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The Role of Graves' Disease in the Development of Thyroid Nodules and Thyroid Cancer

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DESIGNAÇÃO DA ÁREA DO PROJECTO

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TÍTULO DISSERTAÇÃO

The Role of Graves' Disease in the Development of Thyroid Nodules and Thyroid Cancer

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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DEDICATÓRIA

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The Role of Graves' Disease in the Development of Thyroid Nodules and Thyroid Cancer

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ABSTRACT

Aim: The prevalence of thyroid nodules and the risk of thyroid cancer in patients with Graves' disease is uncertain. We aimed to evaluate the prevalence of thyroid nodules and cancer in patients with Graves' disease.

Methods: Retrospective observational study of adult subjects with Graves' disease (positive autoantibodies TRAbs) between 2017 and 2021 at our center. We evaluated the prevalence of thyroid nodules and cancer in this population and characterized the predictive factors for thyroid malignancy using linear and logistic regression models.

Results: We evaluated a total of 539 patients with Graves' disease during a median follow-up of 3.3 years (25^{th}-75^{th} percentiles 1.5-5.2 years). Fifty-three percent had thyroid nodules and 18 (3.3%) were diagnosed with thyroid cancer (12 papillary microcarcinomas). All tumors were classified using TNM classification as T1, and only one had lymph node metastasis; there were no recordings of distant metastasis. Sex, age, body mass index, smoking, TSH and TRAbs levels were not significantly different between patients with and without thyroid cancer. Patients with multiple nodules on ultrasound (OR 1.61, 95%CI 1.04-2.49) and with larger nodules (OR 2.96, 95%CI 1.08-8.14, for 10mm increase in size) had a greater risk of thyroid cancer diagnosis.

Conclusion: Patients with Graves' disease had a higher prevalence of thyroid nodules and their nodules had a significant risk of thyroid cancer compared to general population. The risk was higher in those with multiple and larger nodules. Most had low grade papillary thyroid cancer. More studies are needed to clarify the clinical relevance of these findings.

Keywords: Graves' disease; Papillary Thyroid carcinoma; Thyroid nodule; Hyperthyroidism; Thyrotoxicosis.

INTRODUCTION

Graves' disease is an autoimmune thyroid disease, being the most frequent cause of hyperthyroidism [1]. It is caused by the production of autoantibodies (TRAbs) against the thyrotropin receptor (TSH-R) [2]. These act as TSH-R agonists and induce hypersecretion of thyroid hormones [3]. In addition, TSH-R is also involved in the normal physiology and growth of the thyroid gland, participating in its organogenesis, cell differentiation and iodine uptake, which may lead to the formation of goiter when faced with a strong stimulus [4].

Differentiated thyroid carcinoma, which originates in the epithelial follicular thyroid cells, represents about 95% of thyroid cancer cases. It includes papillary thyroid carcinoma, follicular thyroid carcinoma, and Hürthle cell carcinoma of the thyroid [5]. Papillary thyroid carcinoma (PTC) is the most common histological subtype of differentiated thyroid malignancy, constituting about 80% of cases [6]. The age of presentation, gender, histology and stage of the tumor are factors that influence its prognosis [7].

Graves' disease has been associated with an increased risk of thyroid cancer [8]. Several case reports suggest an aggressive behavior of thyroid cancer in patients with Graves' disease [9]. The mechanism for this increased risk is still not fully understood, but the binding of TRAbs to TSH-R is probably one of the main mechanisms [10]. By positively stimulating thyroid growth, production of growth factors and angiogenesis, TRAbs may promote tumor development and invasion [11]. However, predictive factors for thyroid cancer in patients with Graves' disease are still unknown [12].

Thus, our aim was to evaluate the prevalence of thyroid nodules and thyroid cancer in patients with Graves' disease and to characterize the predictive factors of thyroid malignancy.

MATERIAL AND METHODS

Study Design and Participants

We performed a retrospective longitudinal observational study at Centro Hospitalar Universitário de São João (CHUSJ) in Porto, Portugal, to evaluate the prevalence of thyroid nodules and thyroid cancer in patients with Graves' disease and to characterize the predictive factors of thyroid malignancy. The studied population consisted entirely of adult subjects with positive TRAbs between 2017 and 2021 (all participants under eighteen years of age were excluded from this selection).

Our study was approved by the Ethics Committee of CHUSJ/ Faculty of Medicine of the University of Porto.

The data analyzed in this study was collected retrospectively from electronic clinical records in May 2022.

Clinical Characteristics and Study Outcomes

The following parameters were collected from the patients' clinical records: sex, age, age at diagnosis of Graves' disease, initial TRAbs, FT3, FT4, TSH, height, weight, smoking habits, treatment for Graves' disease (type of antithyroid drug, maximum dose; duration and number of iodine ablative doses; thyroidectomy), diagnosis of ophthalmopathy, diagnosis of dermopathy, thyroid ultrasound results, results of biopsies and thyroid carcinoma (histology, classification and tumor size).

Thyroid biopsies were classified according to the Bethesda classification [13].

Statistical analysis

Baseline characteristics of patients with and without diagnosis of thyroid cancer were compared with Student's t-test, Mann Whitney test for normal and nonnormal continuous variables respectively, and the chi-square test for categorical variables.

The association of predictors with the presence of thyroid nodules and the diagnosis of thyroid cancer was evaluated using linear regression (for continuous

outcomes) and logistic regression (for dichotomic outcomes).

Continuous variables are described as mean ± standard deviation or median (25–75th percentiles) for normal and nonnormal continuous variables respectively, and categorical variables as proportions (percentages).

A two-sided P-value of <0.05 was considered statistically significant. Analyses were performed with Stata (version 17.0).

RESULTS

The baseline characteristics of the 539 patients with Graves' disease are shown in *Table 1*. Eighteen percent were men and their mean age at diagnosis was 45.7 ± 15.1 years. The mean BMI at diagnosis was 25.6 ± 4.9 kg/m^2. Twenty-four percent had ophthalmopathy and 1.3% had dermopathy. Sixty-one percent never smoked, 31.1% were current smokers and 7.6% were former smokers. Regarding treatment, 84.1% received methimazole and 9.5% received propylthiouracil. The median methimazole dose was 7.5 (5-15) mg and the median propylthiouracil dose was 150 (100-300) mg. The median duration of antithyroid treatment was 20.0 (11.0-36.0) months. The follow-up time was 3.3 (1.5-5.2) years. Eighty percent of the patients did not receive any ablative dose with radioactive iodine, 18.3% received one, 1.7% received two and 0.2% received three doses. From the 539 patients evaluated, 361 (67.0%) patients had thyroid function results available before starting antithyroid drugs. The baseline median values of thyroid function were the following: TSH 0.001 (0.0-0.008) UI/mL, FT4 1.7 (1.1- 2.3) ng/dL and FT3 5.7 (3.7-10.1) pg/mL.

Table 1. Baseline Characteristics (n=539)	
Male, n (%)	98 (18.2%)
Age, years	45.7 ± 15.1
BMI, kg/m^2	25.6 ± 4.9
Ophthalmopathy, n (%)	128 (23.9%)
Dermopathy, n (%)	7 (1.3%)
Smoking habits, n (%)	
Non-smoker, n (%)	321 (61.3%)
Current smoker, n (%)	163 (31.1%)
Ex-smoker, n (%)	40 (7.6%)
Antithyroid, n (%)	
Methimazole, mg	408 (84.1%)
Propylthiouracil, mg	46 (9.5%)
Initial TRAbs, U/L	7.5 (3.7 - 21.8)
TSH, UI/mL	0.001 (0.0-0.008)
FT4, ng/dL	1.7 (1.1-2.3)
FT3, pg/mL	5.7 (3.7-10.1)

BMI, body mass index; TRAbs, anti-TSH receptor antibodies; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine

Table 2 shows the data related to the first ultrasounds performed after the diagnosis of Graves' disease. Of the 539 patients, 97.6% were evaluated with thyroid ultrasound. 55.0% had at least one nodule, and 39.1% had multiple nodules. The median size of the largest nodule was 10.8 (7.0-17.0) mm.

Table 2. Results from thyroid ultrasound	
Ultrasound performed, n (%)	521 (97.9%)
Thyroid nodules, n (%)	287 (55.0%)
Multiple nodes, n (%)	204 (39.1%)
Larger nodule dimension, n (%)	10.8 (7.0, 17.0)

Table 3 shows the data related to the biopsies performed. Of the 539 patients, 13.0% performed one biopsy, 3.4% performed two and 2.1% performed three.

Table 3. Results from thyroid biopsies (n = 139)	
I- Non-diagnostic or inadequate, n (%)	23 (16.5%)
II- Benign, n (%)	99 (71.2%)
III- Atypia/follicular lesion of undetermined significance, n (%)	4 (2.9%)
IV- Follicular neoplasm or suspicious for follicular neoplasm, n (%)	7 (5.1%)
V- Suspicious for malignancy, n (%)	1 (0.7%)
VI - Malignant, n (%)	3 (2.2%)
Suspicious for Lymphoma, n (%)	2 (1.4%)

Results shown according to Bethesda classification.

From the patients who underwent total thyroidectomy (n=78, 14.5%), 17 (23.0%) had thyroid cancer. Eight of these patients did not undergo a biopsy prior to surgery. Of the 9 patients submitted to biopsy prior to surgery, 2 were classified as malignant in the biopsy, 2 had follicular neoplasm or suspicious follicular neoplasm, and 5 had benign results. All benign results were from a nodule that did not correspond to the thyroid cancer diagnosed after surgery. Additionally, one patient had a biopsy with a Bethesda classification of “VI – Malignant” but a conservative treatment approach was

used instead of surgery due to severe cardiovascular disease and patient preference.

Table 4 shows data for patients submitted to thyroid surgery and the characteristics of the thyroid cancers identified. From the patients submitted to thyroid surgery (n=78), 93.7% underwent total thyroidectomy, 5.1% underwent hemithyroidectomy and 1.3% did not undergo any surgical procedure and were kept under active surveillance. Eighteen patients had the diagnosis of thyroid cancer (3.3%). Regarding the histological classification of the tumors, 10 (55.6%) were papillary microcarcinomas, 3 (16.7%) were classic papillary carcinomas, 4 (22.2%) were follicular variant papillary carcinomas and 1 (5.6%) was NIFTP (Non-invasive follicular thyroid neoplasm with papillary-like nuclear features). The mean size of the tumors was 7.3 ± 4.1 mm. All tumors were T1 in T category of TMN classification – 12.5% pT1A, 56.3% pT1aN0R0, 12.5% pT1(m)Nx, 12.5% pT1bNxR0 and 6.25% pT1N1R0.

Table 4. Thyroid surgery and histology of thyroid cancers	
Thyroid surgery	
Total thyroidectomy, n (%)	74 (93.7%)
Hemithyroidectomy, n (%)	4 (5.1%)
Thyroid cancer, n (%)	18 (3.3%)
Tumor size, mm	7.3 ± 4.1
Classification	
Papillary microcarcinoma, n (%)	10 (55.6%)
Classic papillary carcinoma, n (%)	3 (16.7%)
Follicular variant papillary carcinoma, n (%)	4 (22.2%)
NIFTP- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features, n (%)	1 (5.6%)
Tumor stage	
pT1A, n (%)	2 (12.5%)
pT1aN0R0, n (%)	9 (56.3%)
pT1(m)Nx, n (%)	2 (12.5%)
pT1bNxR0, n (%)	2 (12.5%)
pT1N1R0, n (%)	1 (6.25%)

Tumor stage shown according to the TNM staging AJCC UICC 8th edition

Table 5 compares the characteristics of patients with and without thyroid cancer diagnosis. Patients with thyroid cancer were more likely to have multiple nodules on ultrasound (64.7% vs 38.2%, p= 0.028) and to have larger nodules (17.8 (8-28) vs 10.4 (7-17), p= 0.048). The odds ratio of having thyroid cancer was 1.6 (95%CI, 1.04-2.49) for patients with multiple thyroid nodules (vs. no nodules or single nodule) and 3.0 (95%CI, 1.1-8.1) for each 10mm increase in the size of the largest nodules. The differences between sex, age, BMI, ophthalmopathy and dermopathy were not statistically significant. Regarding smoking habits, treatment with antithyroid drugs, and the number of ablative doses, the differences were also not significant between groups. Thyroid function biochemical values at diagnosis of Graves' disease (TSH, FT4, FT3, TRAbs) did not show a significant association.

Table 5. Predictors of Malignancy in the development of thyroid cancer

	Without Thyroid cancer (521)	**With Thyroid cancer (18)**	**P value**
Male, n (%)	96 (18.4%)	2 (11.1%)	0.43
Age, years	45.7 ± 15.0	46.4 ± 16.2	0.86
BMI, kg/m^2	25.6 ± 4.9	26.0 ± 5.4	0.76
Ophthalmopathy, n (%)	124 (23.9%)	4 (22.2%)	0.87
Dermopathy, n (%)	7 (1.4%)	0 (0.0%)	0.63
Smoking habits, n (%)			0.91
Nonsmoking	311 (61.3%)	10 (58.8%)	
Smoker	157 (31.0%)	6 (35.3%)	
Ex-smoker	39 (7.7%)	1 (5.9%)	
Antithyroid drug, n (%)			0.31
Methimazole	394 (84.2%)	14 (82.4%)	

Propylthiouracil	43 (9.2%)	3 (17.6%)	
Ablative doses n (%)			0.95
0	408 (79.7%)	14 (82.4%)	
1	94 (18.4%)	3 (17.6%)	
2	9 (1.8%)	0 (0.0%)	
3	1 (0.2%)	0 (0.0%)	
One or more thyroid nodules, n (%)	274 (54.3%)	13 (76.5%)	0.07
Multiple nodes, n (%)	193 (38.2%)	11 (64.7%)	0.028
Largest nodule dimension, mm	10.4 (7.0-17.0)	17.8 (8.0-28.0)	0.048
TSH, UI/mL	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.25
FT4, ng/dL	1.7 (1.1-2.3)	1.4 (1.1-2.2)	0.51
FT3, pg/mL	5.8 (3.6-10.1)	5.5 (4.2-9.5)	0.96
TRAbs	7.5 (3.8-21.8)	5.2 (3.4-10.7)	0.55
Antithyroid drug duration, months	20.0 (10.0-35.0)	16.0 (10.0-37.0)	0.63

BMI, body mass index; TRAbs, anti-TSH receptor antibodies; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine

DISCUSSION

In this retrospective cohort study, we report that patients with Graves' disease have a high prevalence of thyroid nodules and a relevant risk of thyroid malignancy (3.3% of patients during a median follow-up of 3.3 years) compared to the general population [9, 14]. All of the thyroid cancers diagnosed were low-grade papillary carcinomas. Patients with multiple nodules and larger nodules had a higher risk of thyroid malignancy.

Our study is in agreement with previous literature that suggests that thyroid nodules are frequent in patients with Graves' disease [9, 15]. However, whether this risk is higher than the general population is uncertain [16].

Regarding the risk of thyroid carcinoma in Graves' disease, some studies have suggested an increased risk in patients with Graves' disease [12, 14, 17, 18], while others suggest a similar risk [19, 20]. The proposed mechanism for an increased risk in those with Graves' disease is a stimulatory effect of TRAbs on TSH receptor [2]. This is aligned with the studies performed in patients without Graves' disease in which higher levels of TSH were associated with increased risk of thyroid cancer [21, 22]. Some studies have also reported an increased risk of disease progression and distant metastasis in patients with Graves' disease. [15, 17, 23].

Most previous studies compared the risk of thyroid cancer in patients with Graves' disease and in euthyroid individuals. Such approaches may be of interest to understand the increased risk of thyroid cancer in patients with Graves' disease. However, from a clinical perspective, it is more relevant to identify, within those with Graves' disease, the individuals at an increased risk of thyroid cancer.

It is known that there are two well-established risk factors for the development of PTC: previous radiation exposure [24] and family history [25]. A number of other possible risk factors have been reported, such as elevated TSH levels [21]. Although Graves' disease has been proposed as a risk factor, the mechanism is still not fully characterized [26]. TRAbs, by promoting the mechanisms of angiogenesis and production of growth

factors [8], can stimulate the formation of nodules, which may have malignant potential [11].

Therefore, it is very important to do a follow-up on patients with Graves' disease in the long term, using complementary diagnostic tools, such as ultrasound and biopsy, when necessary [27]. Our study suggests that patients that had more and larger nodules have an increased risk of developing thyroid cancer [9, 15]. The prevalence and clinical significance of incidental thyroid carcinoma in patients with Graves' disease are relevant data when deciding on therapy (medical versus surgical) [28].

Our study has limitations that we must acknowledge. The first limitation concerns the retrospective design of our study, which limits the collection of more detailed data. The second limitation is that the study was carried out in a single center, which may decrease the generalizability of our findings. It is important to mention that the prevalence of thyroid cancer may have been higher due to the fact that these patients, with Graves' disease, had a more regular follow-up. Moreover, microcarcinomas are known to exist in many undiagnosed people and have no future repercussions [29]. Regarding the strengths of our study, we analyzed data for all patients in a hospital who had diagnosis of Graves' disease (identified by positive TRAbs over five years). Instead of defining a control group made by euthyroid patients, we chose one with Graves' disease because we found it more clinically relevant. Within patients with Graves' disease, we identified those who had thyroid cancer and compared them with those who did not. We also believe that the large set of potential predictors analyzed is a strength of our study.

In conclusion, Graves' disease patients with more and larger nodules had an increased risk of thyroid cancer. A closer follow-up of this subgroup of patients may be needed to allow earlier identification and treatment of thyroid cancer.

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Author contributions: JSN and MNS conceived and designed the study. JSN provided methodological and statistical advice. MNS drafted the first version of the manuscript. All authors provided clinical feedback in interpreting the results, contributed critically to subsequent revisions, and approved the final version of the manuscript

Ethics approval: The authors state that the procedures followed were in accordance with the regulations of Ethics Committee of the Centro Hospitalar Universitário de São João/ Faculty of Medicine of University of Porto and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Availability of data and material: The datasets analyzed during the current study are not publicly available but are available from the corresponding author on rational request.

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Anexo 1

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	7
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	7
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9, 10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9, 10
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	9, 10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9, 10
		(b) Give reasons for non-participation at each stage	9, 10
		(c) Consider use of a flow diagram	9, 10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9, 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	13,15

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15 15 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,11, 12,13, 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

1 (a) – Página 7: “Retrospective observational study of adult subjects with Graves' disease (positive autoantibodies TRAbs) between 2017 and 2021 at our center.”

1 (b) – Página 7: “Retrospective observational study of adult subjects with Graves' disease (positive autoantibodies TRAbs) between 2017 and 2021 at our center. We evaluated the prevalence of thyroid nodules and cancer in this population and characterized the predictive factors for thyroid malignancy using linear and logistic regression models. (…) We evaluated a total of 539 patients with Graves' disease during a median follow-up of 3.3 years (25^{th}-75^{th} percentiles 1.5-5.2 years). Fifty-three percent had thyroid nodules and 18 (3.3%) were diagnosed with thyroid cancer (12 papillary microcarcinomas). All tumors were classified using TNM classification as T1, and only one had lymph node metastasis; there were no recordings of distant metastasis. Sex, age, body mass index, smoking, TSH and TRAbs levels were not significantly different between patients with and without thyroid cancer. Patients with multiple nodules on ultrasound (OR 1.61, 95%CI 1.04-2.49) and with larger nodules (OR 2.96, 95%CI 1.08-8.14, for 10mm increase in size) had a greater risk of thyroid cancer diagnosis. (...) Patients with Graves’ disease had a higher prevalence of thyroid nodules and their nodules had a significant risk of thyroid cancer compared to general population. The risk was higher in those with multiple and larger nodules. Most had low grade papillary thyroid cancer. More studies are needed to clarify the clinical relevance of these findings.

2 - Página 8: “Graves' disease is an autoimmune thyroid disease, being the most frequent cause of hyperthyroidism. It is caused by the production of autoantibodies (TRAbs) against the thyrotropin receptor (TSH-R). These act as TSH-R agonists and induce hypersecretion of thyroid hormones. In addition, TSH-R is also involved in the normal physiology and growth of the thyroid gland, participating in its organogenesis, cell

differentiation and iodine uptake, which may lead to the formation of goiter when faced with a strong stimulus. Differentiated thyroid carcinoma, which originates in the epithelial follicular thyroid cells, represents about 95% of thyroid cancer cases. It includes papillary thyroid carcinoma, follicular thyroid carcinoma, and Hürthle cell carcinoma of the thyroid. Papillary thyroid carcinoma (PTC) is the most common histological subtype of differentiated thyroid malignancy, constituting about 80% of cases. The age of presentation, gender, histology and stage of the tumor are factors that influence its prognosis. Graves' disease has been associated with an increased risk of thyroid cancer. Several case reports suggest an aggressive behavior of thyroid cancer in patients with Graves' disease. The mechanism for this increased risk is still not fully understood, but the binding of TRAbs to TSH-R is probably one of the main mechanisms. By positively stimulating thyroid growth, production of growth factors and angiogenesis, TRAbs may promote tumor development and invasion. However, predictive factors for thyroid cancer in patients with Graves' disease are still unknown."

3 - Página 8: "Thus, our aim was to evaluate the prevalence of thyroid nodules and thyroid cancer in patients with Graves' disease and to characterize the predictive factors of thyroid malignancy."

4 - Página 9: "We performed a retrospective longitudinal observational study at Centro Hospitalar Universitário de São João (CHUSJ) in Porto, Portugal, to evaluate the prevalence of thyroid nodules and thyroid cancer in patients with Graves' disease and to characterize the predictive factors of thyroid malignancy. The studied population consisted entirely of adult subjects with positive TRAbs between 2017 and 2021 (all participants under eighteen years of age were excluded from this selection). Our study was approved by the Ethics Committee of CHUSJ/ Faculty of Medicine of the University

of Porto. The data analyzed in this study was collected retrospectively from electronic clinical records in May 2022."

5- Página 9: "We performed a retrospective longitudinal observational study at Centro Hospitalar Universitário de São João (CHUSJ) in Porto, Portugal, to evaluate the prevalence of thyroid nodules and thyroid cancer in patients with Graves' disease and to characterize the predictive factors of thyroid malignancy. The studied population consisted entirely of adult subjects with positive TRAbs between 2017 and 2021 (all participants under eighteen years of age were excluded from this selection). Our study was approved by the Ethics Committee of CHUSJ/ Faculty of Medicine of the University of Porto. The data analyzed in this study was collected retrospectively from electronic clinical records in May 2022."

6 (a) - Página 9: "We performed a retrospective longitudinal observational study at Centro Hospitalar Universitário de São João (CHUSJ) in Porto, Portugal, to evaluate the prevalence of thyroid nodules and thyroid cancer in patients with Graves' disease and to characterize the predictive factors of thyroid malignancy. The studied population consisted entirely of adult subjects with positive TRAbs between 2017 and 2021 (all participants under eighteen years of age were excluded from this selection). Our study was approved by the Ethics Committee of CHUSJ/ Faculty of Medicine of the University of Porto. The data analyzed in this study was collected retrospectively from electronic clinical records in May 2022."

6 (b) – Não aplicável uma vez que, neste estudo, não foram estabelecidos critérios de correspondência e os indivíduos não foram classificados como expostos e não expostos.

7 - Página 9: "The following parameters were collected from the patients' clinical records:

sex, age, age at diagnosis of Graves' disease, initial TRAbs, FT3, FT4, TSH, height, weight, smoking habits, treatment for Graves' disease (type of antithyroid drug, maximum dose; duration and number of iodine ablative doses; thyroidectomy), diagnosis of ophthalmopathy, diagnosis of dermopathy, thyroid ultrasound results, results of biopsies and thyroid carcinoma (histology, classification and tumor size). Thyroid biopsies were classified according to the Bethesda classification."

8 - Página 9: "The following parameters were collected from the patients' clinical records: sex, age, age at diagnosis of Graves' disease, initial TRAbs, FT3, FT4, TSH, height, weight, smoking habits, treatment for Graves' disease (type of antithyroid drug, maximum dose; duration and number of iodine ablative doses; thyroidectomy), diagnosis of ophthalmopathy, diagnosis of dermopathy, thyroid ultrasound results, results of biopsies and thyroid carcinoma (histology, classification and tumor size). Thyroid biopsies were classified according to the Bethesda classification."

9 - Página 9, 10: "The association of predictors with the presence of thyroid nodules and the diagnosis of thyroid cancer was evaluated using linear regression (for continuous outcomes) and logistic regression (for dichotomic outcomes)."

10 - Página 9: "The studied population consisted entirely of adult subjects with positive TRAbs between 2017 and 2021 (all participants under eighteen years of age were excluded from this selection)."

11 - Página 9, 10: "Baseline characteristics of patients with and without diagnosis of thyroid cancer were compared with Student's t-test, Mann Whitney test for normal and nonnormal continuous variables respectively, and the chi-square test for categorical variables. The association of predictors with the presence of thyroid nodules and the

diagnosis of thyroid cancer was evaluated using linear regression (for continuous outcomes) and logistic regression (for dichotomic outcomes). Continuous variables are described as mean ± standard deviation or median (25–75th percentiles) for normal and nonnormal continuous variables respectively, and categorical variables as proportions (percentages). A two-sided P-value of <0.05 was considered statistically significant. Analyses were performed with Stata (version 17.0)."

12 (a) e (b) – Página 9, 10: "Baseline characteristics of patients with and without diagnosis of thyroid cancer were compared with Student's t-test, Mann Whitney test for normal and nonnormal continuous variables respectively, and the chi-square test for categorical variables. The association of predictors with the presence of thyroid nodules and the diagnosis of thyroid cancer was evaluated using linear regression (for continuous outcomes) and logistic regression (for dichotomic outcomes). Continuous variables are described as mean ± standard deviation or median (25–75th percentiles) for normal and nonnormal continuous variables respectively, and categorical variables as proportions (percentages). A two-sided P-value of <0.05 was considered statistically significant. Analyses were performed with Stata (version 17.0)."

12 (c) – Não aplicável, uma vez que sendo um estudo retrospetivo tem inerentemente dados a faltar.

12 (d) – Não aplicável, porque não se registaram perdas de follow-up.

12 (e) – Página 9, 10: "Baseline characteristics of patients with and without diagnosis of thyroid cancer were compared with Student's t-test, Mann Whitney test for normal and nonnormal continuous variables respectively, and the chi-square test for categorical variables. The association of predictors with the presence of thyroid nodules and the

diagnosis of thyroid cancer was evaluated using linear regression (for continuous outcomes) and logistic regression (for dichotomic outcomes). Continuous variables are described as mean ± standard deviation or median (25–75th percentiles) for normal and nonnormal continuous variables respectively, and categorical variables as proportions (percentages). A two-sided P-value of <0.05 was considered statistically significant. Analyses were performed with Stata (version 17.0)."

13 (a), (b) e (c) - Página 9,10: "The studied population consisted entirely of adult subjects with positive TRAbs between 2017 and 2021 (all participants under eighteen years of age were excluded from this selection)." (…) "The baseline characteristics of the 539 patients with Graves' disease are shown in *Table 1*."

14 (a) - Página 10: "The baseline characteristics of the 539 patients with Graves' disease are shown in *Table 1*. Eighteen percent were men and their mean age at diagnosis was 45.7 ± 15.1 years. The mean BMI at diagnosis was 25.6 ± 4.9 kg/m^2. Twenty-four percent had ophthalmopathy and 1.3% had dermopathy. Sixty-one percent never smoked, 31.1% were current smokers and 7.6% were former smokers. Regarding treatment, 84.1% received methimazole and 9.5% received propylthiouracil. The median methimazole dose was 7.5 (5-15) mg and the median propylthiouracil dose was 150 (100-300) mg. The median duration of antithyroid treatment was 20.0 (11.0-36.0) months. The follow-up time was 3.3 (1.5-5.2) years. Eighty percent of the patients did not receive any ablative dose with radioactive iodine, 18.3% received one, 1.7% received two and 0.2% received three doses. From the 539 patients evaluated, 361 (67.0%) patients had thyroid function results available before starting antithyroid drugs. The baseline median values of thyroid function were the following: TSH 0.001 (0.0-0.008) UI/mL, FT4 1.7 (1.1- 2.3) ng/dL and FT3 5.7 (3.7-10.1) pg/mL."

14 (b) - Não aplicável.

14 (c) – Página 9, 10: “The studied population consisted entirely of adult subjects with positive TRAbs between 2017 and 2021 (all participants under eighteen years of age were excluded from this selection).” e “The follow-up time was 3.3 (1.5-5.2) years.”

15- Página 13, 15: “Eighteen patients had the diagnosis of thyroid cancer (3.3%).” (…) “Patients with thyroid cancer were more likely to have multiple nodules on ultrasound (64.7% vs 38.2%, p= 0.028) and to have larger nodules (17.8 (8-28) vs 10.4 (7-17), p= 0.048). The odds ratio of having thyroid cancer was 1.6 (95%CI, 1.04-2.49) for patients with multiple thyroid nodules (vs. no nodules or single nodule) and 3.0 (95%CI, 1.1-8.1) for each 10mm increase in the size of the largest nodules.”

16 (a) e (b) – Página 15: “*Table 5* compares the characteristics of patients with and without thyroid cancer diagnosis. Patients with thyroid cancer were more likely to have multiple nodules on ultrasound (64.7% vs 38.2%, p= 0.028) and to have larger nodules (17.8 (8-28) vs 10.4 (7-17), p= 0.048). The odds ratio of having thyroid cancer was 1.6 (95%CI, 1.04-2.49) for patients with multiple thyroid nodules (vs. no nodules or single nodule) and 3.0 (95%CI, 1.1-8.1) for each 10mm increase in the size of the largest nodules. The differences between sex, age, BMI, ophthalmopathy and dermopathy were not statistically significant. Regarding smoking habits, treatment with antithyroid drugs, and the number of ablative doses, the differences were also not significant between groups. Thyroid function biochemical values at diagnosis of Graves' disease (TSH, FT4, FT3, TRAbs) did not show a significant association.”

16 (c) – Não aplicável, não foi considerado relevante para este estudo.

17 – Página 10, 11, 12, 13, 15: “The baseline characteristics of the 539 patients with Graves' disease are shown in *Table 1*. Eighteen percent were men and their mean age at diagnosis was 45.7 ± 15.1 years. The mean BMI at diagnosis was 25.6 ± 4.9 kg/m^2. Twenty-four percent had ophthalmopathy and 1.3% had dermopathy. Sixty-one percent never smoked, 31.1% were current smokers and 7.6% were former smokers. Regarding treatment, 84.1% received methimazole and 9.5% received propylthiouracil. The median methimazole dose was 7.5 (5-15) mg and the median propylthiouracil dose was 150 (100-300) mg. The median duration of antithyroid treatment was 20.0 (11.0-36.0) months. The follow-up time was 3.3 (1.5-5.2) years. Eighty percent of the patients did not receive any ablative dose with radioactive iodine, 18.3% received one, 1.7% received two and 0.2% received three doses. From the 539 patients evaluated, 361 (67.0%) patients had thyroid function results available before starting antithyroid drugs. The baseline median values of thyroid function were the following: TSH 0.001 (0.0-0.008) UI/mL, FT4 1.7 (1.1- 2.3) ng/dL and FT3 5.7 (3.7-10.1) pg/mL.” (…) “*Table 2* shows the data related to the first ultrasounds performed after the diagnosis of Graves' disease. Of the 539 patients, 97.6% were evaluated with thyroid ultrasound. 55.0% had at least one nodule, and 39.1% had multiple nodules. The median size of the largest nodule was 10.8 (7.0-17.0) mm.” (…) “*Table 3* shows the data related to the biopsies performed. Of the 539 patients, 13.0% performed one biopsy, 3.4% performed two and 2.1% performed three.” (…) “From the patients who underwent total thyroidectomy (n=78, 14.5%), 17 (23.0%) had thyroid cancer. Eight of these patients did not undergo a biopsy prior to surgery. Of the 9 patients submitted to biopsy prior to surgery, 2 were classified as malignant in the biopsy, 2 had follicular neoplasm or suspicious follicular neoplasm, and 5 had benign results. All benign results were from a nodule that did not correspond to the thyroid cancer diagnosed after surgery. Additionally, one patient had a biopsy with a Bethesda classification of “VI – Malignant” but a conservative treatment approach was used instead of surgery due to severe cardiovascular disease and patient preference. *Table 4* shows data for patients submitted to thyroid surgery and the characteristics of

the thyroid cancers identified. From the patients submitted to thyroid surgery (n=78), 93.7% underwent total thyroidectomy, 5.1% underwent hemithyroidectomy and 1.3% did not undergo any surgical procedure and were kept under active surveillance. Eighteen patients had the diagnosis of thyroid cancer (3.3%). Regarding the histological classification of the tumors, 10 (55.6%) were papillary microcarcinomas, 3 (16.7%) were classic papillary carcinomas, 4 (22.2%) were follicular variant papillary carcinomas and 1 (5.6%) was NIFTP (Non-invasive follicular thyroid neoplasm with papillary-like nuclear features). The mean size of the tumors was 7.3 ± 4.1 mm. All tumors were T1 in T category of TMN classification – 12.5% pT1A, 56.3% pT1aN0R0, 12.5% pT1(m)Nx, 12.5% pT1bNxR0 and 6.25% pT1N1R0." (…) "*Table 5* compares the characteristics of patients with and without thyroid cancer diagnosis. Patients with thyroid cancer were more likely to have multiple nodules on ultrasound (64.7% vs 38.2%, p= 0.028) and to have larger nodules (17.8 (8-28) vs 10.4 (7-17), p= 0.048). The odds ratio of having thyroid cancer was 1.6 (95%CI, 1.04-2.49) for patients with multiple thyroid nodules (vs. no nodules or single nodule) and 3.0 (95%CI, 1.1-8.1) for each 10mm increase in the size of the largest nodules. The differences between sex, age, BMI, ophthalmopathy and dermopathy were not statistically significant. Regarding smoking habits, treatment with antithyroid drugs, and the number of ablative doses, the differences were also not significant between groups. Thyroid function biochemical values at diagnosis of Graves' disease (TSH, FT4, FT3, TRAbs) did not show a significant association."

18 – Página 17: "In this retrospective cohort study, we report that patients with Graves' disease have a high prevalence of thyroid nodules and a relevant risk of thyroid malignancy (3.3% of patients during a median follow-up of 3.3 years) compared to the general population. All of the thyroid cancers diagnosed were low-grade papillary carcinomas. Patients with multiple nodules and larger nodules had a higher risk of thyroid malignancy."

19 – Página 18: “Our study has limitations that we must acknowledge. The first limitation concerns the retrospective design of our study, which limits the collection of more detailed data. The second limitation is that the study was carried out in a single center, which may decrease the generalizability of our findings. It is important to mention that the prevalence of thyroid cancer may have been higher due to the fact that these patients, with Graves' disease, had a more regular follow-up. Moreover, microcarcinomas are known to exist in many undiagnosed people and have no future repercussions.”

20 – Página 18: “In conclusion, Graves’ disease patients with more and larger nodules had an increased risk of thyroid cancer. A closer follow-up of this subgroup of patients may be needed to allow earlier identification and treatment of thyroid cancer.”

21 – Página 18: “The second limitation is that the study was carried out in a single center, which may decrease the generalizability of our findings.”

22- Não aplicável. Não foi recebido nenhum financiamento para a realização deste estudo.

Anexo 2

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Submission guidelines

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Types of papers

Manuscript categories

1. Editorial

This contribution should be solicited by the Editors and relates to the topic of one or more contributions published in the same issue of the journal. This type of article has a word limit of 1500 and no more than 20 references.

2. Review

This contribution is usually solicited by the Editors. If unsolicited, the authors are advised to contact the Editor-in-Chief (editor.endocrine@gmail.com) with an outline of the proposed review and CV of the authors.

This type of article does not have a strict limit in word and reference number although the editorial recommendation is that the article does not exceed 4000 words and 350 references.

3. Mini-Review

This contribution is also usually solicited by the Editors. If unsolicited, the authors are advised to contact the Editor-in-Chief (editor.endocrine@gmail.com) with an outline of the proposed review and CV of the authors.

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4. Meta-analysis

This contribution should be based on a rigorous methodological/statistical approach described in detail in the methods section applied to a relevant clinical or basic issue. This work could also be submitted to statistical revision. Word limit is 3000 with no more than 100 references.

5. Position statements/Guidelines

Editors of Endocrine can appoint a panel of authoritative experts to write a position paper/guideline article on a new or controversial clinical topic based on available evidence analyzed by the Grade system. Unsolicited position statement and/or guideline papers from expert panels can be submitted to Endocrine but authors are advised to contact in advance the Editor-in-Chief (editor.endocrine@gmail.com) with an outline of the proposed article and CV of the authors. This type of article should not exceed 3000 words and 250 references.

6. Viewpoint

This contribution should be solicited by the Editors and deal with a controversial topic in either basic or clinical endocrinology on which the author, a leading expert in the field, is invited to express his views and interpretation of current literature. This type of article has a word limit of 1500, 1 figure or table and no more than 30 references.

7. Brief report

This contribution contains particularly original preliminary basic or clinical findings that provide new data on controversies of broad interest and long-standing questions, or that present a conceptual advance. Brief reports should be presented in a very concise way (limit of 1600 words (excluding abstract, references, and table/figure legends), 1 table and/or 1 figure and maximum 20 references).

8. Original article

This contribution should contain original controlled experimental data of basic and clinical research. The manuscript should be

This contribution should contain original controlled experimental data of basic and clinical research. The manuscript should be organized in the following sections: Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Figure Legends, Tables, Figures. Manuscripts should not exceed 4,000 words, 60 references, and 7 tables/figures

9. Book review

This contribution should be a short evaluation from an expert in the field on a relevant book in a certain area of endocrinology. This article should not exceed 750 words and no references are allowed.

10. Letter to the Editor

Text is limited to 750 words, with no abstract. There may be 1 figure, up to 3 references, and no more than 3 authors, with author affiliations only including main institution, place name and (state plus) country (i.e. no departments, etc).

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Manuscript Submission

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

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Title Page

Title Page

Please make sure your title page contains the following information.

Please make sure your title page contains the following information:

Title

The title should be concise and informative.

Author information

- The name(s) of the author(s)
- The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
- A clear indication and an active e-mail address of the corresponding author
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If address information is provided with the affiliation(s) it will also be published.

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Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results
- Conclusion

For life science journals only (when applicable)

- Trial registration number and date of registration for prospectively registered trials
- Trial registration number and date of registration followed by "retrospectively registered", for retrospectively registered trials

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

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Text

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

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References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

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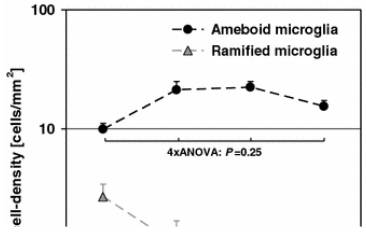
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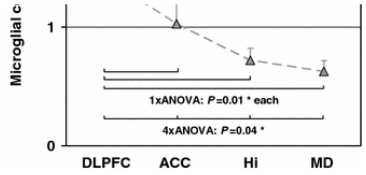
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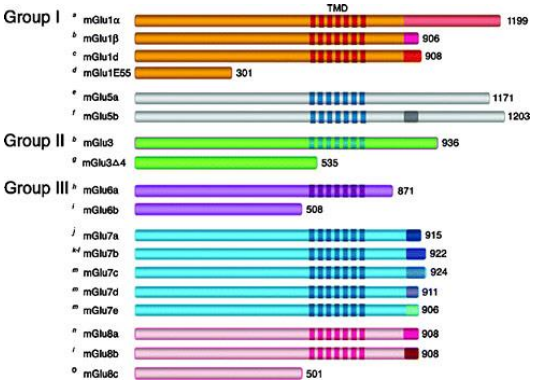
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Authorship issues or disputes

In the case of an authorship dispute during peer review or after acceptance and publication, the Journal will not be in a position to investigate or adjudicate. Authors will be asked to resolve the dispute themselves. If they are unable the Journal reserves the right to withdraw a manuscript from the editorial process or in case of a published paper raise the issue with the authors' institution(s) and abide by its guidelines.

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Authors should treat all communication with the Journal as confidential which includes correspondence with direct representatives from the Journal such as Editors-in-Chief and/or Handling Editors and reviewers' reports unless explicit consent has been received to share information.

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Compliance with Ethical Standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

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Competing Interests

Authors are requested to disclose interests that are directly or indirectly related to the work submitted for publication. Interests within the last 3 years of beginning the work (conducting the research and preparing the work for submission) should be reported. Interests outside the 3-year time frame must be disclosed if they could reasonably be perceived as influencing the submitted work. Disclosure of interests provides a complete and transparent process and helps readers form their own judgments of potential bias. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate.

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Interests that should be considered and disclosed but are not limited to the following:

Funding: Research grants from funding agencies (please give the research funder and the grant number) and/or research support (including salaries, equipment, supplies, reimbursement for attending symposia, and other expenses) by organizations that may gain or lose financially through publication of this manuscript.

Employment: Recent (while engaged in the research project), present or anticipated employment by any organization that may gain or lose financially through publication of this manuscript. This includes multiple affiliations (if applicable).

Financial interests: Stocks or shares in companies (including holdings of spouse and/or children) that may gain or lose financially through publication of this manuscript; consultation fees or other forms of remuneration from organizations that may gain or lose financially; patents or patent applications whose value may be affected by publication of this manuscript.

It is difficult to specify a threshold at which a financial interest becomes significant, any such figure is necessarily arbitrary, so one possible practical guideline is the following: "Any undeclared financial interest that could embarrass the author were it to become publicly known after the work was published."

Non-financial interests: In addition, authors are requested to disclose interests that go beyond financial interests that could impart bias on the work submitted for publication such as professional interests, personal relationships or personal beliefs (amongst others). Examples include, but are not limited to: position on editorial board, advisory board or board of directors or

other type of management relationships; writing and/or consulting for educational purposes; expert witness; mentoring relations; and so forth.

Primary research articles require a disclosure statement. Review articles present an expert synthesis of evidence and may be treated as an authoritative work on a subject. Review articles therefore require a disclosure statement.Other article types such as editorials, book reviews, comments (amongst others) may, dependent on their content, require a disclosure statement. If you are unclear whether your article type requires a disclosure statement, please contact the Editor-in-Chief.

Please note that, in addition to the above requirements, funding information (given that funding is a potential competing interest (as mentioned above)) needs to be disclosed upon submission of the manuscript in the peer review system. This

information will automatically be added to the Record of CrossMark, however it is **not added** to the manuscript itself. Under 'summary of requirements' (see below) funding information should be included in the '**Declarations**' section.

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Funding' and/or 'Competing interests'. Other declarations include Ethics approval, Consent, Data, Material and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

When all authors have the same (or no) conflicts and/or funding it is sufficient to use one blanket statement.

Examples of statements to be used when funding has been received:

- Partial financial support was received from [...]
- The research leading to these results received funding from [...] under Grant Agreement No[...].
- This study was funded by [...]
- This work was supported by [...] (Grant numbers [...] and [...]

Examples of statements to be used when there is no funding:

- The authors did not receive support from any organization for the submitted work.
- No funding was received to assist with the preparation of this manuscript.
- No funding was received for conducting this study.
- No funds, grants, or other support was received.

Examples of statements to be used when there are interests to declare:

- **Financial interests:** Author A has received research support from Company A. Author B has received a speaker honorarium from Company Wand owns stock in Company X. Author C is consultant to company Y.
  Non-financial interests: Author C is an unpaid member of committee Z.
- **Financial interests:** The authors declare they have no financial interests.
  Non-financial interests: Author A is on the board of directors of Y and receives no compensation as member of the board of directors.
- **Financial interests:** Author A received a speaking fee from Y for Z. Author B receives a salary from association X. X where s/he is the Executive Director.
  Non-financial interests: none.
- **Financial interests:** Author A and B declare they have no financial interests. Author C has received speaker and consultant honoraria from Company M and Company N. Dr. C has received speaker honorarium and research funding from Company M

and Company O. Author D has received travel support from Company O.
Non-financial interests: Author D has served on advisory boards for Company M, Company N and Company O.

Examples of statements to be used when authors have nothing to declare:

- The authors have no relevant financial or non-financial interests to disclose.
- The authors have no competing interests to declare that are relevant to the content of this article.
- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.
- The authors have no financial or proprietary interests in any material discussed in this article.

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Research involving human participants, their data or biological material

Ethics approval

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

Retrospective ethics approval

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

Ethics approval for retrospective studies

Although retrospective studies are conducted on already available data or biological material (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of a country. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

Ethics approval for case studies

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on **Informed Consent**.

Cell lines

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

Research Resource Identifiers (RRID)

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

Organism: *Filip1*$^{tm1a(KOMP)Wtsi}$ **RRID:MMRRC_055641-UCD**

Cell Line: RST307 cell line **RRID:CVCL_C321**

Antibody: Luciferase antibody DSHB Cat# LUC-3, **RRID:AB_2722109**

Plasmid: mRuby3 plasmid **RRID:Addgene_104005**

Software: ImageJ Version 1.2.4 **RRID:SCR_003070**

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

Clinical Trial Registration

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively

registered' should be included as the last line of the manuscript abstract.

Standards of reporting

Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal's Instructions for Authors.

Checklists are available for a number of study designs, including:

Randomised trials (CONSORT) and Study protocols (SPIRIT)

Observational studies (STROBE)

Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P)

Diagnostic/prognostic studies (STARD) and (TRIPOD)

Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• 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 Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

• This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

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Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

Exceptions where it is not necessary to obtain consent:

• Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

• Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant information regarding consent. Authors should provide the appropriate attribution for republished images.

Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered "informed". However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

Consent to Participate

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

Consent to Publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies. A consent to publish form can be found

here. (Download docx, 36 kB)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Consent to participate' and/or 'Consent to publish'. Other declarations include Funding, Competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for **"Consent to participate"**:

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for **"Consent to publish"**:

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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Images will be removed from publication if authors have not obtained informed consent or the paper may be removed and replaced with a notice explaining the reason for removal.

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This journal operates a type 1 research data policy. The journal encourages authors, where possible and applicable, to deposit data that support the findings of their research in a public repository. Authors and editors who do not have a preferred repository should consult Springer Nature's list of repositories and research data policy.

List of Repositories

Research Data Policy

General repositories - for all types of research data - such as figshare and Dryad may also be used.

Datasets that are assigned digital object identifiers (DOIs) by a data repository may be cited in the reference list. Data citations should include the minimum information recommended by DataCite: authors, title, publisher (repository name), identifier.

DataCite

If the journal that you're submitting to uses double-blind peer review and you are providing reviewers with access to your data (for example via a repository link, supplementary information or data on request), it is strongly suggested that the authorship in

(for example via a repository link, supplementary information or data on request), it is strongly suggested that the authorship in the data is also blinded. There are data repositories that can assist with this and/or will create a link to mask the authorship of your data.

Authors who need help understanding our data sharing policies, help finding a suitable data repository, or help organising and sharing research data can access our Author Support portal for additional guidance.

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Anexo 3

Parecer da Comissão de Ética do
Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: O papel da Doença de Graves no desenvolvimento de patologia nodular e cancro da tiroide

Nome do Investigador Principal: Dr. João Sérgio de Lima Soares Neves

Onde decorre o Estudo: No Serviço de Endocrinologia do CHUSJ. Apresentou declaração do Prof. Doutor Davide Carvalho.

Objetivos do Estudo:
Entender melhor o papel da Doença de Graves no desenvolvimento de patologia nodular e cancro da tiroide.

Conceção e Pertinência do estudo:
Estudo observacional retrospetivo.
Aprofundar a relação da Doença de Graves no desenvolvimento de patologia nodular e cancro da tiroide
Estão definidos os critérios de inclusão no estudo, bem como as variáveis clínicas a ser recolhidas.
O tamanho da amostra é de 540 participantes: doentes com autoanticorpos (TRAbs) contra o recetor da tireotrofina (TSH-R) no CHUSJ entre 2017 e 2021.
Estudo realizado no âmbito do Mestrado Integrado em Medicina da FMUP de Marta Cristina Nascimento Soares, que faz parte da equipa de investigação.

Benefício/risco: Não aplicável

Confidencialidade dos dados:
Todos os dados recolhidos serão codificados.
Apresentou um pedido de reutilização de registos clínicos para Investigação e Desenvolvimento ao RAI, e uma 'avaliação sobre o impacto da proteção de dados' para o EPD.

Respeito pela liberdade e autonomia do sujeito de ensaio: Não aplicável

***Curriculum* do investigador**: Adequado à investigação.

Data previsível da conclusão do estudo: fevereiro de 2023

Conclusão: Proponho um parecer favorável à realização do estudo.

Porto, 16 de setembro de 2022

O Relator da CE, Doutor Pedro Brito

Pedro Brito

SÃO JOÃO

ENCARREGADO DE PROTEÇÃO DE DADOS (EPD)
CENTRO HOSPITALAR UNIVERSITÁRIO DE S. JOÃO, EPE
Paulo Alexandre Mota da Silva
Encarregado de Proteção de Dados do CHUSJ
epd@chsj.min-saude.pt

Ref.ª CES CHUSJ: **204 / 2022**

Título do Projeto	O papel da Doença de Graves no desenvolvimento de patologia nodular e cancro da tiróide.

Responsável pelo tratamento	João Sérgio de Lima Soares Neves		
Instituição	Centro Hospitalar Universitário São João (CHUSJ)		
	Faculdade de Medicina da Universidade do Porto (FMUP)		
Investigador	**Interno** Externo		
Contacto telefónico	914837245	**Endereço Electrónico**	u011761@chsj.min-saude.pt
Profissional de Ligação	Não aplicável		
Amostra	540		

Análise de Risco | Tolerável | **Baixo** | Elevado | Muito Elevado

Parecer do EPD:

Data: 03/10/2022

Finalidade: avaliar o impacto da Doença de Graves no desenvolvimento de patologia nodular e cancro da tiróide

Licitude: fundamento previsto no artigo **9(2)(j)**, com as garantias do **89(1)** do **RGPD**, e artigo **31(1)** da **LERGPD**.

Categorias de dados pessoais: variáveis identificadas com detalhe na AIPD, datada de 29/09/2022, **ponto 13**, tendo presente o **princípio da minimização dos dados.**

Conservação: os dados serão alvo de **pseudonimização**, armazenados em **local seguro**, em área restrita com acesso limitado ao Investigador Principal, com acesso a ficheiros protegido por **palavra-passe**, efetuando-se a conservação até a conclusão da investigação, que se estima ser até **30 de setembro de 2023**. Os dados recolhidos **serão destruídos** após a finalização do estudo.

Comunicação de Dados: **não há partilha** de dados pessoais.

Face ao exposto, e observadas as recomendações, entende-se que a presente AIPD apresenta os elementos necessários para assegurar que o **tratamento é realizado em conformidade com o RGPD.**

Recomendações:

1. Garantir medidas de segurança adicionais no transporte dos dados com recurso a dispositivos electrónicos de armazenamento (Laptop, Disco Externo), nomeadamente através de medidas de cifragem e autenticação;
2. Em caso de necessidade de extensão de prazo e/ou de qualquer alteração dos pressupostos atinentes ao presente parecer o Investigador Principal deverá solicitar a reapreciação do projeto de investigação junto do EPD.

Revisão AIPD:

☐ Data da próxima revisão: ___ /___ / _____ ☒ Não carece de revisão.

Anexos:

1. Processo CES n.º 204/2022
2. Parecer CES (16/09/2022)
3. AIPD (29/09/2022)
4. Protocolo de Investigação

Encarregado de Proteção de Dados
Assinado por: **PAULO ALEXANDRE MOTA DA SILVA**
Data: 2022.10.03 17:20:39+01'00'
Localização: CHUSJ

CARTÃO DE CIDADÃO