Enhancing Health Outcomes: A Comprehensive Study on the Biochemical and Clinical Management of Graves' Disease in Coastal Andhra Pradesh

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ABSTRACT

This retrospective study explored the biochemical and clinical management of Graves' disease (GD) in coastal Andhra Pradesh, India, involving 225 consecutive patients (171 females and 54 males) aged 20 to 70 years who were diagnosed with GD between August 2022 and December 2024. The demographic information was documented including anthropometric measurements, clinical signs and symptoms, socio-demographic profiles, dietary habits, smoking status, and disease co-morbidities. Biochemical analysis revealed insights into thyroid function through tests (TSH, T3, T4, FT4, FT3) and revealed the significance of TSH receptor antibodies (TRAb). Thyroid scintigraphy and ultrasound examinations in a few patients were performed to undergo radioiodine ablation therapy. The mean age at presentation was 41.82 ± 12.62 years, with women often presenting at a younger age than men. An impressive 99.5% of the cohort tested positive for TRAb. The study highlighted significant correlations between smoking, alcohol consumption, and iodized salt intake, demonstrating how these factors influence the progression of GD. Among the 50-59 age group, notable frequencies of diabetes mellitus (17.3%), hypertension (19.5%), and post-hysterectomy status (10.2%) were found. The presence of goiter was prominently reported in the 20-39 age group (p=0.022). Ultrasound findings brought to light a greater prevalence of enlarged thyroids compared to multi-nodular goiters and solitary nodules. This study exemplifies the critical role of TRAb testing in the diagnosis and management of GD and emphasizes the profound impact of environmental factors on disease progression in the coastal Andhra Pradesh population.

Introduction:

The thyroid gland is one of the most prominent endocrine glands located inferior to the cricoid cartilage in the human body. It is a butterfly-shaped organ comprising two lobes, which produce thyroid hormones T3 (tri-iodothyronine) and T4 (thyroxine). Hyperthyroidism, commonly known as an overactive thyroid, is a significant disorder of the endocrine system characterized by the excessive production of hormones by the thyroid gland. The production of these hormones is meticulously regulated by thyroid-stimulating hormone (TSH), secreted by the pituitary of the brain.

Grave's Disease (GD) represents the predominant etiology of hyperthyroidism in iodine-repleted parts of the world.GD is a multi-systemic disorder of autoimmune complexity with contributions from both environmental and genetic interactions.

Graves' disease (GD) manifests in genetically predisposed individuals when thyroid receptor autoantibodies (TRAb's) activate the thyroid-stimulating hormone receptors (TSHR) in the thyroid gland. This mechanism unequivocally represents the hallmark of GD's pathogenesis.

According to the (status of Goiter or Thyroid Disorders in India;2022) implementation of salt iodization from 1995, by NIDDC (National Iodine Deficiency Disorder Control Program) India has completed its transition from Iodine deficiency to iodine-replete status. It is postulated that supplementation of Iodine can cause a spurt in autoimmune thyroid dysfunction, thereby damaging the thyroid gland due to an autoimmune response, thereby rendering the thyroid gland more vulnerable to various thyroid disorders (Stefan et al;2017)

GD affects 16.7% of India's adult population with an observed prevalence of 3% among females and 0.5% among males (Burch;2012). In Iodine replete areas, people with thyroid disease possess an autoimmune disease. A high prevalence of 36.6% has been documented in East Godavari district of Andhra Pradesh. Based on information from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the condition is 7.5 times more prevalent in women compared to men. The highest incidence occurs among individuals aged between 40 and 60, although it can impact people in any age group. It is more frequently found in smokers, those with other autoimmune disorders, or individuals with a family history of thyroid autoimmunity. (Manji et al;2006). Environmental factors such as stressful life events, recent childbirth, hormonal fluctuations, infections, and exposure to elevated levels of iodine reveal the underlying causes of hyperthyroidism in women.

Role of Iodine in Thyroid Metabolism:

Iodine is a trace element in a dietary supplement that is present naturally in some foods. Iodine is an essential element of thyroid hormones (T4) and (T3) which regulates many biochemical reactions, enzymatic activity, and metabolism. The Earth's soil contains varying amounts of iodine, which in turn affects the iodine content of the crops. Iodine present in several forms in food is quickly and almost completely absorbed in the stomach and duodenum. Iodate is reduced in the GI tract and absorbed as iodide. When iodide enters the circulation, the thyroid gland concentrates it for appropriate amounts of thyroid hormone synthesis, and the remaining is excreted in urine. The sources of Iodine are Seaweed (kelp) a best source of Iodine, Fish, and seafood. Breast milk, Dairy products, and infant formula also contain Iodine. Cows receive iodine feed, Iodophor sanitizing agents were used to clean cow's and milk processing units. Plant-based soy and almond beverages also contain traces of iodine. Commercially prepared breads and processed food contain traces of Iodine. Erythrosine an iodine-containing food dye is used as a flavoring agent in fruit-flavored cereals and also in some medicines such as multivitamins and dietary supplements. About 88% of households use iodide salt. The daily recommended dietary intake of iodine is 150mcg in adults and teens.

Graves' Disease (GD) is marked by a diffuse toxic goiter, infiltrative ophthalmopathy, and dermopathy (Munjal et al; 2012). The methods of investigation and treatment for GD differ according to the disease's location, severity, and manifestation.

A course of antithyroid drugs (ATD) therapy serves as the primary treatment for the condition. The main objective of the study treatment is to achieve normalization of thyroid hormone levels and induce disease remission. The treatment approach includes various aspects related to epidemiology, pathogenesis, and disease management. This entails the prompt regulation of the excessive secretion of thyroid hormones with the assistance of beta-adrenergic blockers. Furthermore, it encompasses the management of thyroid hormone production through the use of antithyroid drugs (ATDs), radioactive iodine (RAI), and surgical interventions, guided by established protocols and situational considerations. This multifaceted approach aims to enhance the understanding of Graves' disease and its implications for patients and healthcare in the population of coastal Andhra Pradesh.

Materials and Methods:

Study Population

The present study is a retrospective study involving patients with Graves' disease who sought outpatient care at endocrine hospitals located in coastal Andhra Pradesh during the period from August 2022 to December 2024.

Admission criteria

The study encompasses participants aged between 20 and 70 years. Both male and female subjects were included in the research. The selected cases comprised individuals diagnosed with clinical Graves' disease who were either undergoing treatment or had completed radioiodine (RAIA) therapy. Additionally, patients with other metabolic syndromes who were newly diagnosed with GD were included in the study.

Rejection Criteria

Individuals under the age of 18 and those over the age of 70 were excluded from the study. Additionally, females who were pregnant during the study or the postpartum women were also excluded.

Sample and Data Collection

The samples were collected with prior informed consent of the participants, fostering an ethical research approach. A total of 225 consecutive patients diagnosed with Graves' disease (GD) were incorporated into this study, providing a robust sample for analysis. The patients were reviewed and a questionnaire was developed in both English and Telugu to facilitate consent procurement and data collection from the study population, with the endorsement of the institutional ethical committee at Andhra University in Visakhapatnam.

Demographic information and anthropometric measurements, including height, weight, and body mass index (BMI), were systematically documented. Additionally, the study evaluated clinical signs and symptoms, socio-demographic profiles, physical characteristics, dietary habits, smoking status, duration of the disease, co-morbid conditions, family histories, and

the pedigrees of patients with established family histories of GD, as well as the evolution and progression of the disease.

Physical Examination

The medical evaluation was conducted primarily about the physical characteristics of the patient. This physical examination serves to identify the signs and symptoms associated with Graves' Disease. A general assessment of the patients was performed, and symptoms such as Graves Ophthalmopathy and Graves dermopathy, which are related to Graves' Disease, were documented. The stage of Goitre was assessed with the oversight of the Endocrinology Department.

By the guidelines and recommendations established by the World Health Organization (WHO), Goiter is classified into the following grades:

Grade 0: No goiter is either palpable or visible.

Grade 1: The goiter is palpable but not visible when the neck is positioned normally.

Grade 2: The goiter is both palpable upon examination and visible when the neck is in a normal position.

Biochemical / Immunological studies

Upon receiving informed consent, a physical examination was conducted, followed by the collection of 5ml of venous blood by Phlebotomists for subsequent analysis. The samples were permitted to equilibrate at room temperature before undergoing centrifugation at 1100 rpm for 10 minutes; the serum was then extracted and preserved at -20°C for further examination. Biochemical analysis was executed utilizing the fully automated analyzer Roche, model (Cobas e 11), from Germany. The thyroid function test (TFT) profile was evaluated, which included the quantification of Thyroid Stimulating Hormone (TSH), Total Tri-iodothyronine (T3), Total Thyroxine (T4), Free Thyroxine (FT4), and Free Tri-iodothyronine (FT3). Additionally, the TSH receptor antibody (TRAb) was measured to affirm the diagnosis, as this marker is pivotal in the identification of Graves' Disease (GD). The reference ranges for normal values associated with the various laboratory investigations were enumerated as follows: T3 is 0.80-2.0 ng/mL, T4 is 5.1-14.1 µg/dL, TSH is 0.27-4.20 µIU/mL, FT3 is 2.00-4.40 pg/mL, FT4 is 0.93-1.70 ng/dL, and an Anti-TSHR antibody level below 1.75 IU/L is classified as negative, whereas a level exceeding 1.75 IU/L is deemed positive.

Thyroid Imaging

After laboratory investigations, patients who experienced a relapse while undergoing treatment with antithyroid drugs (ATDs) were administered with radioiodine ablation (RIA) therapy as an additional course of treatment. Thyroid scintigraphy was performed in conjunction with follow-up assessments.

A technetium-99m ($99^{m}Tc$) uptake scan was executed to evaluate gland size and to calculate the appropriate dosage for radioiodine ablation. The assessment of thyroid uptake and scintigraphy was conducted 20 minutes post-administration of an intravenous injection of $99^{m}Tc$-pertechnetate. Images were captured while the patient was in a supine position, utilizing a gamma camera with a pinhole collimator. A $99^{m}Tc$ uptake ranging from 0.4% to 7.1% was deemed to be within normal limits.

The upper limit for the uptake of 99mTc was determined based on the gland's ability to trap iodine, which indicates areas of iodine deficiency.

Graves' disease (GD) was diagnosed based on clinical features, thyroid function test (TFT) results, and TRAb levels, along with the detection of diffuse uptake in thyroid imaging using 99mTc scintigraphy.

TRAb (Thyroid receptor Antibodies)

The measurement of anti-TSHR antibodies in the bloodstream decisively assesses the stimulation of antibodies. TSHR-stimulating antibodies are pivotal in the immune response associated with Graves' disease (GD). The presence of TRAb is a prerequisite for the manifestation of GD, serving as a definitive marker of the disease's progression. The testing of TRAb is highly advantageous in both the diagnosis and therapeutic management of GD, as it effectively distinguishes GD from other thyroid-related disorders and allows for precise monitoring of disease recurrence.

The TRAb test represents a cost-effective initial diagnostic strategy for the identification of individuals with GD and is essential for determining the appropriate treatment protocols, including radioactive iodine (RAI) therapy, anti-thyroid drugs (ATDs), or thyroid surgery.

Ultrasound Examination of the Thyroid

A neck ultrasound (US) was conducted by consultant radiologists to evaluate the presence of thyroid nodules or malignancies. The ultrasounds are systematically classified as follows:

1. Normal (size and shape are within acceptable limits)

2. Solitary nodule

3. Two large nodules (each exceeding 1 cm in size)

4. Multinodular goiter (MNG) characterized by thyroid gland enlargement

5. Dominant nodule identified within an MNG

6. Additional findings (including diffuse enlargement without nodules, presence of micro nodularity, or asymmetrical enlargement.

After the serological evaluation, the imaging data was meticulously recorded in a structured proforma within the database.

Statistical Analysis

The statistical analysis was conducted using data analyzed with SPSS software version 24.0. The analysis included an independent t-test and a chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results:

The present study included 225 consecutive patients diagnosed with GD, comprising 171 females and 54 males; with a female-to-male ratio of 3.17:1.0 (Table 1). According to the age distribution of GD patients, the 40-49 years age group showed 28% of the highest frequency than other age groups (Table 2).

The mean age at the presentation was 41.82±12.62 years with women relatively younger than men. The mean value of Thyroid antibodies (TRAB) is 13.15 (±11.88) and the TRAB'S (n=224) is 99.5% positive among total cohorts with GD. The mean systolic blood pressure and diastolic blood pressure at presentation were 126.93 (±18.90) and 79.66(±10.41), respectively, with no significant differences between genders (Table 3). The presenting signs and symptoms with the frequency were listed (Table 4). At the time of assessment, several patients had already been on anti-thyroid medication for a variable period. The other associated Co-morbidities include Diabetes mellitus, Hypertension, CAD, Post-hysterectomy women, Iron deficiency anemia, and Osteoporosis were also presented. The age group between 50 to 59 showed the highest frequency of Diabetes mellitus (17.3%), Hypertension (19.5%), and post-hysterectomy (10.2%) compared to other age groups (Table 5). The distribution of patients with Grave's disease based on clinical features at the first presentation of Grave's Ophthalmopathy with a P-value of 0.488 and the presence of Goitre was high among the age groups of 20-39 with a significant P-value of 0.022 (Table 6).

Comparative analysis of various parameters according to gender was observed among smokers, alcoholics, and intake of iodized salt. The study showed a strong significant correlation among smokers and alcoholics with Grave's disease patients with a P-value of <0.0001; which shows a strong association in the progression of Grave's disease in the population of coastal Andhra Pradesh. The intake of iodized salt among the cohorts was also high with a significant P-value of 0.002.

The T3/T4 ratio reflects the ratio between the two thyroid hormones. A significant T3/T4 ratio suggests that the body's ability to convert T4 to T3 might be impaired. This could be a potential issue with the conversion of thyroid hormones and impaired metabolism (Table 7). The US findings suggest a high number of enlarged thyroids was observed when compared to MNG (multi-nodular goiter) and solitary nodules (Table 8).

Table 1: **Age distribution of patients**

Age Distribution	Frequency	%
20-29	41	18.2
30-39	59	26.2
40-49	63	28.0
50-59	43	19.1
60-69	13	5.8
70	6	2.7

Table 2: Gender Distribution of Patients

Gender Distribution	Frequency	%
Female	171	76
Male	54	24

Table 3: Baseline Characteristics of the Patients with Grave's Disease

Variables	Total Cohort (n=225)	
	Mean ±SD	95% Confidence Interval (CI)
Age (years)	41.82 ± 12.62	40.16 to 43.48
BMI kg/m²	25.95 ± 4.80	25.3183 to 26.5799
SBP mm Hg	126.93 ± 18.90	124.4506 to 129.4160
DBP mm Hg	79.66 ± 10.41	78.2899 to 81.0257
Smoker n (%)	33	14.70%
Alcohol n (%)	19	8.40%
Iodized salt use n (%)	206	92%
T3 ng/ mL	38.07 ± 96.67	25.3673 to 50.7660
T4 mcg/dL	21.72 ± 31.50	17.5763 to 25.8536
T3 / T4 Ratio	3.41 ± 11.45	1.9046 to 4.9126
TSH (micro IU /ml)	0.8258 ± 4.3275	0.2573 to 1.3943
FT4 ng/dL	1.7824 ± 1.21	1.623 to 1.941

FT3 pg/mL	3.345 ± 1.33	3.1701 to 3.5203
TRABS (n = 224)	13.1582 ± 11.8828	11.5971 to 14.7193
Use of Anti thyroid drugs (%)	88	39%
Hypothyroid episodes n (%)	43	19.10%

SD: Standard deviation; BMI: Body mass index; TSH: Thyroid-stimulating hormone; T4: Total Thyroxine; T3: Triiodothyronine, FT4: Free Thyroxine TRABS: TSH receptor antibodies; ATD: Anti-thyroid drugs.

Table 4: Frequency of Signs and Symptoms

Symptoms	**n**	**%**	**Signs**	**n**	**%**
Tremors	55	24.4	Goitre	42	18.67
Palpitations	67	29.8	Tremors	55	24.44
Weight Loss	63	28	Dermopathy	3	1.33
Heat Intolerance	31	13.8	Ophthalmopathy	18	8.00
ssProfuse Sweating	35	15.6			
Fatigue	55	24.4			
Insomnia	31	13.8			
Increased Bowels	18	8			
Dysphagia	9	4			
Confusion	11	4.9			
Skin Irritation	20	8.9			
Pretibial Oedema	9	4			

Table 5: Associated co-morbidities with Grave's disease patients based on age groups

Age Group	Diabetes Mellitus (n=39)	Hypertension (n=44)	Post Hysterectomy (n=23)	CAD (n=3)	Iron Deficiency (n=5)	Osteoporosis (n=6)
20-29	2	1	1	0	1	0
30-39	2	1	1	2	2	0
40-49	13	9	5	0	1	1
50-59	14	24	12	0	1	2
60-69	6	7	2	0	0	3
70	2	2	2	1	0	0

Table 6: Distribution of clinical features at diagnosis of Grave's disease

Age Group	Ophthalmopathy present	Ophthalmopathy Absent	P-Value	Goitre (+)	Goitre (-)	P-Value
20-29	2	39	0.488	14	27	**0.022***
30-39	7	52		14	45	
40-49	7	56		9	54	
50-59	6	37		4	39	
60-69	0	13		1	12	
70	0	6		0	6	

Goitre (+): Present; Goitre (-): Absent; P- value of 0.022* is significant

Table 7: Comparative analysis of various parameters based on gender.

Variables	Total Cohort (n=225)				P-Value
	Males (Mean ± SD) n=54	95% Confidence Interval (CI)	Females (Mean ± SD) n=171	95% Confidence Interval (CI)	
Age (years)	43.83 ± 13.51	40.1447 to 47.5220	41.18 ± 12.30	39.3248 to 43.0378	0.364
BMI kg/m²	25.05 ± 4.82	23.7346 to 26.3651	26.23 ± 4.78	25.5122 to 26.9540	0.751
SBP mm Hg	131.80 ± 19.02	126.6060 to 136.9866	125.40 ± 18.65	122.5818 to 128.2136	0.755
DBP mm Hg	82.44 ± 11.65	79.2650 to 85.6238	78.78 ± 9.86	77.2887 to 80.2669	0.086
Smoker n (%)	28	52%	5	3%	**<0.0001**
Alcohol n (%)	19	35%	0	0%	**<0.0001**
Iodized salt intake n (%)	44	81%	162	95%	0.002
T3 ng/ mL	29.84 ± 78.17	8.5021 to 51.1724	40.67 ± 101.88	25.2861 to 56.0447	0.147
T4 mcg/dl	24.96 ± 42.75	13.2920 to 36.6310	20.69 ± 27.08	16.6017 to 24.7778	0.269
T3 / T4 Ratio	1.71 ± 4.24	0.5482 to 2.8627	3.95 ± 12.88	2.0022 to 5.8906	**0.019**
TSH micro IU /ml	0.60 ± 2.56	0.0989 to 1.2989	0.90 ± 4.76	0.1793 to 1.6149	0.439
FT4 ng/dL	1.81 ± 1.41	1.4141 to 2.1741	1.77 ± 1.14	1.6052 to 1.9519	0.822
FT3 pg/mL	3.23 ± 0.74	3.0058 to 3.4123	3.38 ± 1.47	3.1665 to 3.6121	0.467
TRABS (n =224)	12.55 ± 11.15	9.5022 to 15.5889	13.35 ± 12.13	11.5205 to 15.1827	0.144
Use of Anti thyroid drugs (%)	25	46%	63	37%	0.215
Hypothyroid episodes n (%)	8	15%	35	20%	0.357

SD: Standard deviation; BMI: Body mass index; TSH: Thyroid-stimulating hormone; T4: Total Thyroxine; T3: Triiodothyronine, FT4: Free Thyroxine TRABS: TSH receptor antibodies; ATD: Anti-thyroid drugs P-value:<0.0001 is significant in smokers and alcoholics; T3/T4 ratio: P- value 0.019 is significant.

Table 8: Clinical findings with ultrasound findings in Grave's disease

US Findings (n=32)	Solitary Nodule (n=5) 15.6%	MNG (n=7) 21.8%	Enlarged (n=20) 62.5%
Normal	1	0	17
Solitary Nodule	1	0	0
MNG	2	7	1
Others	1	0	2

US findings: Ultrasound findings; MNG: Multinodular goiter; Others include: Diffuse enlargement with no nodularity, asymmetrical enlargement with thyroiditis

Discussion:

India has a high burden of thyroid diseases, and the morphology of the thyroid gland could be variable. GD shows varied clinical presentations, therefore, a proper understanding of detection and diagnosis by the clinicians is required for a genuine understanding of the biochemical patterns and manifestation of GD. According to previous studies, autoimmune diseases tend to affect more females than males. The females outnumbered than males in the present study, this might be due to the implementation of the universal iodization program there is an increase in the tendency of autoimmune Grave's disease. Smoking and alcoholics showed a strong significant correlation with the patients of Grave's disease.

Ethical variations, recent childbirths, lifestyle, poor accessibility to medical facilities for women living in rural areas, poor diagnosis and exposure to fertilizers, people residing near the coastal belt, and intake of high iodine-rich foods along with intake of iodized salt might be the reasons for increased risk for progression of patients with Grave's disease in the population of Andhra Pradesh. No age group is immune to GD. In the study cohort, the patients of middle age showed a high frequency of Grave's disease.

Palpitations, weight loss, and tremors were consistent with the documented literature. Goitre was observed significant with a P-value of 0.022, while Ophthalmopathy did not show any significance in study cohorts. Ultrasonography of the neck showed a marked association of MNG with GD patients. Previous literature suggests that there is a chance of developing thyroid cancer in patients who detected MNG with GD.

Conclusion:

This study represents the first biochemical retrospective analysis conducted within the population of Coastal Andhra Pradesh. Longitudinal studies involving larger patient cohorts are necessary to enhance the understanding of the disease progression associated with Graves' disease (GD). Furthermore, the implementation of thyroid screening is crucial for raising awareness among the population. It is also imperative to conduct thyroid profile screenings for patients with diabetes, hypertension, women of reproductive age, and individuals who are post-menopausal or have undergone hysterectomy.

The inadequacy of proper diagnosis and treatment for patients with Graves' disease who present with ophthalmopathy often results in their seeking care at ophthalmology clinics rather than consulting with endocrinologists. It is essential to engage in comprehensive discussions regarding the various treatment modalities, including antithyroid drugs (ATDs), radioactive iodine (RAI) therapies, and surgical options. Such discussions can enhance patients' understanding of their condition and assist them in making informed treatment decisions, ultimately improving their prognosis. Furthermore, the implementation of screening initiatives and heightened awareness programs may contribute significantly to enhancing thyroid health within our population.

Limitations:

This study is subject to several limitations inherent to its retrospective design. A primary limitation is the restricted availability of thyroid auto-antibody testing, which is not widely accessible at affordable rates within public facilities. Furthermore, access to essential data, including thyroid scintigraphy, RIA therapy, and patient follow-up for the prediction of remission and relapse in Graves' disease (GD), is limited. Additionally, ultrasonography data were absent for the entire cohort, which hampers the ability to exclude the presence of thyroid cancers and malignancies associated with GD.

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References:

1) Salman, A. G., Mahdi, I. A. J., Mukhlef, A. K., Abd Alsattar Mohammad, R., Zaghir, M. S. H., & Muatez Wadaa'ass, N. (2024). Physiological aspects of thyroid disorders: Anatomy, hormones, diagnosis and management. *Current Clinical and Medical Education*, *2*(5), 17-32.

2) Schifter, M., McLean, M., & Sukumar, S. (2021). Disorders of the endocrine system and metabolism. *Burket's Oral Medicine*, 817-902.

3) Singh, A. K., Chatterjee, S., Singh, A., & Bhattacharjee, R. (2024). Diet in Thyroid Disorders: A Survey among Clinicians and a Review of the Current Perspective. *Indian Journal of Endocrinology and Metabolism*, *28*(4), 378-384.

4) Kustrimovic, N., Gallo, D., Piantanida, E., Bartalena, L., Lai, A., Zerbinati, N., ... & Mortara, L. (2023). Regulatory T cells in the pathogenesis of Graves' disease. *International journal of molecular sciences*, *24*(22), 16432.

5) Stefan, M., & Faustino, L. C. (2017). Genetics of thyroid-stimulating hormone receptor—relevance for autoimmune thyroid disease. *Frontiers in Endocrinology*, *8*, 57.

6) Burch, H. B., Burman, K. D., & Cooper, D. S. (2012). A 2011 survey of clinical practice patterns in the management of Graves' disease. *The Journal of Clinical Endocrinology & Metabolism*, *97*(12), 4549-4558.

7) Sepuri, M., Basumitra, D., & Lakshmikantham, A. (2018). Spectrum of thyroid dysfunction in North Coastal Andra Pradesh. *J. Evid. Based Med. Healthc*are *5*(28), 2091-2094.

8) Manji, N., Boelaert, K., Sheppard, M. C., Holder, R. L., Gough, S. C., & Franklyn, J. A. (2006). Lack of association between serum TSH or free T4 and body mass index in euthyroid subjects. *Clinical endocrinology*, *64*(2), 125-128.

9) Lee, I. T., Sheu, W. H. H., Liau, Y. J., Lin, S. Y., Lee, W. J., & Lin, C. C. (2003). Relationship of stressful life events, anxiety, and depression to hyperthyroidism in an Asian population. *Hormone Research in Paediatrics*, *60*(5), 247-251.

10) *Iodide Metabolism and Effects* (pp. 25–33). (2020). igi global. https://doi.org/10.4018/978-1-5225-9655-4.ch004

11) Nyenwe, E. A., & Dagogo-Jack, S. (2009). Iodine deficiency disorders in the iodine-replete environment. *The American journal of the medical sciences*, *337*(1), 37-40.

12) Hussain, Y. S., Hookham, J. C., Allah Abadia, A., & Balasubramanian, S. P. (2017). Epidemiology, management, and outcomes of Graves' disease—real-life data. *Endocrine*, *56*, 568-578.

13) Khan, S. H., Mahajan, A., Laway, B. A., Rasool, R., & Rather, T. A. (2018). Technetium-99m thyroid scintigraphy and human leukocyte antigen–B35 in sub-acute thyroiditis. *Indian Journal of Nuclear Medicine*, *33*(4), 306-311.

14) Patel, K. A., Knight, B., Aziz, A., Babiker, T., Tamar, A., Findlay, J., ... & Vaidya, B. (2019). Utility of systematic TSHR gene testing in adults with hyperthyroidism lacking overt autoimmunity and diffuse uptake on thyroid scintigraphy. *Clinical endocrinology*, *90*(2), 328-333.

15) Girgis, C. M., Champion, B. L., & Wall, J. R. (2011). Current concepts in Graves' disease. *Therapeutic advances in endocrinology and metabolism*, *2*(3), 135-144.

16) Gupta, A. K., & Kumar, S. (2022). Utility of antibodies in the diagnoses of thyroid diseases: a review article. *Cureus*, *14*(11).

17) Varadhan, L., Varughese, G. I., & Sankaranarayanan, S. (2016). Hyperthyroidism and Graves' disease: Is an ultrasound examination needed? *Indian Journal of Endocrinology and Metabolism*, *20*(6), 866-869.

18) Subasree, S. (2014). Prevalence of thyroid disorders in India: an overview. *Research Journal of Pharmacy and Technology*, *7*(10), 1165-1168.

19) BHAT, M. H., BHAT, J. A., MASOODI, S. R., QURESHI, W., DAR, J. R., & BHAT, M. H. (2021). Clinical Spectrum and Outcome of Patients with Graves' Disease: A Single-Centre Experience from a Tertiary Care Institution in the Kashmir Valley, India. *Turkish Journal of Endocrinology & Metabolism*, *25*(1).

20) Sarfo-Kantanka, O., Sarfo, F. S., Ansah, E. O., & Kyei, I. (2018). Graves' Disease in Central Ghana: clinical characteristics and associated factors. *Clinical Medicine Insights: Endocrinology and Diabetes*, *11*, 1179551418759076.

21) Ahsan, T., Banu, Z., Jabeen, R., & Farooq, M. U. (2013). Clinical spectrum and various forms of thyrotoxicosis in endocrine clinic of Jinnah Postgraduate Medical Centre. *JPMA. The Journal of the Pakistan Medical Association*, *63*(3), 354-357.

22) Cappelli, C., Braga, M., Martino, E. D., Castellano, M., Gandossi, E., Agosti, B., ... & Rosei, E. A. (2006). Outcome of patients surgically treated for various forms of

hyperthyroidism with differentiated thyroid cancer: experience at an endocrine center in Italy. *Surgery Today*, *36*, 125-130.

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