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RESEARCH

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Characterization, treatment preferences, and outcomes of 390 Egyptian Graves' disease patients: a retrospective study

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Abstract

Background Graves' disease is the most common cause of thyrotoxicosis worldwide. Patient characteristics may vary according to ethnicity, iodine status, and age. Studies on characterization of Graves' disease in Egypt are lacking. The present study aims to report the patient characteristics, as well as treatment preferences and outcomes of Graves' disease patients from Alexandria, Egypt.

Methods A retrospective review of demographic, biochemical, serological, sonographic, and treatment data of Graves' disease patients attending endocrinology outpatient clinic, Alexandria faculty of medicine, Egypt.

Results Three hundred ninety patients were included. Females were 75.9%, peak age was 21–40 years representing 53.1%, and family history of thyroid disease was positive in 60% of patients. Overt hyperthyroidism was present in 93.9%, TSH receptor antibodies were positive in 97.1%, and thyro-peroxidase antibodies in 74.8%. Goiter was present in 72.8%, nodularity in 18.4%, and thyroid eye disease in 17.7%. Medical treatment was used in 90% of patients, surgery in 5.4%, and radioiodine in 4.3%. For patients on medical treatment, 17.7% achieved remission, 29% relapsed, and 2.85% developed hypothyroidism.

Conclusion A typical Graves' disease patient in Egypt is a middle-aged female with a positive family history of thyroid disease. Overt hyperthyroidism was the most common presentation and goiter was a common sign at presentation. The sensitivity of TRAb's for diagnosing Graves' disease was excellent (97.1%). ATD's was the commonest treatment modality with a remission rate of 17.7% and a relapse rate of 29%.

Keywords Graves' disease, Hyperthyroidism, Egypt, Africa, TRAb's

Background

Graves' disease is the most common cause of thyrotoxicosis worldwide. It is an autoimmune disease where TSH receptor autoantibodies (TRAb's) – acting on thyrotropin (TSH) receptors – lead to a diffuse goiter and variable degrees of hyperthyroidism. It may be associated with extra-thyroidal manifestations like thyroid eye disease (TED), dermopathy, or acropachy. It is more common in females, middle age, and in iodine replete areas [1].

Lines of treatment include medical treatment with antithyroid drugs (ATD's), thyroidectomy, or radioiodine ablation. Treatment with antithyroid drugs (ATD's) may lead to remission of the disease, however, a patient may relapse even years after achieving remission. Ablative treatments whether surgery or radioiodine ablation, lead to hypothyroidism in almost all the patients. Hypothyroidism may occur after treatment with medical treatment in up to 20 percent of the patients [2, 3].

Patient characteristics may vary according to ethnicity, iodine status, and age. Characterization of patients with

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Graves' disease has been previously reported from west Africa and Europe [4, 5]. Treatment preferences and outcomes were also reported from Europe and Asia [5, 6]. Studies on prevalence and characterization of Graves' disease in Egypt are lacking.

The present study aims to fill a part of the knowledge gap about Graves' disease in Egypt by reporting the demographic, biochemical, serological, sonographic data, treatment preferences and outcomes of 390 Graves' disease patients from Alexandria, Egypt.

Methods

The medical records of all patients who received a diagnosis of graves' disease, attending endocrinology outpatient clinic, Alexandria faculty of medicine were retrospectively reviewed. This clinic is a tertiary referral center serving patients from 3 Egyptian governorates; Alexandria, Beheira, and Mersa Matruh. All Graves' disease patients attending the clinic in the period from October 2020 to September 2022 were included in the review. When available, a diagnosis of Graves' disease was made based on a positive TSH receptor autoantibodies (TRAb's) (Roche Diagnostics, Mannheim, Germany on Cobas E 8000 platform, [Normal < 1.75 IU/L]). When TRAb's were not available, a diagnosis of Graves' disease was made based on the presence of persistent thyrotoxicosis showing a good response to antithyroid drugs plus a single or a combination of other parameters: an increased radioactive iodine uptake, the presence of thyroid eye disease, high thyro-peroxidase (TPO) autoantibodies, or a sonographic pattern consistent with autoimmune thyroid disease.

Demographic data included sex of the patient and age at the time of presentation. Clinical data included the presence of a goiter, the presence of thyroid eye disease, family history of thyroid disease, and comorbidity history. Biochemical data of thyroid function tests at the time of presentation were reviewed. Patients were classified into 3 categories: T3-toxicosis, subclinical, and overt hyperthyroidism [2]. T3-toxicosis was diagnosed when the patient presents with suppressed TSH, a normal free T4, and a high free T3. Subclinical hyperthyroidism was diagnosed when TSH is suppressed and both Free T3 and Free T4 are normal. Overt hyperthyroidism (OH) was diagnosed when TSH was suppressed and Free T4 was high. Overt hyperthyroidism was further subdivided according to degree of elevation of Free T4 into mild hyperthyroidism when free T4 was 1.7 to 3.9 ng/dl, moderate when free T4 was 3.9 to 7.7 ng/dl, and severe when free T4 was > 7.8 ng/dl [7] (Roche Diagnostics, Mannheim, Germany on Cobas E 411 analyzer [Normal 0.93–1.7 ng/dL]).

When available, serological data were reviewed including thyro-peroxidase (TPO) and thyroglobulin (Tg) autoantibodies status. Also, when available, sonographic data were reviewed including the presence of a goiter, as well as signs of autoimmune thyroid disease (AITD) namely: hypo-echogenicity, heterogenicity, pseudo-nodules, micro-nodulation, fibrous septae and pseudo-lobulation [8].

Treatment modality whether medical treatment, surgery, or radioiodine ablation were reviewed. Antithyroid drugs (ATD's) dose and duration of treatment were reviewed. Remission was defined as maintenance of euthyroidism for six months after discontinuation ATD's [9]. The numbers of patients who achieved remission and time to remission were reviewed. Numbers of patients who relapsed and time to relapse were also reviewed. Lastly, time to ablation and doses of radioiodine were reviewed.

The protocol of the study was approved by the ethical committee of Alexandria faculty of medicine [IRB number 12098].

Results

A total of 390 graves' disease patients were included in this retrospective review. Main findings of the review are summarized in Table 1.

Demographic data

Most of the patients were females 296/390 (75.9%), males were only 94/390 (24.1%), with a female to male ratio of 3.1:1. The age of patients at the time of presentation ranged from 7 to 78 years. The median age was 33 years, the mean ± standard deviation (SD) was 35.3 ± 13.6 years. Peak age was from 21 to 40 years of age representing 53.1% of all patients (Fig. 1).

Family and comorbidity history

Family history of thyroid disease was positive in 234/390 (60%) of patients, with the number of affected relatives ranging from 1 to 10 relatives and a mean and a median of 2 relatives. The history of comorbidity was significant for metabolic syndrome components; hypertension in 62, dyslipidemia in 28, prediabetes in 12, type 2 diabetes in 26, and polycystic ovary syndrome in 2 patients. Autoimmune endocrinopathies; type 1 diabetes in 5, and primary ovarian insufficiency in one patient. Non-endocrine autoimmune diseases; vitiligo in 3, systemic lupus in 2, rheumatoid arthritis in 5, Crohn's disease in 1, ulcerative colitis in 1, celiac disease in 1, and myasthenia gravis in 1 patient. Cancer breast in 5 patients. Cardiovascular disease; heart failure in 3, atrial fibrillation in 7, coronary heart disease in 3, wolf Parkinson white syndrome in 1, and peripheral

Table 1 Demographic, biochemical, serological characteristics, treatment preferences and outcomes of 390 graves' disease patients

Patient's characteristics	Number (Percent)
Sex	
Females	296 (75.9%)
Males	94 (24.1%)
Family history of thyroid disease	234 (60%)
Thyroid function at presentation	344 (88.2%)
T3-Toxicosis	10 (2.9%)
Subclinical hyperthyroidism	11 (3.2%)
Overt hyperthyroidism	323 (93.9%)
mOH – mild overt hyperthyroidism	144 (44.6%)
MOH – moderate overt hyperthyroidism	118 (36.5%)
SOH – severe overt hyperthyroidism	61 (18.9%)
TSH receptor autoantibodies	
Order rate	340 (87.2%)
Positivity rate	330 (97.1%)
Thyro-peroxidase autoantibodies	
Order rate	226 (57.9%)
Positivity rate	169 (74.8%)
Thyroglobulin autoantibodies	
Order rate	119 (30.5%)
Positivity rate	65 (54.6%)
Thyroid eye disease	69 (17.7%)
Goiter	284 (72.8%)
Treatment modality	
Medical treatment (ATD's)	351 (90%)
Surgery	21 (5.4%)
Radioiodine ablation	17 (4.3%)
Medical treatment outcomes	
Remission	62 (17.7%)
Relapse	18 (29%)
Hypothyroidism	10 (2.85%)

arterial disease in 1 patient. Allergic disorders; bronchial asthma in 14, and allergic rhinitis in 8 patients. Gastrointestinal disorders; irritable bowel syndrome in 15, peptic ulcer disease in 8, and gastro-esophageal reflux in 3 patients (Table 2).

Biochemical data

Thyroid function tests at the time of diagnosis were available for 344 patients (88.2%). T3 toxicosis was present in 10/344 patients (2.9%). Subclinical hyperthyroidism was present in 11 patients (3.2%). Overt hyperthyroidism was present in 323 patients (93.9%) classified as follows: mild OH 144/323 (44.6%), moderate OH 118/323 (36.5%), and severe OH 61/323 (18.9%) (Table 1).

Serological data

TRAb's were available for 340 patients (87.2%) at the time of initial presentation. 330 patients were positive and only 10 patients were negative yielding a sensitivity of the used assay of 97.1% for the diagnosis of Graves' disease. The 10 patients who were negative for TRAb's and the remaining 50 patients received a diagnosis of Graves' disease based on the presence of a single or a combination of other parameters. An increased RAIU in 3 patients, high TPO antibodies in 20 patients, a sonographic pattern consistent with AITD in 45 patients, or the presence of TED in 18 patients. Thyroperoxidase antibodies were available for 226 patients. TPO antibodies were positive in 169/226 (74.8%). Thyroglobulin antibodies were available for 119 patients. Tg antibodies were positive in 65/119 (54.6%) (Table 1).

Sonographic data

Goiter was detectable either by clinical examination or by ultrasound in 284 patients (72.8%). Ultrasound of the thyroid was available for 348 patients (89.2%). Sonographic signs consistent with autoimmune thyroid disease were detectable in the following frequencies: hypo-echogenicity in 98/348 (28.2%), heterogenicity in 244/348 (70.1%), micro-nodulation in 55/348 (15.8%), fibrous septae with pseudo-lobulation in 101/348 (29%), and pseudo-nodules in 46/348 (13.2%). Nodularity was detected by ultrasound in 64 patients representing 18.4% of those with available ultrasound examination. Less than half 29/64 (45.3%) had a solitary nodule (Fig. 2).

Thyroid eye disease

Thyroid eye disease was present in 69 patients at the time of presentation representing 17.7% of the whole cohort.

Treatment preferences

Most of the patients were treated medically using antithyroid drugs 351/390 (90%). Both carbimazole and propylthiouracil (PTU) are available in Egypt, so basically patients were treated with carbimazole except during the first 16 weeks of pregnancy when they are switched to PTU. One patient was diagnosed early in pregnancy with subclinical hyperthyroidism and was observed throughout pregnancy without treatment. Thirty-eight patients (9.7%) received definitive treatment in the form of surgery in 21 patients (5.4%) and radioiodine ablation in the remaining 17 patients (4.3%).

Medical treatment outcomes

A record of carbimazole doses and duration of treatment were available for 350 patients. Maximum

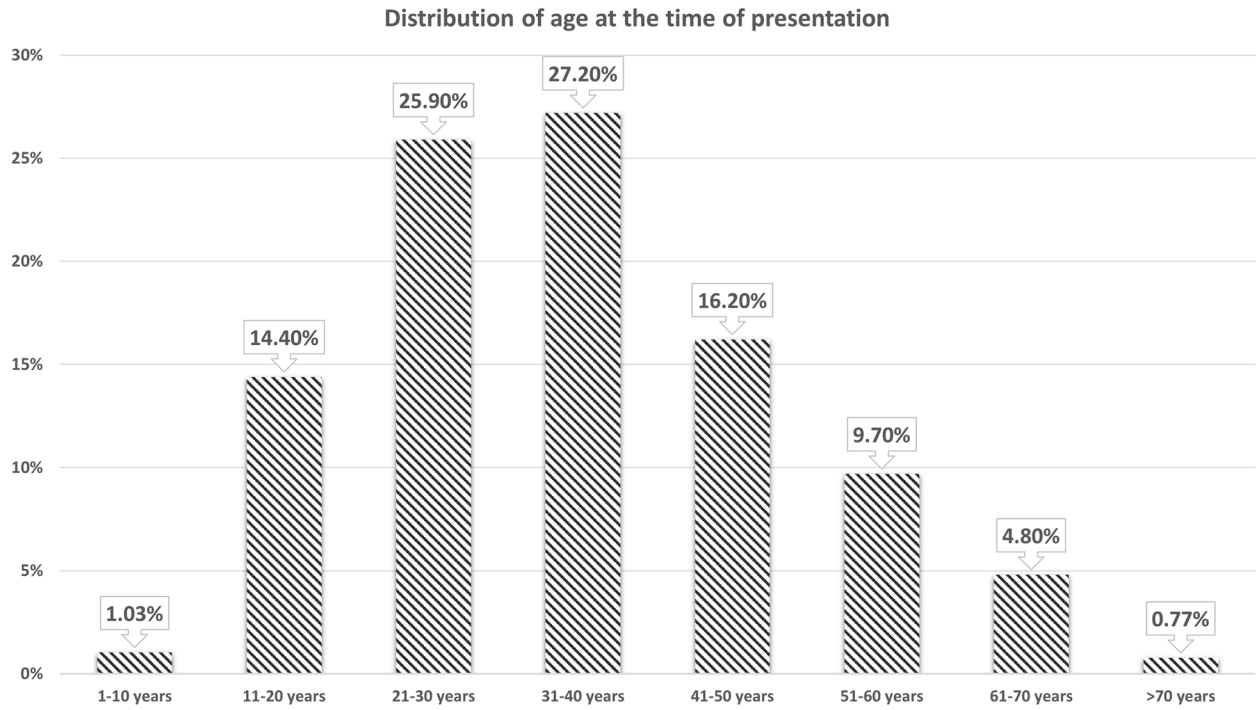

Fig. 1 Distribution of age at the time of presentation

Table 2 History of comorbidity in graves' disease patients

Comorbidity categories	Number (percentage)
Metabolic syndrome components	**128 (32.8%)**
Hypertension, dyslipidemia, pre-diabetes, type 2 diabetes	
Autoimmune disorders	**20 (5.1%)**
Type 1 diabetes, primary ovarian insufficiency, celiac disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis, systemic lupus erythromatosis, vitiligo, myasthenia gravis	
Cardiovascular disease	**15 (3.8%)**
Coronary artery disease, heart failure, atrial fibrillation, peripheral artery disease, Wolff Parkinson white syndrome	
Allergic disorders	**22 (5.6%)**
Bronchial asthma, allergic rhinitis	
Gastrointestinal diseases	**26 (6.7%)**
Irritable bowel syndrome, peptic ulcer disease, gastroesophageal reflux disease	

carbimazole dose prescribed for patients during their treatment ranged from 5 mg/day to 100 mg/day. The median dose was 30 mg/day, the mean ± SD was 27 ± 14 mg/day. Among patients who did not achieve remission nor opted for a definitive treatment, the duration of treatment ranged from 1 to 240 months. The median duration of treatment was 16 months, while the mean was 34 ± 44 months. Four patients developed agranulocytosis. Two opted for surgery, one opted for RAI ablation, and one achieved remission.

Sixty-two patients achieved remission in the reviewed cohort representing 15.9% of the total cohort, 17.7% after excluding those who opted for ablative therapies. Time to remission ranged from 4 to 180 months, with a median of 23.5 months and a mean ± SD of 34 ± 30.2 months. TRAb's were available for 44 patients at the time of ATD's discontinuation. They ranged from 0.1 to 40, they were positive in 13/44 patients (29.5%), with a median of 0.97 and a mean ± SD of 2.62 ± 6.2. 18 patients relapsed after achieving remission (29%). Time to relapse ranged from 6 to 180 months, with a median of 21 months and a mean ± SD of 29.44 ± 39.7 months. TRAb's were available for 11 patients at the time of relapse. They ranged from 1.13 to 34.4, they

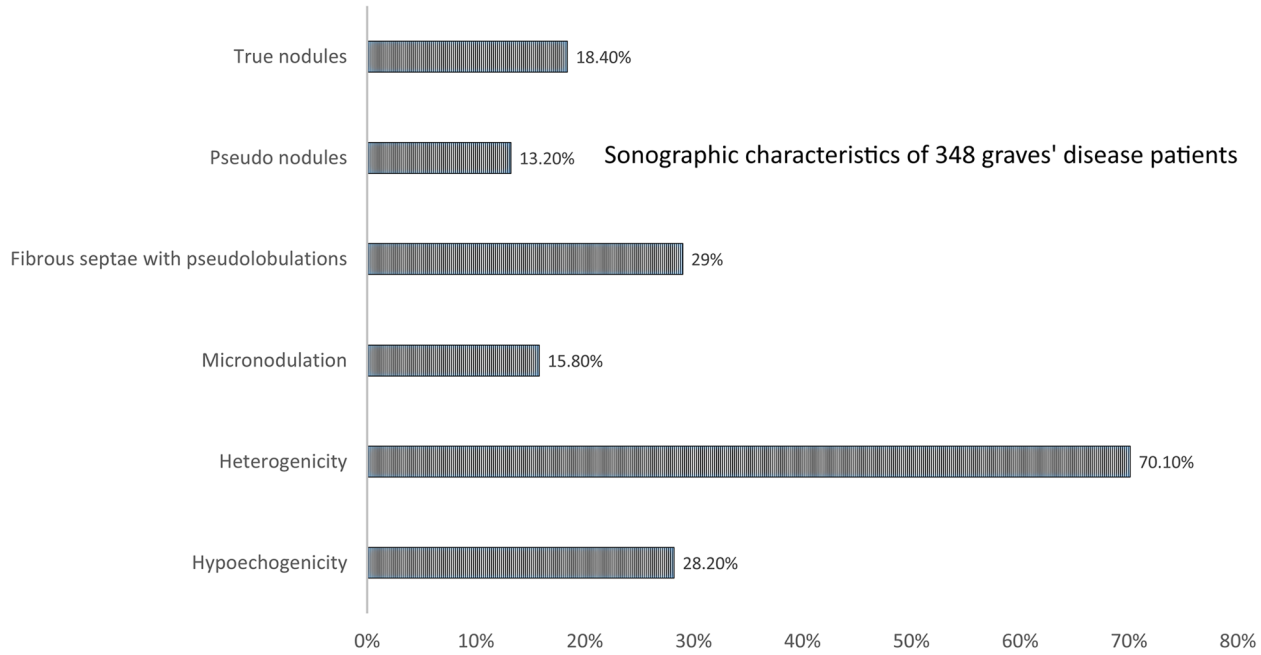

Fig. 2 Sonographic characteristics of 348 graves' disease patients

were positive in 10/11 patients (91%), with a median of 4.16 and a mean ± SD of 9.75 ± 11.2.

Spontaneous hypothyroidism after remission of graves' disease occurred in 10/351 (2.85%). Time to hypothyroidism after remission ranged from 2–60 months. 6 patients developed subclinical hypothyroidism and 4 developed overt hypothyroidism.

Ablative treatments

Time to surgery ranged from 3–180 months. The median time was 17 months, the mean ± SD was 17 ± 36.9 months. Two patients who opted for surgery were found to have papillary thyroid carcinoma. Time to radioiodine ranged from 1–240 months. The median time was 24 months, the mean ± SD was 49.4 ± 63.4 months. 5 patients required 2 doses of radioiodine to achieve hypothyroidism. One patient required 3 doses of radioiodine to achieve hypothyroidism. A single dose of radioiodine ranged from 6 to 25 millicurie (mCi). Cumulative doses of radioiodine ranged from 6 to 45 mCi.

Discussion

This is the first study to characterize a large cohort of Graves' disease patients from the north African country, Egypt. A retrospective review of the medical records of 390 graves' disease patients attending endocrinology outpatient clinics, Alexandria faculty of medicine in the period from October 2020 to September 2022 was reported.

Graves' disease is the most common cause of hyperthyroidism in iodine sufficient areas accounting for about 80% of the cases, especially in adults below 50 years of age [1, 10]. 84.7% of the patients reviewed in the present study were 50 years of age or younger. Egyptian national universal salt iodization has started in 1996. The latest Egyptian national health survey has demonstrated that 91% of household used iodized salt. A large subnational survey showed that only 10% of school children were iodine deficient defined as urinary iodine excretion of less than 100 µg/L [11, 12]. Salt iodization initially increases incidence of hyperthyroidism, mainly due to thyroid autonomy, however it does not affect the incidence of Graves' disease [10].

In the present study, the mean age was 35.3 years compared to 39.9 in a west African cohort of 182 patients, 36.3 in an Asian cohort of 2736 patients, and 43.3 in a French cohort of 802 patients [4–6].

TSH receptor auto-antibodies (TRAb's) has been recommended by the European thyroid association (ETA) to be the test of choice to confirm the diagnosis of Graves' disease. Compared to radioactive iodine uptake, TRAb's saves time to diagnosis and costs by almost 50% [2]. TRAb's were ordered for 87% of our patients, whereas only 3 patients were diagnosed using radioactive iodine uptake studies (less than 1%). Reported sensitivities of second and third generation TRAb's assays were 97.1%, and 97.4% respectively, which is the same sensitivity found in our patients, 97.1% [13].

In the west African cohort, the test was performed in 67% and it was positive in 99%, while in the French cohort, the test was performed in 60.6% and it was positive in 95.8% [4, 5]. The test was least used in the Asian cohort where only 3.7% had the test at initial presentation [6].

Ultrasound thyroid is currently recommended to support the diagnosis of Graves' disease after serology [2]. Sonographic signs of autoimmune thyroid disease include hypo-echogenicity, heterogenicity, pseudo-nodules, micro-nodulation, fibrous septae and pseudo-lobulation. The infiltration by immune cells and decreased colloid leads to a decreased colloid cell interface resulting in the hypo-echogenicity characteristic of Graves' disease [8, 14]. Heterogenicity, septae with pseudolobulation, and hypo-echogenicity were the most common sonographic signs in our patients.

Currently, medical treatment using antithyroid drugs is the recommended first line treatment for Graves' disease. In the latest ETA guidelines, lifelong medical treatment has been suggested for patients who did not achieve remission after 30 months of treatment or those who relapsed who prefer this line of treatment. It was also considered a satisfactory treatment for older individuals with mild disease [2]. In a recent systematic review, long term antithyroid drugs of more than 18 months was considered safe, in low doses and in adults, with only 0.8% incidence of major complications [15]. Ninety percent of our patients were treated with antithyroid drugs for a mean duration of 34 ± 44 months. Some of the patients received medical treatment for durations up to 20 years. 4/351 patients (1.1%) developed agranulocytosis, 3 patients required definitive treatment, while one patient achieved remission.

In the French cohort, treatment preferences were 91%, 6.1%, and 2.9% for medical treatment, surgery, and radioiodine, respectively [5]. For the Asian cohort, treatment preferences were 72.6%, 0.9%, and 26.5% for medical treatment, surgery, and radioiodine, respectively [6]. The combination of ATD's and levothyroxine or the block-replace regimen was never used in the present cohort. In the French cohort, it was used in 41.2%, while in the Asian cohort, it was used in only 1.9% [5, 6].

Among patients who opted for medical treatment, 17.7% achieved remission, and later 29% of whom relapsed. In the Asian cohort, 30.7% achieved remission, and 56.3% relapsed, while in the west African cohort, remission rate was 54.9% [4, 6]. The low rates of remission in the present study may be related to racial or environmental factors. A prospective trial with focus on known predictors of remission is needed to confirm this rate and provide predictive factors in Egyptians.

Spontaneous persistent hypothyroidism occurs as a sequel of Graves' disease patients treated with antithyroid drugs in 5–20% of the cases. The mechanisms involved were either blocking TSH receptor antibodies or destructive thyroiditis [16]. In the present study, 10 patients (2.85%) developed hypothyroidism following treatment with ATD's. time to hypothyroidism ranged from 2 months and up to 5 years after stopping ATD's. A similar incidence was reported from the Asian cohort of 2.3% [6].

The present study has the strength of being the first and only to characterise graves' disease patients in Egypt with a relatively large number of patients compared to similar studies conducted in Africa [17].

The present study has few limitations. The data about initial clinical presentation were lacking in most of the reviewed records, such data would have been useful in reporting the pattern of clinical presentation of Egyptian patients with Graves' disease. Variable length of follow up data for the reviewed patients – from 3 months and up to 20 years – may have affected the reported rates of remission and adverse events of ATD's. The record of 20 pregnancies were found in the patients' files, pregnancy may have affected treatment preferences and outcomes.

Conclusions

In conclusion, a typical Graves' disease patient in Egypt is a middle-aged female with a positive family history of thyroid disease, overt hyperthyroidism was the most common presentation and goiter was a common sign at presentation, the sensitivity of TRAb's for diagnosing Graves' disease was excellent (97.1%), thyroid eye disease was present in 17.7%, and ATD's was the commonest treatment modality with a remission rate of 17.7% and a relapse rate of 29%.

Abbreviations

TRAb's	TSH receptor autoantibodies
TED	Thyroid eye disease
ATD's	Antithyroid drugs
TPO	Thyro-peroxidase
OH	Overt hyperthyroidism
Tg	Thyroglobulin
AITD	Autoimmune thyroid disease
PTU	Propylthiouracil
mCi	Millicurie
ETA	European thyroid association

Authors' contributions

The author contributed to the study conception, design, material preparation, data collection, and writing the manuscript.

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Availability of data and materials
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol of the study was approved by the ethical committee of Alexandria faculty of medicine, [IRB number 12098].

Competing interests
The authors have no relevant financial or non-financial interests to disclose.

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References

1. De Leo S, Lee SY, Braverman LE (2016) Hyperthyroidism. Lancet 388(10047):906–918
2. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH (2018) 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J 7(4):167–186
3. Tamai H, Hirota Y, Kasagi K, Matsubayashi S, Kuma K, Iida Y, Konishi J, Okimura MC, Walter RM, Kumagai LF et al (1987) The mechanism of spontaneous hypothyroidism in patients with Graves' disease after antithyroid drug treatment. J Clin Endocrinol Metab 64(4):718–722
4. Sarfo-Kantanka O, Sarfo FS, Ansah EO, Kyei I (2018) Graves Disease in central Ghana: clinical characteristics and associated factors. Clin Med Insights Endocrinol Diabetes 11:1179551418759076
5. Goichot B, Bouée S, Castello-Bridoux C, Caron P (2017) Survey of Clinical Practice Patterns in the Management of 992 Hyperthyroid Patients in France. Eur Thyroid J 6(3):152–159
6. Thewjitcharoen Y, Karndumri K, Chatchomchuan W, Porramatikul S, Krittiyawong S, Wanathayanoroj E, Lekpittaya N, Kittipoom W, Anuntakulnatee T, Vongterapak S, Butadej S, Nakasatien S, Rajatanavin R, Himathongkam T (2021) Practice patterns and outcomes in the management of Thai patients with Graves' disease. Thyroid Res 14(1):5
7. Iglesias P, Dévora O, García J, Tajada P, García-Arévalo C, Díez JJ (2010) Severe hyperthyroidism: aetiology, clinical features and treatment outcome. Clin Endocrinol (Oxf) 72(4):551–557
8. Mahmoud R, Azeem KM, Sayed ASA et al (2022) Role of ultrasound and Doppler findings as a predictor of thyroid hormonal levels in cases of Hashimoto thyroiditis. Beni-Suef Univ J Basic Appl Sci 11:28. https://doi.org/10.1186/s43088-022-00197-0
9. Song A, Kim SJ, Kim MS, Kim J, Kim I, Bae GY, Seo E, Cho YS, Choi JY, Cho SY, Jin DK (2021) Long-term antithyroid drug treatment of graves' disease in children and adolescents: a 20-year single-center experience. Front Endocrinol (Lausanne) 12:687834
10. Zimmermann MB, Boelaert K (2015) Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 3(4):286–295
11. Elsayed HH, El-Rahman MKA, ATawwfik A (2015) Iodine Status of primary School Children in Different Egyptian Environments. Egyptian J Hosp Med 61:451–458
12. Ministry of Health and Population [Egypt], El-Zanaty and Associates [Egypt], ICF International (2015) Egypt Demographic and Health Survey 2014. Ministry of Health and Population and ICF International, Cairo
13. Tozzoli R, Bagnasco M, Giavarina D, Bizzaro N (2012) TSH receptor autoantibody immunoassay in patients with Graves' disease: improvement of diagnostic accuracy over different generations of methods. Systematic review and meta-analysis. Autoimmun Rev 12(2):107–113
14. Yuen HY, Wong KT, Ahuja AT (2016) Sonography of diffuse thyroid disease. Australas J Ultrasound Med 19(1):13–29
15. Azizi F, Malboosbaf R (2019) Safety of long-term antithyroid drug treatment? A systematic review. J Endocrinol Invest 42(11):1273–1283
16. Tamai H, Kasagi K, Takaichi Y, Takamatsu J, Komaki G, Matsubayashi S, Konishi J, Kuma K, Kumagai LF, Nagataki S (1989) Development of spontaneous hypothyroidism in patients with Graves' disease treated with antithyroidal drugs: clinical, immunological, and histological findings in 26 patients. J Clin Endocrinol Metab 69(1):49–53
17. Azeez TA, Adetunji TA, Adio M (2022) Thyrotoxicosis in Africa: a systematic review and meta-analysis of the clinical presentation. Egypt J Intern Med 34:57. https://doi.org/10.1186/s43162-022-00145-5

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