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Kinetics and Time to Normalization of Thyroid Function during Antithyroid Drug Treatment of Hyperthyroidism in Yaoundé (Cameroon)

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Abstract

Introduction: Antithyroid drugs (ATD) are the first-line treatment of hyperthyroidism. The aim of this study was to assess the kinetics and the time to normalization of thyroid function during ATD treatment of hyperthyroidism in Yaoundé (Cameroon). **Methods:** We conducted a descriptive longitudinal study with retrospective recruitment over 5 years, from January 2016 to December 2020 and prospective recruitment over 2 years from July 2021 to July 2023, at the Endocrinology Department of the Central Hospital of Yaoundé. We included patients followed for hyperthyroidism and treated with ATD for 24 months who had at least two TSH and free T4 measurements taken at least 6 weeks apart. Normalization of thyroid function was defined as achieving normal TSH and free T4 levels sustained over at least two consecutive follow-up assessments. Associations between variables and failure to normalize thyroid function were assessed using the chi-square test or Fisher's exact test, as appropriate. Crude odds ratios (OR) with 95% confidence intervals were calculated. The significance threshold was set at 0.05. **Results:** We included 79 cases of hyperthyroidism treated with ATD. The mean age was 41.8 ± 14.3 years, with a predominance of Graves' disease (67.1%). The median initial TSH and initial free T4 was 0.005 (0.004 - 0.01) mU/L and 54.9 (31 - 78) ng/L. Normalization of TSH and of free T4 was achieved in 22.8% and 59.5% of patients, within a mean of 10.1 ± 6 months and 4.5 ± 3.4 months, respectively. Factors associated with failure to normalize free T4 were age ≥ 40 years (p = 0.001), presence of insomnia (p = 0.019) and unemployment (p = 0.002). No factor was associated with failure to normalize TSH. **Conclusion:** These data are useful in practice for therapeutic adjustments, while reducing the fre-

quency of follow-up tests and the overall cost of treating hyperthyroidism with ATD.

Keywords

Kinetics, Normalization, Thyroid Function, Hyperthyroidism, Antithyroid Drugs

1. Introduction

Hyperthyroidism is the most common endocrinopathy after diabetes mellitus, with an estimated overall prevalence of 1.3% [1]. In Africa, prevalence varies between 0.5% and 3% depending on the study [2]. In Cameroon, Nouedoui *et al.*, reported a prevalence of 24% in 1999 in a population of patients followed for various thyroid disorders [3]. It is a condition burdened with complications due to cardiac involvement, which is responsible for morbidity and mortality and for impaired quality of life [4]. The management of hyperthyroidism, depending on its cause, can be long and tedious. Therapeutic options include symptomatic treatment with beta-blockers and specific treatment with antithyroid drugs (ATD), surgery and radioactive iodine [5]. ATD are widely used as first-line treatment, whatever the aetiologies of hyperthyroidism; they inhibit thyroid peroxidase, thereby reducing thyroid hormone synthesis [6]. The duration of treatment varies according to the aetiology. In Graves' disease, it is approximately 12 to 18 months [7]. This treatment can be long and requires regular monitoring, because its side effects can themselves worsen the patient's prognosis. Euthyroidism is confirmed by the normalization of triiodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH), although serum TSH may remain low for several months after the start of ATD treatment [7] [8]. Biochemically, hyperthyroidism is characterized by TSH suppression; while during treatment, peripheral thyroid hormone levels normalize first, followed later by recovery of the hypothalamic–pituitary axis [8]. Data on the time to normalization of the thyrotropic axis during ATD treatment remain limited in Central Africa. Gebreyohannes *et al.*, in Ethiopia reported a mean normalization time of 13 ± 13.28 months for TSH and 11.53 ± 13.39 months for free T4, with age and initial T4 level as factors associated with normalization [9]. Given the lack of data in Cameroon, the need to adjust treatments while reducing the frequency of hormonal tests and the overall cost of care in our resource-limited context, we conducted this study, whose objective was to assess the kinetics and the time to normalization of thyroid function during ATD treatment of hyperthyroidism in Yaoundé (Cameroon).

2. Methodology

2.1. Study Design

We conducted a descriptive longitudinal study with retrospective recruitment

over 5 years, from January 2016 to December 2020 and prospective recruitment over 2 years from October 2021 to July 2023, at the Endocrinology Department of the Central Hospital of Yaoundé. This department is a specialized service in Metabolic diseases and Endocrinology that comprises an outpatient unit, a pharmacy, a biochemistry laboratory, a nutrition unit, and a clinic for the management of diabetic foot wounds. The outpatient department has a monthly flow of approximately 650 patients. Patients were recruited from among those attending this department.

Inclusion criteria: we included all patients followed for hyperthyroidism for at least 24 months under ATD and having at least 2 hormonal tests spaced at least 6 weeks apart.

Exclusion criteria: we excluded all patients with unusable medical records and patients lost to follow-up during the study.

Sample size: based on the prevalence of 24% of hyperthyroidism reported by Nouedoui *et al.*, in Cameroon in 1999 [3] and using the Cochran formula for estimating a proportion, with a 95% confidence level and a 10% margin of error, the minimum our sample size was estimated at 70 participants.

2.2. Data Collection

We used a pre-designed and pretested data collection form. It included sociodemographic data (age, sex, occupation, residence, marital status and education level), personal and family history of thyroid disease, clinical data (clinical signs of hyperthyroidism, causes of hyperthyroidism, thyroid status, drugs used, initial therapeutic doses and course under treatment), and biological data (TSH and free T4 values at the start of treatment, at least six weeks after treatment onset, and then every two months for 24 months).

For the retrospective phase: we used the complete records of patients meeting the inclusion criteria who had previously been followed for hyperthyroidism during the period mentioned above.

For the prospective phase: patients were enrolled and followed by the departmental endocrinology team under the principal investigator's coordination, with all clinical and therapeutic data systematically collected. Patients at their first consultation underwent a complete clinical examination, followed by an initial workup consisting of a complete blood count (CBC), a cervical ultrasound, and a hormonal assessment of TSH and free T4. TSH receptor antibodies (TRAb) were measured in patients with a clinical suspicion of Graves' disease. After clinical and paraclinical assessment, patients were classified by the underlying etiology of hyperthyroidism. Treatment was initiated with carbimazole 40 - 60 mg/day in one dose or propylthiouracil (PTU) 50 mg at 300 mg/day, given in three divided doses, selected according to patient tolerance and ATD availability. This baseline treatment was combined with symptomatic treatment with propranolol 80 - 120 mg in 2 or 3 doses. Patients were reviewed on day 10 of treatment with a CBC for clinical reassessment and screening for agranulocytosis, then at 6 weeks with a panel in-

cluding TSH and free T4 to adjust the treatment. The hormonal panel was thus monitored every two months for 24 months. Treatment was titrated based on free T4 concentrations. As free T4 levels decreased, the ATD dosage was progressively tapered by 10 - 20 mg for carbimazole and 50 - 100 mg for PTU to establish the minimum effective maintenance dose.

2.3. Outcome Measures

Normalization of thyroid function was assessed separately for TSH and free T4. It was defined as achieving values within the normal reference range (TSH: 0.4 - 4.3 mU/L; free T4: 7 - 17 ng/L), which had to be maintained for at least two consecutive follow-up assessments [10].

Failure to normalize thyroid function was defined as the absence of normalization of TSH and free T4.

Time to normalization of thyroid function was defined as the time required to obtain normal values of TSH and free T4.

2.4. Ethical Considerations

We obtained ethical clearance from the Institutional Ethics Committee of the Faculty of Medicine and Biomedical Sciences (FMSB), No. 0220, and a research authorization from the Central Hospital of Yaoundé, No. 089/23. All patients included in the prospective phase signed an informed consent form.

2.5. Statistical Analyses

The data collected were entered into the Statistical Package for the Social Sciences (SPSS), version 26.0. Quantitative variables were presented as medians (and interquartile range) or means (and standard deviation), depending on the distribution of the data. Qualitative variables were presented as counts and percentages. Student's t-test for independent samples was used to compare means. Associations between categorical variables and failure to normalize thyroid function were assessed using the chi-square test or Fisher's exact test, as appropriate. Crude odds ratios (OR) with 95% confidence intervals were calculated. A p-value below 0.05 was considered statistically significant.

3. Results

We identified 96 cases of hyperthyroidism. However, 17 cases were excluded, namely 15 in the retrospective phase and 2 in the prospective phase (**Figure 1**).

3.1. Characteristics of the Study Population

Women accounted for 79.7% of our study population. The mean age was 41.8 ± 14.3 years, and 57% of patients were unemployed. The median TSH level was 0.005 (0.004 - 0.01) mU/L, and Graves' disease was the most common etiology. Carbimazole was the most frequently used antithyroid drug (**Table 1**).

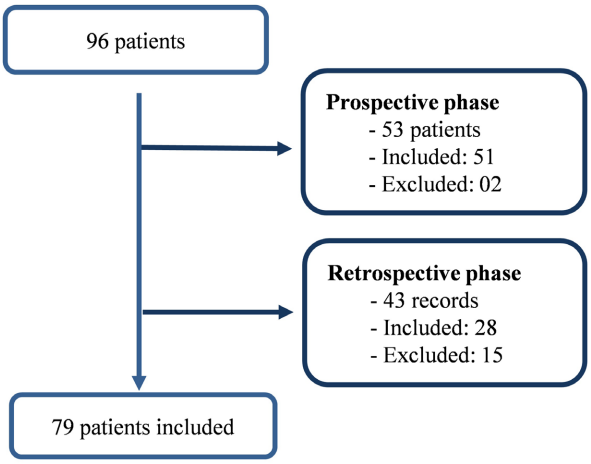

Figure 1. Flow diagram of the study population.

Table 1. General characteristics of the study population.

Variable	N = 79
Age (years), mean ± SD	41.8 ± 14.3
Sex, n (%)	
Female	63 (79.7)
Male	16 (20.3)
Occupation, n (%)	
Unemployed	45 (57)
Employed	34(43)
Signs and symptoms, n (%)	
Goitre	69 (87.3)
Palpitations	63 (79.7)
Weight loss	54 (68.4)
Heat intolerance	51 (64.6)
Mood disorders	41 (51.9)
Exophthalmos	39 (49.4)
Insomnia	32 (40.5)
Biological data, median (Q1 - Q3)	
Initial TSH, mU/L	0.005 (0.004 - 0.01)
Initial Free T4, ng/L	54.9 (31 - 78)
TRAb, IU/L	13.7 (7.9 - 34.2)
Aetiologies, n (%)	
Graves' disease	53 (67.1)
Toxic multinodular goitre	21 (26.6)
Toxic adenoma	5 (6.3)
ATS, n (%)	
Carbimazole	77 (97.5)
Propylthiouracil (PTU)	2 (2.5)

3.2. Kinetics of TSH during ATD Treatment

The TSH curve showed a flat trace from the start of treatment until the 9th month (M9), followed by an increase from M9 to M21, with a maximum value of 1.35 mU/L. We then observed a rapid decline from M21 to M24 of treatment (Figure 2).

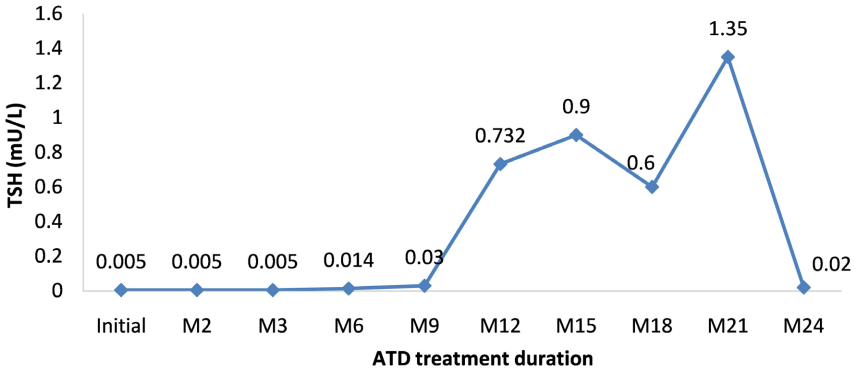

Figure 2. Kinetics of TSH during ATD treatment.

3.3. Kinetics of Free T4 during ATD Treatment

We noted a decrease in free T4 levels until the 2nd month (M2), followed by a relatively stable trace until the 24th month of treatment (Figure 3).

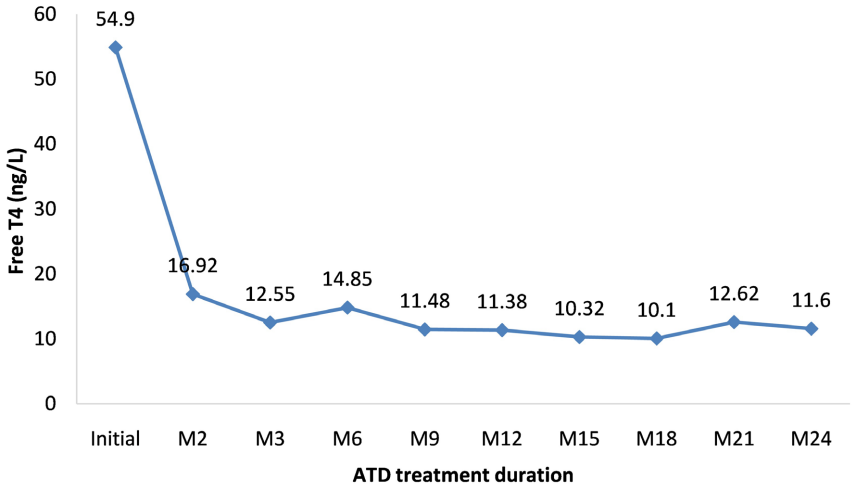

Figure 3. Kinetics of free T4 during ATD treatment.

3.4. Time to Normalization of Thyroid Function

Normalization of TSH was achieved in 18 patients (22.8%) within a mean time of 10.1 ± 6 months, with extremes ranging from 2 to 21 months. Normalization of free T4 was achieved in 47 patients (59.5%) within a mean time of 4.5 ± 3.4 months, with extremes ranging from 2 to 15 months (Table 2).

3.5. Factors Associated with Failure to Normalize TSH

We found no factor associated with failure to normalize TSH (Table 3).

Table 2. Time to normalization of thyroid function.

Variable	Results
TSH normalization	
Number, n (%)	18 (22.8)
Mean time (months), mean ± SD	10.1 ± 6
Minimum time (months)	2
Maximum time (months)	21
Free T4 normalization	
Number, n (%)	47 (59.5)
Mean time (months), mean ± SD	4.5 ± 3.4
Minimum time (months)	2
Maximum time (months)	15

SD: Standard deviation.

Table 3. Factors associated with failure to normalize TSH.

Variable	Not normalized (n = 61)	Normalized (n = 18)	OR (95% CI)	p
Age (years), n (%)				
<40	22 (36.1)	11 (61.1)	–	–
≥40	39 (63.9)	7 (38.9)	2.7 (0.9 - 8.2)	0.064
Sex, n (%)				
Male	12 (19.7)	4 (22.2)	0.8 (0.2 - 3.1)	0.813
Female	49 (80.3)	14 (77.8)	–	
Occupation, n (%)				
Unemployed	35(57.4)	10(55.6)	1.1 (0.4-3.1)	0.89
Employed	26 (42.6)	8 (44.4)	_	
Symptoms, n (%)				
Palpitations	47 (77)	16 (88.9)	1.7 (0.5 - 5.9)	0.366
Exophthalmos	30 (49.2)	9 (50)	0.9 (0.3 - 2.8)	0.945
Weight loss	39 (63.9)	15 (83.3)	1 (0.3 - 3.4)	0.931
Insomnia	25 (41)	7 (38.9)	0.8 (0.2 - 2.3)	0.693
Mood disorders	32 (52.4)	9 (50)	1.1 (0.4 - 3.2)	0.804
Heat intolerance	40 (65.6)	11 (61.1)	1.2 (0.4 - 3.8)	0.664
Goitre	53 (86.9)	16 (88.9)	1.2 (0.2 - 6.6)	0.798
Aetiologies, n (%)				
Graves' disease	38 (62.3)	15 (83.3)	1.5 (0.1 - 14.9)	0.715
Toxic multinodular goitre	19 (31.1)	2(11.1)	1.1 (0.9 - 13.3)	0.915
Toxic adenoma	4 (6.5)	1 (5.6)	–	

OR: Odd Ratio, CI: Confidence Interval.

3.6. Factors Associated with Failure to Normalize Free T4

Age ≥ 40 years, the presence of insomnia and being unemployed were associated with failure to normalize free T4. (Table 4)

Table 4. Factors associated with failure to normalize free T4.

Variable	Not normalized (n = 32)	Normalized (n= 47)	OR (95% CI)	p
Age (years), n (%)				
<40 years	6 (18.7)	27 (57.4)	–	–
≥40 years	26 (81.3)	20 (42.6)	5.8 (2.0 - 16.8)	**0.001**
Sex, n (%)				
Male	4 (12.5)	12 (25.5)	0.4 (0.1 - 1.4)	0.254
Female	28 (87.5)	35 (74.5)	–	
Occupation, n (%)				
Unemployed	25(78.1)	20(42.5)	4.8 (1.7-13.3)	**0.002**
Employed	7 (21.9)	27 (57.5)	_	
Symptoms, n (%)				
Palpitations	26 (81.2)	37 (78.7)	1.1 (0.3 - 3.6)	0.784
Exophthalmos	13 (40.6)	26 (55.3)	0.5 (0.2 - 1.3)	0.202
Weight loss	24 (75.0)	30 (63.8)	0.5 (0.1 - 1.5)	0.254
Goitre	25 (78.1)	44 (93.6)	0.3 (0.1 - 1.2)	0.144
Insomnia	18 (56.2)	14 (29.8)	3.0(1.2-7.7)	**0.019**
Mood disorders	19 (59.4)	22 (46.8)	1.8 (0.7 - 4.5)	0.210
Heat intolerance	17 (53.1)	34 (72.3)	0.5 (0.2 - 1.2)	0.112
Aetiologies, n (%)				
Graves' disease	18 (56.3)	35 (74.5)	3.0 (0.4 - 20.2)	0.240
Toxic multinodular goitre	11 (34.4)	10 (21.3)	1.3 (0.1 - 9.9)	0.759
Toxic adenoma	3 (9.4)	2 (4.3)	–	
Initial ATD dose (mg/day), n (%)				
Carbimazole				
≤40	13 (40.6)	19 (40.4)	1.0 (0.4 - 2.5)	0.970
>40	19 (59.4)	26 (55.3)	-	
Propylthiouracil (PTU)				
≥300	0(0)	2(4.3)	-	-

4. Discussion

We conducted a two-part longitudinal study aimed at assessing the kinetics and the time to normalization of thyroid function in patients with hyperthyroidism treated with ATD. We included 79 cases of hyperthyroidism, and the main findings were a mean age of 41.8 ± 14.3 years with a female predominance (79.7%).

Normalization of TSH was achieved in 18 patients (22.8%) within a mean time of 10.1 ± 6 months, whereas normalization of free T4 was observed in 47 patients (59.5%) within a mean time of 4.5 ± 3.4 months. Factors associated with failure to normalize free T4 were age, the presence of insomnia and unemployment. No associated factor was found for failure to normalize TSH.

The female predominance found in our study is identical to that reported by Nouedoui *et al.* in Cameroon [3], by Jin *et al.* in South Korea [11] and by Gebreyohannes *et al.* in Ethiopia [9]. Female susceptibility to thyroid dysfunction is attributed to several factors, such as hormonal fluctuations during the reproductive period and a stronger immune response in women [12].

Regarding the kinetics of TSH during ATD treatment, we observed a persistent suppression of TSH until the 9th month of treatment, followed by normalization from the 10th to the 21st month, and finally a renewed decrease of TSH from the 21st to the 24th month. Prolonged suppression of TSH during treatment is common in the literature. Paragliola *et al.* found that a prolonged disease duration and the initial level of TSH receptor autoantibodies were associated with this prolonged suppression, in patients with Graves' disease treated by total thyroidectomy [13]. Likewise, Han *et al.* in Taiwan Region found that body mass index, initial free T4 levels and treatment with propylthiouracil were associated with delayed normalization of TSH [14]. The relapse observed from the 21st month may reflect patient exhaustion due to the long duration of treatment, as well as the cost of ATD and of repeated laboratory tests, all of which may lead to non-adherence or treatment discontinuation. Moreover, in our study, about 57% of patients had no formal employment; these were students, workers in the informal sector and retirees. Patel *et al.* in the United Kingdom in 2006 estimated the overall cost of a 30-month course of ATD at 5644 dollars [15].

TSH normalization was achieved in only 18 patients (22.8%) within a mean time of 10.1 ± 6 months, with extremes ranging from 2 to 21 months. Gebreyohannes *et al.* in Ethiopia reported longer delays of 13 ± 13.28 months in 29.81% of patients [9]. The low rate of TSH normalization may be related to poor therapeutic adherence and to the prolonged suppression of TSH despite normalization of free T4, as described in the literature [13] [14] [16].

Regarding the kinetics of free T4, we observed a rapid decline in free T4 with normalization from the 2nd month of treatment and maintenance of euthyroidism until the 24th month. This is consistent with data from the literature, especially in the context of Graves' disease treatment [17] [18].

More than half of the patients (59.5%) had normalized free T4 within a mean time of 4.5 ± 3.4 months, with extremes ranging from 2 to 15 months. These results are similar to those of Abbara *et al.* in the United Kingdom [18] and Priscu *et al.* in the United States [17], who reported mean times to normalization of free T4 of 66.5 days and 10 weeks, respectively. In contrast, in Ethiopia, Gebreyohannes *et al.* reported longer delays of 11.53 ± 13.39 months [9]. This may reflect the different aetiologies of hyperthyroidism across the populations studied: the pre-

dominant aetiology in our cohort was Graves' disease, whereas toxic multinodular goitre was more frequent in Ethiopia.

In our series, factors associated with failure to normalize free T4 were age ≥ 40 years, the presence of insomnia and unemployment. Maldey *et al.* in Ethiopia found that factors associated with failure to normalize thyroid function were age ≥ 40 years, toxic multinodular goitre, the presence of a grade 3 goitre according to World Health Organization (WHO), and an elevated initial free T4 [16]. Minasie *et al.*, also in Ethiopia, likewise found as associated factors the use of Propylthiouracil (PTU), therapeutic non-adherence and a very high initial heart rate [19]. Associated factors differ from one study to another because of differences in population size, in the aetiologies of hyperthyroidism and in the therapeutic modalities used by the various authors. No factor was found for failure to normalize TSH, probably because of the small size of our study population.

The primary limitations of our study include its partially retrospective design, which introduces a potential selection bias due to the systematic exclusion of incomplete medical records, as well as patient loss to follow-up during the prospective phase.

5. Conclusion

This preliminary study identified the kinetics and the time to normalization of thyroid function in patients with hyperthyroidism of various aetiologies treated with ATD in Yaoundé. These results may help guide the adjustment of treatments and biological monitoring, in order to reduce the costs of comprehensive patient care in our resource-limited context. However, a larger multicentre study is needed to confirm our findings.

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Author Contributions

Conceptualization, Martine Claude Etoa Etoga and Francine Mendane Ekobena; **methodology**, Francine Mendane Ekobena; **software**, Khadidja Abdouramani; **validation**, Martine Claude Etoa Etoga, Eugène Sobngwi, Francine Mendane Ekobena; **formal analysis**, Khadidja Abdouramani; **investigation**, Khadidja Abdouramani.; **resources**, Mesmin Dehayem, Suzanne Doris Essama Bibi, Ghislaine Biwolé Sida and Anne Ongmeb Boli; **data curation**, Francine Mendane Ekobena, Khadidja Abdouramani; **writing original draft preparation**, Francine Mendane Ekobena; **writing reviuew and editing**, Mesmin Dehayem, Suzanne Doris Essama Bibi, Ghislaine Biwolé Sida and Anne Ongmeb Boli; **visualization**, Eugène Sobngwi; Martine Claude Etoa Etoga, **supervision**, Martine Claude Etoa Etoga; **project administration**, Eugène Sobngwi; **funding acquisition**, Khadidja Abdouramani.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

ATD: Antithyroid Drugs
TSH: Thyroid-Stimulating Hormone
Free T4: Free Thyroxine
M: Months
PTU: Propylthiouracil
CBC: Complete Blood Count
TRAb: TSH Receptor Antibodies
WHO: World Health Organization