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Clinical Spectrum and Outcome of Patients with Graves' Disease: A Single-Center Experience from a Tertiary Care Institution in the Kashmir Valley, India

Graves Hastalığı Olan Hastaların Klinik Spektrumu ve Sonuçları: Keşmir Vadisindeki (Hindistan) Üçüncü Basamak Bir Sağlık Kurumunda Tek-Merkezli Deneyim

Mohammad Hayat BHAT, Javaid Ahmad BHAT, Shariq Rashid MASOODI,* Waseem QURESHI,** Junaid Rashid DAR,** Moomin Hussain BHAT*

Department of Endocrinology, Superspeciality Hospital, GMC, Srinagar, INDIA
*Department of Endocrinology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, INDIA
**Department of Medicine, Government Medical College, Srinagar, INDIA

Abstract

Objective: Graves' disease (GD) is a common autoimmune disorder with variable outcomes. We aim to study the clinical manifestations and treat-ment outcome of GD in the post-iodization scenario. **Material and Met-hods:** The present study was designed as a cross-sectional study, in which a total of 180 patients with GD (127 females and 53 males) attending our center were reviewed retrospectively. The demographic data, modes of tre-atment, comorbidities, remission, and recurrence rates were determined for the patients. All patients were initially treated with anti-thyroid drugs (ATDs), with the subsequent management depending on the course of the disease. **Results:** The mean (±SD) age at diagnosis was 38.30 (10.73) years and the lag period between the onset of symptoms and the diagno-sis was 5.12 (2.69) months, with the male patients having a significantly shorter duration of illness compared to females (4.36 vs. 5.44 months; P=0.015). Majority of the patients presented with the typical symptoms and signs associated with hyperthyroidism and/or goiter, although the aty-pical presentations were not uncommon. ATDs were the most preferred treatment modality employed to achieve clinical and biochemical remis-sion. The mean duration of achieving euthyroidism and the normalization of TSH levels were 3.31±1.51 and 7.45±3.35 months, respectively. On fol-low-up at three months, 46.1% of the patients were euthyroid, with nor-malization of the TSH levels in 15.6% of them. Failure to achieve early remission/disease control was significantly higher in males (p=0.003) and smokers (p=0.036). Among the 72 patients who completed medical the-rapy, 49 patients achieved remission, of whom 20 patients relapsed with a first-year relapse rate of 20.4%. Disease relapse was significantly asso-ciated with higher initial 99 mTechnetium ($99^{m}Tc$) uptake (p=0.022) and higher grade of goiter (p=0.026) at presentation. The logistic regression analysis revealed male gender (p=0.048) and orbitopathy (p=0.036) as the independent risk factors predicting relapse of the GD. **Conclusion:** Graves' disease manifests with varied clinical manifestations, including the atypical ones, warranting careful clinical assessment to ensure an accu-rate diagnosis. Gender and orbitopathy are the independent risk factors predicting the relapse of the disease.

Keywords: Anti-thyroid drugs; diffuse toxic goiter; hyperthyroidism; total thyroidectomy; thyrotoxicosis

Özet

Amaç: Graves hastalığı (GD), çeşitli sonuçları olan yaygın bir otoimmün bozukluktur. İyodizasyon sonrasında GD'nin klinik belirtilerinin ve tedavi sonuçlarının incelenmesi. **Gereç ve Yöntemler:** Bu çalışma, merkezimize başvuran toplam 180 GD'li (127 kadın ve 53 erkek) hastanın retrospektif olarak incelendiği kesitsel bir çalışma olarak tasarlandı. Hastaların demografik verileri, tedavi şekilleri, komorbiditeleri, remisyon ve relaps oranları belirlendi. Tüm hastalar başlangıçta anti-tiroid ilaçlar (ATD'ler) ile tedavi edildi ve ardından hastalığın seyrine bağlı olarak yönetildi. **Bulgular:** Tanı anındaki ortalama (±SS) yaş 38,30 (10,73) idi, semptomların başlangıcı ile tanı arasındaki gecikme süresi 5,12 (2,69) aydı, erkek hastalar kadınlara göre anlamlı olarak daha kısa hastalık süresine sahipti (4,36 vs 5,44 ay; p=0,015). Hastaların çoğunluğu hipertiroidizm ve/veya guatr ile ilişkili tipik semptom ve bulgularla başvurdu, ancak atipik tablolar da nadir değildi. ATD'ler, klinik ve biyokimyasal remisyon sağlamak için en çok tercih edilen tedavi yöntemiydi. Ötiroidizme ulaşılması ve TSH düzeylerinin normalleşmesi için geçen ortalama süre sırasıyla 3,31±1,51 ve 7,45±3,35 aydı. Üç aylık takipte, hastaların %46,1'i ötiroid oldu ve %15,6'sında TSH seviye-leri normalleşti. Erken remisyon/hastalık kontrolü sağlanamaması erkek-lerde (p=0,003) ve sigara içenlerde (p=0,036) anlamlı olarak daha yüksekti. Medikal tedaviyi tamamlayan 72 hastadan 49'unda remisyon sağ-landı, bunlardan 20'sinde relaps izlendi, ilk yıl relaps oranı %20,4 idi. Has-talığın relapsı, başvuru sırasındaki daha yüksek başlangıç 99 mTechnetium ($99^{m}Tc$) alımı (p=0,022) ve daha yüksek guatr derecesi (p=0,026) ile anlamlı şekilde ilişkiliydi. Lojistik regresyon analizine göre, GD relapsını öngördüren bağımsız risk faktörleri erkek cinsiyet (p=0,048) ve orbitopati (p=0,036) idi. **Sonuç:** Graves hastalığı, atipik olanlar da dahil olmak üzere çeşitli klinik belirtilerle kendini gösterir ve doğru tanı için dikkatli bir klinik değerlendirme gereklidir. Cinsiyet ve orbitopati, hastalığın relapsını öngördüren bağımsız risk faktörleridir.

Anahtar kelimeler: Antitiroid ilaçlar; toksik diffüz guatr; hipertiroidizm; total tiroidektomi; tirotoksikoz

Address for Correspondence: Javaid Ahmad BHAT, Department of Endocrinology, Superspeciality Hospital, GMC, Srinagar, INDIA
Phone: 7006802402 **E-mail:** javaidrasool711@gmail.com

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Introduction

Graves' disease (GD) is a multi-systemic disorder of autoimmune etiology, which results from complex interactions between genetic and environmental factors (1,2). It is the most common cause of hyperthyroidism, accounting for 60% to 80% of the cases, with an annual incidence of 20 to 50 cases per 100,000 individuals (3). As with the other autoimmune diseases, GD affects women more than men, with a peak incidence occurring between the age of 30 and 50years, although people may be affected at any age. According to the data from Nurses' Health Study II (NHSII), the 12-year incidence of GD among women aged between 25 to 42years was as high as 4.6/1000 (4). Hyperthyroidism, diffuse goiter, and/or orbitopathy are the cardinal manifestations of GD, although other organ systems may also be affected, resulting in a plethora of clinical signs and symptoms. The severity and duration of the disease, as well as the patient's age at onset, determine the presentation and the course of the disease (5). The manifestation of the disease either results from hyperthyroidism (goiter in certain cases) or is a consequence of underlying autoimmunity (6). Impaired quality of life, resulting in an inability to work (7,8) and an increased risk of death (9) associated with GD render it imperative to understand the natural history of GD. While trying to study GD, there is a need to renew focus on epidemiology, pathogenesis, and the subsequent management to restore euthyroidism for a favorable outcome of the disease. Clinical and biochemical features of thyrotoxicosis, particularly those with a long duration and/or orbitopathy, along with a diffuse increase in radioactive iodine or technetium uptake scan, confirm the diagnosis of GD. The treatment for GD comprises rapid control of the symptoms, generally with a beta-adrenergic blocker, and reduction of thyroid hormone secretion using one of the several modalities available, including ATDs, radioactive iodine therapy (RAI), and surgery; the selection of the treatment modalities often varies according to different guidelines and local traditions.

The Kashmir Valley, located in the North-Indian Union territory of Jammu and Kashmir, has been a known iodine-deficient area (10). With the universal implementation of salt iodization, a marked improvement in the overall iodine nutrition was observed in the Kashmir Valley (11). It is well known that the incidence of hyperthyroidism, including GD, may increase after salt iodization (12). Therefore, it is imperative to study the clinical manifestations and the treatment outcome of GD in the Kashmir Valley in the post-iodization scenario.

Aims and Objectives

To have an in-depth discussion on GD through the study of clinical manifestations and treatment outcomes of GD in the post-iodization scenario.

Material and Methods

Study setting

The present study reports a two-year retrospective analysis of GD patients who presented to the Endocrine outpatient department of the super-speciality hospital of Government Medical College, Srinagar, between June 2017 and December 2019. The study was performed in accordance with the Declaration of Helsinki statement for medical research involving human subjects.

Study population and sample size

A total of 180 consecutive patients with GD were included in the present study.

Methods

The medical records of all patients were reviewed, and questionnaire sessions were conducted to obtain information regarding the demographics (age, gender, weight, and height), presentation (signs and symptoms), smoking status, duration of the disease, history of disease evolution and progression, routine laboratory investigations, thyroid function tests, treatment modality, outcomes, presence of comorbidities, and the last-available status of the disease. Various thyroid function tests were performed, including the estimation of Thyroid Stimulating Hormone (TSH), Total Thyroxine (T4), Total Triiodothyronine (T3), Free Thyroxine (FT4), Free Triiodothyronine (FT3), TSH Receptor Antibody (TRAb), and anti-thyroid peroxidase (anti-TPO). Informed consent was obtained from each pa-

tient, after which a general physical examination and a detailed systemic examination, was carried out and the relevant data were recorded and tabulated. The goiters were classified according to the World Health Organization (WHO) recommendations: Grade 0, no goiter is palpable or visible; Grade 1, palpable goiter not visible when the neck is held in normal position; Grade 2, goiter visible when the neck is held in normal position. The reference ranges for normal values for the various laboratory investigations included: 0-6.1 IU/mL for TPO, 0.35-5.5 mIU/L for TSH, 12-22 pmol/L for FT4, 3.2-12.6 mcg/dL for tT4, 0.6-1.81 ng/mL for tT3, and 3.1-6.8 pmol/L for FT3. Thyroid uptake evaluation and scintigraphy were performed twenty minutes after the administration of an intravenous injection of 370 MBq (10 mCi) of $^{99\,m}$Tc-pertechnetate. Images were captured in a supine position using a gamma camera with a pinhole collimator. ^{99m}Tc uptake between 0.4% and 7.1% was considered normal (13). The higher upper limit of ^{99m}Tc uptake was in accordance with the normal reference range results obtained for the thyroid uptake of ^{99m}Tc pertechnetate, which is used as a measure of the iodide-trapping function in the areas with iodine deficiency (14).

The diagnosis of GD was based on the clinical features of thyrotoxicosis and the biochemical evidence of hyperthyroxinemia (raised levels of FT3, FT4, tT4, and tT3) along with suppressed TSH complemented by diffuse uptake detection in thyroid imaging by ^{99m}Tc scintigraphy. In the absence of thyroid scintigraphy, a diagnosis of GD was considered in patients with a long duration of thyrotoxic symptoms, requirement of ATDs for a prolonged period, and the presence of an infiltrative ophthalmopathy.

Data collection

After obtaining written informed consent from the eligible patients, a detailed history from each patient was obtained from the patient and/or a reliable person well acquainted with the patient. The sociodemographic and clinical data were obtained from the patients and/or their relatives and recorded in semi-structured formats. Besides various thyroid function tests, different routine blood investigations like complete hemogram, ESR, blood glucose levels, serum urea/creatinine levels, lipid profile, liver function tests, levels of serum electrolytes, and imaging, were carried out as per need of the patient and were recorded in a structured proforma.

Statistical analysis

The obtained data were first entered into Microsoft Excel datasheets. All statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences) version 25.0 software from IBM Corporation, NY, United States. The data were analyzed using the independent student's t-test and one-way ANOVA, along with multiple range tests. Appropriate non-parametric tests, such as Mann Whitney, Kruskal Wallis, and the other tests, were used wherever applicable. Multiple logistic regression analysis was performed using relapse as the dependent variable while age, gender, smoking status, goiter, the grade of goiter, dermopathy, orbitopathy, T3, T4, T3/T4 ratio, anti-TPO level, and the initial ^{99m}Tc uptake as the independent variables. A P-value of less than 0.05 was considered significant.

Results

The present study included 180 consecutive patients diagnosed with GD, comprising of 127 females and 53 males, with a female to male ratio of 2.4:1.0 (Table 1). The mean age at presentation was 38.30±10.73 years, with men relatively younger than the women. The anti-TPO antibody levels prior to the initiation of medical therapy were positive in 90.6% (n=145) of the patients with available levels (n=160). The mean lag period between the onset of symptoms and the diagnosis was 5.12 ±2.69 months, with males presenting earlier compared to females (p=0.015) (Table 2). The presenting signs and symptoms in decreasing order of frequency are listed in Table 3. The mean (±SD) pulse rate, systolic blood pressure, and diastolic blood pressure at presentation were 109.68 (±11.53), 118.36 (±11.20), and 77.64 (±7.21), respectively, with no significant differences between the genders. At the time of assessment, several patients had already been on anti-thyroid medication for variable periods of time. At the first assessment at three months, most of the pa-

Table 1. Baseline characteristics of the patients with Graves' disease and their treatment outcomes.

Variables	Total Cohort (n=180) Mean±SD	95% Confidence Interval (C.I)
Age Yrs.	38.30±10.73	36.72-39.87
BMI Kg/m^2	22.27±4.16	21.63-22.92
Smoker n (%)	43	23.9%
Duration of disease (months)	22.12±11.50	18.91-25.33
T3 ng/mL	3.71±1.72	3.46-3.97
T4 mcg/dL	19.15±5.18	19.14-20.62
T3/T4 ratio	18.42±6.57	17.44-19.41
^TSH microIU/mL	0.005	0.00-0.009
Anti-TPO level (IU/mL)	584.02±411.79	501.46-666.58
Anti-TPO Status n (%)	87	90.6%
TRABS (n=21)	4.80±3.59	1.47-8.12
Total 99mTechnetium uptake (Initial)%	38.03±24.34	34.06-42.00
Duration of symptoms prior to presentation (months)	5.12±2.69	4.73-5.52
Dose of ATD (mg)	32.25±11.01	30.63-33.87
Mean duration of treatment (months)	22.51±12.56	19.30-25.73
Mean duration on follow up (months)*	25.96±7.94	22.52-29.39
Active n (%)	69	38.3%
Control n (%)	83	46.1%
Duration to Euthyroidism months	3.31±1.51	3.06-3.55
Patients with normal TSH n (%)	28	15.6%
Duration to TSH normalization months	7.45±3.53	6.73-8.16
Hypothyroid episodes n (%)	32	17.8%

SD: Standard deviation; Yrs: Years; Anti-TPO: Anti-thyroid Peroxidase; BMI: Body mass index; TSH: Thyroid-stimulating hormone; T4: Total Thyroxine; T3: Total Triiodothyronine, TRABS: TSH receptor antibodies; ATD: Anti-thyroid drugs; median (minimum-maximum), *Follow up of patients post completion of the first course of ATDs.

Table 2. Comparative analysis of various parameters according to gender.

Variables	Males (n=53) Mean±SD (95% C.I)	Females (n=127) Mean±SD (95% C.I)	Sig
Age years	37.62±10.73 (34.66-40.58)	38.58±10.76 (36.69-40.47)	0.586
Smoker n (%)	37 (69.8)	6 (4.7)	0.001*
T4 mcg/dL	21.02±5.24 (19.56-22.49)	19.39±4.75 (18.53-20.24)	0.045*
Duration of symptoms before presentation (months)	4.36±2.73 (3.60-5.12)	5.44±2.62 (4.98-5.90)	0.015*
PR beats/minute	108.49±14.28 (104.55-112.42)	110.18±10.18 (108.38-111.97)	0.372
SBP mmHg	119.05±8.38 (116.74-121.36)	118.07±12.21 (115.92-120.23)	0.596
DBP mmHg	78.71±5.92 (77.08-80.35)	77.19±7.66 (75.84-78.55)	0.199
Active n (%)	27 (50.9)	42 (33.1)	0.003*
Control n (%)	24 (45.3)	59 (46.5)	0.003*
Patients with normal TSH n (%)	2 (3.8)	26 (20.5)	0.007*

SD: Standard deviation; *- Significant; Anti-TPO: Anti-thyroid peroxidase; TSH: Thyroid-stimulating hormone; T4: Total Thyroxine; T3: Total Triiodothyronine; M: Male; F: Female.

Table 3. Frequency of signs and symptoms.

Symptoms	n (%)
Palpitation	155 (86.1)
Heat intolerance with sweating	153 (85.0)
Weight loss	118 (65.6)
Increased frequency of Stools	97 (53.9)
Sleep disturbance	96 (53.3)
Pruritus	71 (39.9)
Muscle weakness and fatigue	40 (22.2)
Hyperpigmentation	34 (18.9)
Dysphagia	32 (17.8)

Signs		n (%)
Goitre		173 (96)
Grade of Goitre	2	147 (85)
	1	26 (15)
Sinus Tachycardia		140 (78.2)
Peripheral Tremor		164 (91.1)
Warm Moist hands		118 (65.6)
Ophthalmopathy		104 (57.8)
Clinical activity score	0-2	50 (88)
	≥3	7 (12)
Proptosis		48 (26.7)
Bruit		15 (8.3)
Thrill		8 (4.4)
Dermopathy		01 (0.6)
Atrial Fibrillation		07 (3.9)

tients were controlled (46.1%), with normalization of the TSH levels in 15.6% of them. Although 53.9% of the patients were still having hyperthyroxinemia, the intensity of symptoms and the degree of hyperthyroxinemia had improved.

The mean duration to achieve euthyroidism and the normalization of the TSH levels was 3.31±1.51 months and 7.45±3.35 months, respectively. In the course of treatment, 17.8% (n=32) of the patients developed overt hypothyroidism requiring a transient reduction/termination of ATDs along with the reintroduction of the drug in several of these patients once the biochemical euthyroidism (euthyroxinemia) was achieved. Infiltrative ophthalmopathy occurred in 57.8% (n=104) of the patients, while proptosis occurred in 26.7% (n=48) of the patients. Detailed information regarding TAO obtained in the present study would be published in a separate manuscript. Atypical presentation in the form of Hashimoto's encephalopathy and recurrent acute pericarditis were observed in one patient each, atrial fibrillation occurred in seven patients, and pyrexia of unknown origin was the presenting manifestation in four patients. The other associated comorbid conditions included diabetes mellitus in seven patients and hypertension in ten patients. In regard to the treatment offered, almost all the patients received ATDs to achieve biochemical and clinical remission, with the majority receiving treatment with carbimazole. Beta-blockers were prescribed to all symptomatic patients after excluding contraindications. Thionamides were generally well-tolerated in our cohort, with few patients developing common and mild adverse effects, including rash, pruritus, and gastrointestinal symptoms in the form of gastric irritation, dysgeusia, and loose stools. Two patients developed transaminitis and required transient interruption of the ATDs. These adverse effects were managed with symptomatic measures only.

The remission rate among the patients who completed 18-24 months of the first-line treatment with ATDs was 68% (n=49/72), with the mean duration of remission being 12.87±6.88 months. Remission was considered when the period of euthyroidism lasted for over six months after the termination of ATDs following a standard duration of 18-24 months of drug therapy. A comparison of various characteristics between remitters and non-remitters is provided in Table 4. Higher initial levels of TSH (p=0.007), smoking status (p=0.026), and higher ^{99m}Tc uptake (p=0.05) were associated with remission. Similarly, the development of hypothyroidism during therapy was significantly (p=0.018) associated with remission. Among the 49 patients who achieved remission, 20 patients (41%) relapsed after a mean duration of 11.86±3.34

Table 4. Comparative analysis of the remission and non-remission groups.

Variables		Remission (n=49) Mean±SD	Non Remission (n=23) Mean±SD	Sig.
Age (Years)		38.49±10.96	35.73±8.36	0.123
T3 ng/mL		3.63±1.42	3.71±1.80	0.124
T4 mcg/dL		19.89±5.23	20.46±4.15	0.216
T3/T4 ratio		17.76±5.87	17.95±7.54	0.267
TSH microIU/mL		0.015±0.026	0.009±0.013	0.007*
Anti-TPO level IU/mL		686.28±395.12	557.00±398.98	0.993
Duration of symptoms (months)		5.24±2.31	5.52±3.21	0.069
Duration for Euthyroidism (months)		8.79±3.51	7.36±2.95	0.322
Total 99 mTechnetium uptake%		43.85±24.59	38.56±25.19	0.05*
Gender	M-n (%)	12 (24.5)	10 (43.5)	0.089
	F-n (%)	37 (75.5)	13 (56.5)	
Smoker n (%)		9 (18.4)	10 (43.5)	0.026*
Goitre n (%)		48 (98)	23 (100)	0.681
Goitre grade	1 n (%)	3 (6)	4 (17)	0.264
	2 n (%)	45 (92)	19 (83)	
Orbitopathy n (%)		19 (38.8)	5 (21.7)	0.122
Hypothyroid n (%)		19 (38.8)	3 (13)	0.023*

SD: Standard deviation; *- Significant; Anti-TPO: Anti-thyroid Peroxidase; TSH: Thyroid-stimulating hormone; T4:Total Thyroxine; T3: Total Triiodothyronine; M: Male; F: Female.

Table 5. Comparative analysis of the relapse and non-relapse groups.

Variables		Relapse (n=20) Mean±SD	Non-relapse (n=29) Mean±SD	Significance
Age (Years)		39.50±12.02	37.79±10.32	0.597
T3 ng/mL		4.00±1.72	3.37±1.13	0.131
T4 mcg/dL		21.29±4.43	19.88±3.92	0.246
T3/T4 ratio		18.85±7.32	17.02±4.61	0.287
TSH microIU/mL		0.016±0.026	0.015±0.026	0.910
Anti-TPO level IU/mL		803.76±403.02	607.95±379.12	0.154
Duration of symptoms (months)		5.65±2.71	4.96±1.99	0.314
Total duration of disease (months)		47.40±17.01	52.00±23.10	0.452
Duration for Euthyroidism (months)		8.71±2.94	8.83±3.80	0.923
Total 99 mTechnetium uptake		54.07±26.64	37.28±21.13	0.022*
Gender	M-n (%)	7 (35)	5 (17)	0.140
	F-n (%)	13 (65)	24 (83)	
Smoker n (%)		5 (25)	14 (27.5)	0.543
Goitre n (%)		19 (95)	29 (100)	0.408
Goitre grade	1-n (%)	0	11 (37.9)	0.026*
	2-n (%)	19 (95)	18 (62.1)	
Orbitopathy n (%)		9 (45)	15 (29.4)	0.166

SD: Standard deviation; *- Significant; Anti-TPO: Anti-thyroid Peroxidase; TSH: Thyroid-stimulating hormone; T4:Total Thyroxine; T3: Total Triiodothyronine; M: Male; F: Female.

months (Table 5). Relapse was defined as a reappearance of the signs and symptoms of thyrotoxicosis and the elevation of serum T3 and T4 levels, at least after six months of discontinuation of the ATDs. The relapse rate after the first and second year was

22.5% and 41%, respectively. A comparison between the patients with and without relapse is presented in Table 5. Higher initial ^{99m}Tc uptake (p=0.022) and higher grades of goiter (p=0.026) were significantly associated with the relapse of the disease. Several factors were evaluated in the logistic regression analysis for their potential to predict the relapse of GD, and therefore, the requirement for definitive treatment. Male gender [odds ratio (OR)=0.548, p=0.048] and orbitopathy (OR=0.393, p=0.036) were identified as the independent risk factors predicting the relapse of GD.

Among the patients who failed to achieve remission (n=23), seven patients (mostly young and unmarried patients) were radioablated, while three patients having a large goiter with compressive features underwent surgery. The remaining patients (n=13) preferred undergoing another course of ATDs over the other treatment modalities. The remission rate in both radioablated and surgically-managed patients was 100%. However, Levothyroxine replacement was required in 71.4% (n=5) of the RAI-treated (n=7) and 66.7% (n=2) of the surgically-treated patients, as well as in 17% (n=5) of the initially ATD-treated patients in remission (n=29).

Discussion

Patients with Graves' disease (GD) constitute a major proportion of the patients presenting to the endocrine clinics across the world. GD is a disease with varied clinical presentations, including typical and atypical, and a relatively prolonged course on account of higher rates of recurrences and relapse. Therefore, a proper understanding of the epidemiology and the clinical manifestations of the GD cases, including the atypical ones, is crucial for detecting these disorders at the preclinical stage and preventing the subsequent complications associated with the disease. The association of GD with morbidity and an increased risk of mortality add to the necessity of proper management of this disease and the associated complications. The present retrospective study reports the clinical data, investigative profile, management, and outcome of the GD patients who presented to the endocrine unit of a tertiary-care hospital.

The predominant involvement of women in the present study is in agreement with the findings documented in the literature (4,15,16). This is also consistent with the autoimmune nature of GD, as autoimmune diseases tend to affect females more than males (17). While the females outnumbered the males in the present study, the proportion was less than that reported in the other studies (4,16). This could be the result of the improved iodine status of the population (11), following the universal iodization program and a consequent increase in the tendency for autoimmune disorders (18), which might have ultimately resulted in a lower female to male ratio. Moreover, ethnic variation, regional differences, and/or poor accessibility to medical facilities among females due to various socio-religious factors might also explain the lower female to male ratio.

Although no age group is immune to GD, it most commonly occurs in the third and fourth decade of life. The results of the present study also supported the occurrence of GD in this age group. The mean age (±SD) of presentation of GD in our study cohort was 39.46 (±11.59) years, which is in line with the results reported by a previous study (14). While the youngest age of presentation of GD was 13 years, a 67 year male was also diagnosed with this condition. GD presents with a plethora of characteristic manifestations, resulting from hyperthyroidism, the associated goiter in certain cases, or the underlying autoimmunity. The signs and symptoms observed in our study cohort (Table 2) were consistent with the results documented in the literature (15). Sleep disturbances were present in a significant number of patients in the present study. The exact reason for the same is not known, although factors such as palpitations, heat intolerance, and pruritus could be contributors. The proportion of ophthalmopathy in the present study was 57.4%, which is close to the range of 25-50% reported in the literature (18). One of the highlights of the present study was the presence of pruritus in a significant number of patients (40%), as was reported in a previous study (20), although much higher than the percentage reported in another study (21). Most of our patients responded to antihis-

tamines, although they attained complete relief of their symptoms only upon achieving euthyroidism (21). It is postulated that cell-mediated immunity results in the lowering of the mast cell threshold and the subsequent release of histamine responsible for pruritus in these patients.

One of the important observations of our study was the higher values of ^{99m}Tc uptake in the study cohort notwithstanding the marked improvement in the overall iodine nutrition in the Kashmir Valley (11). However, despite much improvement in the iodization status of the population in the Kashmir region, 49% of the population continued to have urinary iodine excretion below 100 µg/day (11); the fact that under mild to moderate iodine deficiency conditions, the thyroid uptake of ^{99m}Tc-pertechnetate exhibits an inverse correlation with the urinary iodine excretion to compensate for the iodine supply (23) could explain the higher ^{99m}Tc uptake levels observed in our study.

Thionamides are invariably used as first-line medication to control hyperthyroidism and induce remission of the disease, thereby relieving the symptoms. In case of failure of the medical therapy, which is quite common, definitive treatment with surgery or RAI was considered and discussed with the patients. In our cohort, carbimazole was the most common thionamide, used in 98.2% of the patients. Titration regimen is preferred over the block and replace regimen in this part of the world owing to its reduced side effect profile (24,25), independence of the remission rates from the drug type and dosage (26), and non-inferiority to the block and replace regimen. As far as the preferred dosage of carbimazole was concerned no specific criteria was used. However, the dose of carbimazole to be used was influenced by the severity of the disease, the level of T4, and the presence or absence of goiter, orbitopathy, and underlying comorbid conditions.

At the first assessment at three months, most of the patients were controlled (46.1%), with normalization of the TSH levels in 15.6% of them. Although 53.9% of the patients continued to have hyperthyroxinemia, the intensity of its symptoms and the degree of hyperthyroxinemia had improved. Failure to achieve early remission/disease control was significantly higher in male gender (51.7% vs. 48.3%; p=0.003) and smokers (44% vs. 22.5%; p=0.036).

Another important observation in the present study was the development of overt hypothyroidism in 18% of the patients during treatment with anti-thyroid medication, requiring termination/tapering of the dosage, and a few patients requiring thyroxine replacement, as well as its significant association with remission (p=0.023). This could be the result of the progression of autoimmune thyroiditis and/or the development of thyroid-inhibiting immunoglobulins compared to thyroid-stimulating immunoglobulins. Moreover, poor follow-up among patients resulting in failure of drug tapering at the appropriate time could be another reason for the development of hypothyroidism. However, the significant association of drug-induced hypothyroidism with remission favors the possible role of the former in the progression of underlying autoimmune thyroiditis and/or the development of TBII, leading to the remission of the disease in the long run.

The ATDs used for the treatment of GD help to maintain the euthyroid state in the majority of the patients, although they were not curative. Therefore, the possibility of relapse after the discontinuation of ATD remained. In the present study, the remission rate of 68% was observed in the patients who had completed 18-24 months of treatment with ATDs. Those who were uncontrolled (31%) after the initial treatment with ATDs for 24 months, including those who relapsed while the tapering of the drug dose, were considered for definitive treatment modalities, which was consistent with the findings that a treatment duration greater than 12-18 months did not improve the remission rate (27).

The remission rate of 68% after the initial treatment with ATDs in our study was in the range of 61-74% remission rate reported by the other studies (4,26,27). Higher initial TSH (p=0.007), smoking status (0.026), higher ^{99m}Tc uptake (p=0.05), and pharmaceutical hypothyroidism (p=0.023) were significantly associated with remission. The level of ^{99m}Tc uptake at initial presentation

is reported to predict remission in a previous study as well (30). Similarly, smoking status and higher TSH levels are associated with remission (29). The goiter, ophthalmopathy, and dermopathy did not have any association with remission in the present study, similar to the findings of a previous study (30). Among the 49 patients who went into remission, 20 (41%) patients relapsed with a first-year relapse rate of 22.4% (n=11), which is lower than relapse rate values reported in most of the published literature (31,32). However, this observation was consistent with the findings of a study from India, which reported a relapse rate of 19% (30).

Higher ^{99m}Tc uptake (p=0.022) and the presence of goiter (p=0.026) were significantly higher in the relapse group. The association of relapse with higher ^{99m}Tc uptake (30) and the presence of goiter (30) was consistent with the existing literature. Several studies have attempted to identify the factors that might predict the outcome of the disease and assist in selecting the appropriate treatment modality, although with contradictory results. These contradictions are attributed to regional differences, differences in the iodine status of different populations, and different study designs (33). The present study revealed male gender [odds ratio (OR)=0.548, p=0.048] and orbitopathy (OR=0.393, p=0.036) at the onset of disease as the independent factors for predicting the relapse of the disease. Similar results have been documented in the literature, with the studies reporting gender (34,35) and orbitopathy (36) as the independent risk factors known to predict the relapse of the disease.

In this our part of the world, ATDs continue to be the basic treatment option in GD, despite the high frequency of relapse and the potential for adverse effects upon prolonged exposure to ATD. Development of hypothyroidism necessitating lifelong levothyroxine replacement and impaired quality of life limits the use of surgery and RAI as the preferred modalities of management, despite the better outcome of GD reported for them. However, given the unpredictable course of GD and the associated morbidity and increased risk of mortality, discussing the short and long-term risks and efficacy of the different treatment modalities available is crucial for patient satisfaction. Meanwhile, long-term studies with a larger cohort of patients aimed to understand further the natural course of GD and its outcome after the use of different treatment modalities are required to establish the treatment preference for a better prognosis.

Limitations

The limitations of the present study are the same as those of any retrospective cohort study. First and foremost is that selection bias may exist as the outcome had already occurred at the time of data collection. Second, the quality of the available data was not good as the records used were not designed for the present study. This study is further limited by the inability of the participants to undergo thyroid auto-antibody (TRABS) testing due to the absence of such facility at an affordable cost in public or private setup and the absence of ultrasonographic data on thyroid size, thereby preventing us from assessing their role in the prediction of remission and relapse of GD. The other limitation of the present study was a lack of consideration for non-autoimmune diffuse hyperthyroidism and Hashitoxicosis as differentials for GD in the presence of atypical features. A prospective study design would allow a better understanding of the association of the various risk factors with the treatment outcome Graves' disease.

Conclusion

GD is the most common cause of hyperthyroidism and is associated with significant morbidity and an increased risk of mortality. GD predominantly affects females and occurs commonly in the third and fourth decade of life. Varied non-specific clinical manifestations, particularly the atypical presentations, warrant early recognition and subsequent management to minimize the morbidity associated with an undiagnosed condition. ATDs are applied as the primary modality for the management of GD, despite the high frequency of disease relapse reported for them. The other treatment modalities, namely, RAI and surgical management of disease, despite their respective shortcomings, should be discussed with the

patients and offered at an appropriate time to avoid the side effects of ATDs and the anxiety associated with long-term drug intake. Long-term studies assessing the disease outcome after different treatment modalities should be conducted to better understand the course of the disease and establish a treatment preference for a better prognosis.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mohammad Hayat Bhat, Shariq Rashid Maoodi; Design: Mohammad Hayat Bhat, Javaid Ahmad Bhat, Sharig Rashid Maoodi; Control/Supervision: Mohammad Hayat Bhat, Sharig Rashid Maoodi, Waseem Qureshi; Data Collection and/or Processing: Javaid Ahmad Bhat, Junaid Rashid Dar, Moomin Hussain Bhat; Analysis and/or Interpretation: Mohammad Hayat Bhat, Javaid Ahmad Bhat, Sharig Rashid Maoodi, Waseem Qureshi, Junaid Rashid Dar, Moomin Hussain Bhat; Literature Review: Mohammad Hayat Bhat, Javaid Ahmad Bhat, Sharig Rashid Maoodi, Waseem Qureshi, Junaid Rashid Dar, Moomin Hussain Bhat; Writing the Article: Mohammad Hayat Bhat, Javaid Ahmad Bhat, Sharig Rashid Maoodi; Critical Review: Waseem Qureshi, Javaid Ahmad Bhat, Moomin Hussain Bhat, Junaid Rashid Dar; References and Fundings: Mohammad Hayat Bhat, Javaid Ahmad Bhat, Sharig Rashid Maoodi, Waseem Qureshi; Materials:Mohammad Hayat Bhat, Javaid Ahmad Bhat, Waseem Qureshi, Junaid Rashid Dar.

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