secondary hypothyroidism, the goal of this study was to develop an understanding of the current approach and determine if there is a consensus on prophylactic treatment in pediatric CPB patients across the United States and United Kingdom.

2. METHODS

The cross-sectional study used a 10-item questionnaire to evaluate trends regarding the use of Thyroid Function Tests (TFTs), pediatric endocrinology consults, and use of prophylactic thyroid hormone replacement therapy for pediatric CPB patients (Table 1). The study met exemption criteria as determined by the Spectrum Health Institutional Review Board. The web-based (www.surveymonkey.com) survey was dispersed via email to a total of 1,153 pediatric cardiologists, cardiothoracic surgeons, intensivists, and mid-level providers. The email addresses were sourced from the institutional websites of the U.S. News & World Report 50 top-ranked pediatric heart centers and all pediatric heart centers in the United Kingdom. An initial email was sent with a hyperlink to the survey, with two identical reminder emails sent out at two-week intervals for a total of three contact attempts. The email informed participants that completion of the survey implied consent to participate. The data was collected from November 2014 to January 2015. The results were downloaded from www.surveymonkey.com and stored in an electronic file on a secure server. Two-sided t-tests, chi-squared tests, and frequencies were tabulated using IBM SPSS Software 19.0.

Table 1. Questionnaire to evaluate trends regarding the use of thyroid function tests (TFTs), pediatric endocrinology consults, and use of prophylactic thyroid hormone replacement therapy for pediatric CPB patients.

1.	What is your current area of specialty or profession? a. Cardiologist b. Intensivist c. Mid-level provider d. Surgeon e. Other: _____
2.	Do you order routine thyroid function tests (TFTs) prior to or after cardiopulmonary bypass surgery? a. Yes b. No
3.	When do you order TFTs? (select all that apply) a. Before cardiopulmonary bypass surgery b. 1 week after cardiopulmonary bypass surgery c. Other: _____ d. Not applicable
4.	Do you routinely consult pediatric endocrinology prior to the TFT screening labs? a. Yes b. No
5.	Do you instead base your decision to order TFT screening labs on newborn screening results? a. Yes b. No
6.	If you do perform TFTs, which ones do you commonly use? (select all that apply) a. TSH test b. T ₄ tests c. T ₃ tests d. Thyroid-stimulating immunoglobulin (TSI) test e. Anti-thyroid antibody test, also known as thyroid peroxidase antibody test (TPOab) f. Other: _____
7.	Do you consult pediatric endocrinology after the TFT screening labs? a. Yes b. No
8.	Do you routinely treat children with thyroid hormone replacement therapy after cardiopulmonary bypass surgery? a. Yes b. No
9.	If yes, what dose do you use (select all that apply): a. 2µg/kg on the first day after surgery b. 1µg/kg on subsequent days c. Dependent on inotropic support d. Dependent on thyroid function test(s) result(s) e. Variable: _____
10.	Duration of thyroid hormone replacement therapy: a. 0-2 days b. 3-6 days c. 7-14 days d. > 2 weeks e. Other: _____

A retrospective chart review was conducted at a large regional referral center in the Midwest. The study was approved by the Spectrum Health Institutional Review Board with waiver of consent. All subjects between the ages of 0-18 who underwent CPB surgery at this center between 2005 and 2015 were eligible for inclusion. Information obtained from the record included a unique identifier, date of birth, age in years, procedure performed, CPB time, date of surgery, date of thyroid testing ordered, and type of TFT ordered. Any subject taking thyroid replacement medication and those with missing records were excluded. If a subject had serial pre- or post-operative testing, only the first event was considered. Subjects with both pre and post TFT testing were excluded from analysis to ensure independence between groups. Patients with multiple CPB surgeries were included in the analysis, with each CPB surgery tallied as a unique event. Patients meeting criteria were divided into three groups: no TFT testing, pre-operative TFT testing, and post-operative TFT testing based on TFT being ordered 90 days prior to or 7 days after surgery. Normality tests, Kruskal Wallis tests, and Dunn's Post Hoc analysis test were performed using SAS 9.4.

3. RESULTS

A total of 1,153 individuals from 64 congenital heart centers were contacted for participation in the survey study with responses received from 129 individuals, yielding a response rate of 11.2%. Cardiologists comprised the majority of completed responses at 55%, followed by intensivists at 17%, surgeons at 15%, "others" at 8%, and the remaining 5% by mid-level providers (Fig. 1). Of the 129 respondents, 7.7% indicated that they routinely order TFTs prior to or after CPB. Only one provider, a cardiologist, indicated that newborn screening results play a role in the decision to order TFT screening labs.

The respondents that order TFTs included 7 cardiologists, 1 intensivist, and 2 mid-level providers (Fig. 2). A chi-squared test was performed to evaluate provider differences in ordering TFTs; the results were not significant ($t=0.140$). All 10 providers order TSH, 7 order T4, 3 order T3, 1 orders free T4, and no provider indicated ordering thyroid-stimulating immunoglobulin or anti-thyroid antibody tests. The specific types of tests ordered by each provider as well as chi-squared values for interprovider differences are provided in Table 2. Thyroid function tests were ordered pri-

Respondents by Specialty

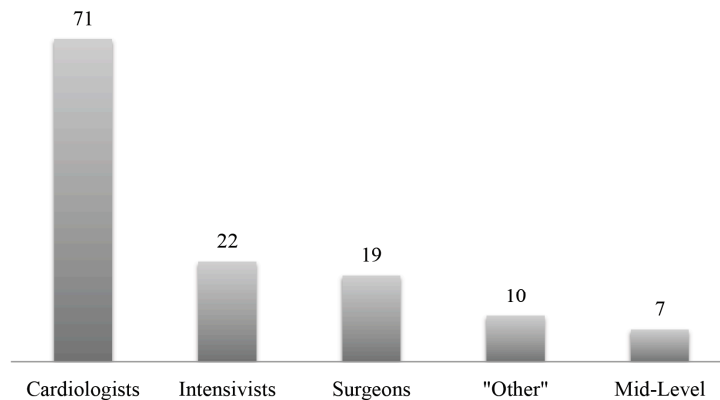


Fig. (1). The bar chart illustrates the respondents (n=129) by specialty (cardiologists, intensivists, surgeons, other, and mid-level providers).

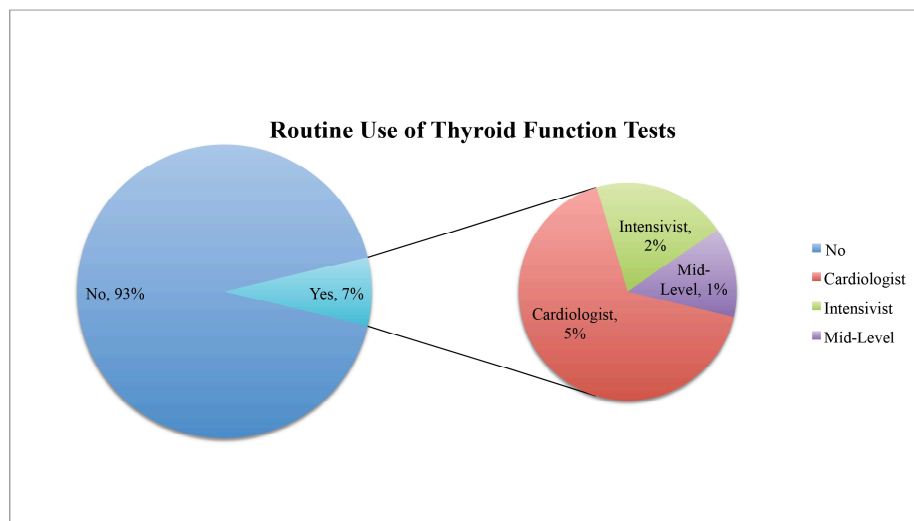


Fig. (2). The pie chart illustrates the number of providers out of the total of 129 respondents that routinely order thyroid function tests (n=10; 7%) and their area of specialty.

Table 2. Specific types of tests ordered by each provider.

Provider Type	TSH	T3*	T4**	Free T4	TSI	Anti-Thyroid Antibody
Cardiologist	✓	✓	✓			
Cardiologist	✓	✓	✓			
Cardiologist	✓	✓	✓			
Cardiologist	✓		✓			
Cardiologist	✓		✓			
Cardiologist	✓			✓		
Cardiologist	✓					
Intensivist	✓		✓			
Mid-Level	✓		✓			
Mid-Level	✓		✓			

*Chi-Squared test for inter-provider difference, $t=0.399$.

**Chi-Squared test for inter-provider difference, $t=0.399$.

marily before surgery (n=7); other responses included after surgery (n=1), and only when clinically indicated (n=2).

One cardiologist routinely consults pediatric endocrinology prior to TFT screening labs while a separate cardiologist and the two mid-level providers consult pediatric endocrinology after the results of the TFT screening labs. Only one of ten respondents, a mid-level provider, indicated treating children with prophylactic thyroid hormone replacement therapy after CPB surgery.

A total of 612 events were included in the retrospective chart review. The following numbers of events were excluded: 95 for incorrect CPB coding, 9 for having both pre and post-testing performed, 5 for chronic thyroid supplement replacement, and 1 for serial testing. After exclusions, 502

CPB events were included for analysis containing 442 unique patients (Fig. 3). Two patients had 4 events, 6 patients had 3 events, 42 patients had 2 events, and the remaining 392 patients each had one event recorded. A Kruskal Wallis test showed there was no significant difference of CPB time between the three groups ($p=0.9401$). However, there was a significant difference in age among the groups ($p=0.0005$) (Table 3).

Of the 502 events, 471 patients received no testing, 20 received preoperative testing, and 11 received post-operative testing. The specific testing in the 11 post-operative events included 11 TSH orders, 1 T3 order, 10 T4 orders, and no reverse T3 orders (Table 4). The timing of preoperative testing was variable; however, 54% of the post-operative testing occurred in the first 48 hours (Fig. 4).

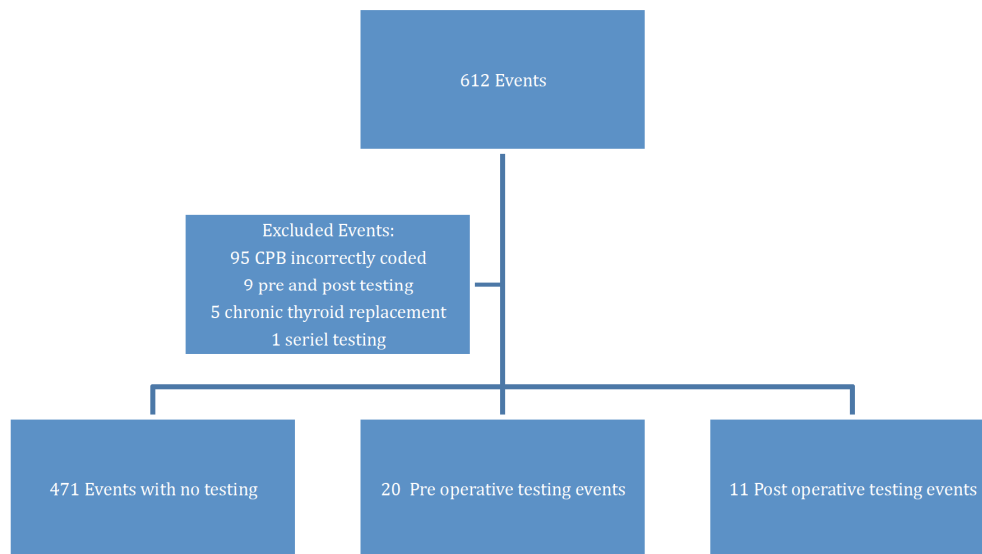


Fig. (3). This flow chart indicated the number of events enrolled in the trial, number of events excluded, and number of events in each arm of the study.

Table 3. Comparison of CPB time and age between the no testing, pre testing, and post testing groups.

	No Testing	Pre Testing	Post Testing	P Value
N	471	20	11	
Mean CPB Time	100.9	83.7	115.6	0.9401
Mean Age	7.0	4.5	2.2	0.0005

Table 4. Specific testing in the post-operative period.

Postoperative Event	TSH	T3	T4	rT3
Event 1	✓		✓	
Event 2	✓		✓	
Event 3	✓		✓	
Event 4	✓			
Event 5	✓		✓	
Event 6	✓		✓	
Event 7	✓	✓	✓	
Event 8	✓		✓	
Event 9	✓		✓	
Event 10	✓		✓	
Event 11	✓		✓	

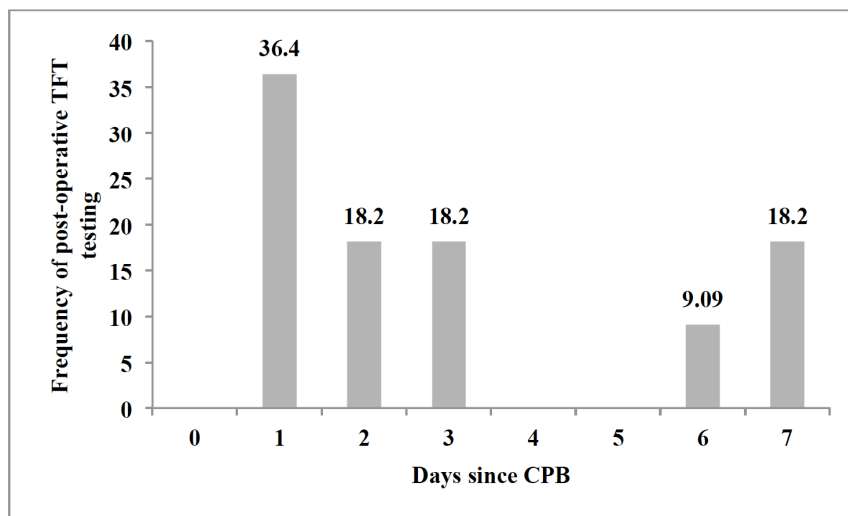


Fig. (4). This bar chart illustrates the frequency of when providers ordered TFTs.

CONCLUSION

The survey and retrospective review aimed to evaluate providers’ practice patterns regarding transient secondary hypothyroidism in the pediatric population. The survey results indicate that majority of providers do not routinely evaluate thyroid function in the perioperative period. Of the 10 providers that order TFTs, 70% order tests preopera-

tively. The retrospective review similarly found 65% of all TFT testing events were preoperative. Preoperative testing indicates a search for a pre-existing thyroid disorder. Only 1 provider in the survey routinely orders TFTs postoperatively. Our retrospective review demonstrated a postoperative event testing rate of 2.0%, only 11 individual events. Postoperative testing is where an expected transient secondary hypothyroidism may be observed requiring critical

management of patients. Furthermore, the survey demonstrates 1 provider routinely treats children with thyroid hormone replacement therapy after surgery, a practice that is not associated with increased adverse events [8, 11-13]. Both the survey and retrospective review results suggest a universal lack of observation of a known complication of CPB.

Initial experiments on supplemental T3 performed in animal models with ischemic myocardial injury demonstrated improved myocardial function and left ventricular contractility [10, 14-16]. These findings, coupled with a lack of adverse effects are promising for T3 supplementation in human subjects. However, studies in pediatric and adult patients have failed to reproduce consistent results [2, 11, 17-20].

There are several clinical trials in adults using T3 supplementation after cardiac surgery with conflicting results. A randomized prospective study involving 142 patients undergoing coronary artery bypass graft demonstrated T3 supplementation increased cardiac output and decreased systemic vascular resistance. No significant differences in morbidity, mortality, or postoperative management were found [17]. A similar prospective randomized trial with 170 participants on supplementation after CPB surgery reported higher cardiac index and lower inotropic requirements. Although there was no significant difference in mortality, the T3 supplementation group demonstrated lower postoperative myocardial ischemia, mechanical assistance, and pacemaker dependence [18]. Another blinded randomized controlled trial enrolled 211 adults to receive intravenous T3, dopamine, or saline. There were no significant differences in hemodynamic variables or inotropic support [11]. Moreover, none of these studies reported significant differences in postoperative mortality between patients with and without T3 supplementation [11, 17, 18]. It is likely that supplemental T3 improves hemodynamic parameters in adults, but its clinical significance remains unclear.

In pediatric cardiac surgery, four randomized controlled trials of T3 supplementation with variance in patient size, age, and cardiac morphology demonstrated improved myocardial function in neonates and younger children. A double-blind, placebo-controlled trial evaluated T3 supplementation of 40 patients undergoing cardiac surgery between the ages of 2 days and 11 years. Triiodothyronine supplementation resulted in improved cardiac output and systolic ventricular function and decreased intensive care measures, especially in longer procedures [9]. A similar trial in 42 patients undergoing congenital heart repair demonstrated T3 supplementation resulted in faster negative fluid balance. The study did not find significant differences between the treatment and placebo groups in adverse events, cardiac output, inotrope score, and length of intensive care unit or hospital days [13].

Two other trials were unique in their use of subgroup analysis based on the child's age. First, a randomized trial enrolled 28 pediatric patients who underwent surgery for congenital heart disease. Triiodothyronine levels did not change postoperative care, use of inotropes, mechanical ventilation or duration of hospital stay. An analysis of neonates

less than 1-month-old showed a significant decrease in the need for postoperative care and inotropic support. A trend toward shorter ventilator support and hospital stay was also noted in the same subgroup [21]. Second, a randomized placebo-controlled study with 198 patients under the age of 2 years did not show change in hemodynamic variables or decreased time to extubation on T3 supplementation. However, an analysis of neonates less than 5 months old demonstrated improved cardiac function, decreased inotropic support with a shorter time to extubation [12].

Interestingly, our retrospective review shows a significant difference in the mean age of those who received postoperative TFT testing compared with either preoperative or no TFT testing. The mean age for those receiving post-operative testing was 2.2 years old compared with 4.5 and 7.0 years old for pretesting and no testing, respectively. This could indicate that a younger population presented clinical cues that prompted providers to order TFTs. Or, it may simply be a unique observance of the literature among the small subset of providers who did order postoperative TFTs.

Despite lack of evidence of widespread T3 supplementation, researchers have focused on the best route of thyroid hormone administration. Most studies have evaluated intravenous T3 administration, however, there is a high cost, low availability, and burdensome storage conditions associated with this preparation [19]. One study evaluated oral T3 supplementation in children younger than 2 years of age undergoing CPB concluding that oral T3 is effective in maintaining normal range total and free T3 levels after CPB without increased adverse effects. Furthermore, they postulate oral T3 may be superior to intravenous forms since oral administration does not cause rapid serum rises in hormone levels [20].

Limitations. The survey study aimed for a comprehensive understanding of provider practice patterns and a high response rate. However, the brevity of the survey led to an inability in evaluating the providers' years of training or depth of understanding of transient secondary hypothyroidism. The survey study was limited in power due to the observed response rate, which also raises concern for non-response bias. Furthermore, evaluation of regional bias is not possible due to an inability to track response locale secondary to privacy concerns. Our retrospective study corroborated the results of our survey study, which hopefully alleviates some of the shortcomings. The retrospective review was limited by the number of pre- and post-operative test events making it difficult to draw conclusions regarding clinical effects of testing. A prospective randomized controlled trial would be better able to evaluate this.

The limited number of studies in the pediatric population on the clinical utility of T3 supplementation makes it difficult to reach a consensus and does not support standard practice protocols for prophylactic treatment. Perhaps, it is not surprising that both our survey and retrospective review suggests there exists a lack of awareness with inadequate testing for postoperative transient secondary hypothyroidism. However, current evidence is supportive for use of thyroid hormone screening and T3 supplementation in neo-

nates undergoing CPB. As thyroid hormones are critical for the normal development of the neonatal brain, transient secondary hypothyroidism may be detrimental for growth and development [12, 21]. Therefore, the promising trend in clinical improvement with T3 supplementation in younger pediatric patients demands additional, large randomized controlled trials with meaningful age stratification as well as timing, dosage and duration of supplementation [2, 12, 21].

These studies both indicate there is a general lack of uniformity in the evaluation, diagnosis and treatment of transient secondary hypothyroidism in pediatric postoperative CPB patients. This is not surprising considering the limited and often conflicting data on the clinical utility of T3 supplementation in this population. There is a clear need for large well-designed trials with meaningful age stratification to further determine the value of T3 supplementation in postoperative CPB patients.

LIST OF ABBREVIATIONS

CPB	=	Cardiopulmonary Bypass
SES	=	Sick Euthyroid Syndrome
TFT	=	Thyroid Function Test
TSH	=	Thyroid Stimulating Syndrome
T3	=	Triiodothyronine
T4	=	Thyroxine

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The survey study met exemption criteria as determined by the Spectrum Health Institutional Review Board.

The retrospective chart review study was approved by the Spectrum Health Institutional Review Board with waiver of consent.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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