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CAROLINE CARDO

"A CORRELAÇÃO ENTRE OS NÍVEIS DE COLESTEROL E A DOENÇA OCULAR TIREOIDIANA."

"THE RELATIONSHIP BETWEEN COLESTHEROL LEVELS AND THE THYROID EYE DISEASE."

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Dissertação apresentada à Faculdade de Ciências Médicas da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Ciências na área de Clínica Médica.

ORIENTADOR: PROF. DR. DANILO GLAUCO PEREIRA VILLAGELIN NETO.

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CAROLINE CARDO

ORIENTADOR: PROF. DR. DANILO GLAUCO PEREIRA VILLAGELIN NETO

MEMBROS TITULARES:

1. PROF. DR. DANILO GLAUCO PEREIRA VILLAGELIN NETO

2. PROFA. DRA. LAURA STERIAN

3. PROFA. DRA. VALÉRIA BAHDUR CHUEIRE

Programa de Pós-Graduação em Clínica Médica da Faculdade de Ciências Médicas da Universidade Estadual de Campinas.

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RESUMO

Contexto: A Doença Ocular Tireoidiana (DOT) é a manifestação extratireoidiana mais prevalente da doença de Graves (DG). Evidências emergentes sugerem uma relação entre níveis elevados de colesterol total e LDL e a TED. Este estudo teve como objetivo investigar essa correlação na população brasileira, por meio da análise de dados de dois centros de atendimento terciário.

Métodos: Foram coletados dados de pacientes com DG tratados com metimazol entre 1999 e 2021, excluindo aqueles que receberam outros tratamentos. Foram analisados exames laboratoriais e informações sobre tabagismo, uso de estatinas e medicamentos que afetam o perfil lipídico durante o estado eutireoideo.

Resultados: O tabagismo e os níveis elevados de colesterol LDL foram significativamente associados à atividade e severidade da DOT. A regressão logística revelou correlações entre níveis elevados de colesterol LDL e total e o aumento do Clinical Activity Score (CAS) ($p < 0,01$, OR 1,012, IC 95% 1,003–1,021; $p < 0,01$, OR 1,010, IC 95% 1,002–1,018). Esses parâmetros também se associaram a formas mais severas da doença, conforme definido pela EUGOGO ($p < 0,01$, OR 1,015, IC 95% 1,006–1,024; $p < 0,005$, OR 1,011, IC 95% 1,004–1,019). A regressão múltipla confirmou que a atividade da DOT estava significativamente correlacionada com colesterol LDL ($p < 0,01$) e tabagismo ($p < 0,01$). A gravidade da doença foi associada à redução do colesterol HDL ($p < 0,05$, OR 0,973, IC 95% 0,948–0,999), ao aumento do colesterol LDL ($p < 0,005$, OR 1,013, IC 95% 1,004–1,023) e ao tabagismo ativo ($p < 0,05$, OR 2,881, IC 95% 1,190–6,971).

Conclusão: O colesterol LDL pode ser um indicador potencial para a DOT. São necessárias mais pesquisas para determinar se o tratamento para redução do colesterol pode diminuir o risco de DOT e melhorar seu manejo clínico.

Palavras-chave: Doença Ocular da Tireoide, Hipertireoidismo, Colesterol, Doença de Graves

ABSTRACT

Background: Thyroid eye disease (TED) is the most prevalent extrathyroidal manifestation of Graves' disease (GD). Emerging evidence suggests a relationship between elevated total and LDL cholesterol levels and TED. This study aimed to investigate this correlation in the Brazilian population by analyzing data from two tertiary care centers.

Methods: Data were collected from GD patients treated with methimazole between 1999 and 2021, excluding those receiving other treatments. Laboratory results and information on smoking habits, statin use, and medications affecting lipid profiles during the euthyroid state were analyzed.

Results: Smoking and elevated LDL cholesterol levels were significantly associated with TED activity and severity. Logistic regression revealed correlations between higher LDL cholesterol, total cholesterol, and increased Clinical Activity Score (CAS) ($p < 0.01$, OR 1.012, CI 95% 1.003–1.021; $p < 0.01$, OR 1.010, CI 95% 1.002–1.018). These were also associated with more severe disease forms as defined by EUGOGO ($p < 0.01$, OR 1.015, CI 95% 1.006–1.024; $p < 0.005$, OR 1.011, CI 95% 1.004–1.019). Multiple regression confirmed TED activity was significantly correlated with LDL cholesterol ($p < 0.01$) and smoking status ($p < 0.01$). Disease severity was associated with reduced HDL cholesterol ($p < 0.05$, OR 0.973, CI 95% 0.948–0.999), elevated LDL cholesterol ($p < 0.005$, OR 1.013, CI 95% 1.004–1.023), and active smoking ($p < 0.05$, OR 2.881, CI 95% 1.190–6.971).

Conclusion: Elevated LDL cholesterol may serve as a potential indicator of TED. Further research is needed to determine whether lipid-lowering interventions could reduce TED risk or improve its management.

Keywords: Thyroid Eye Disease, Hyperthyroidism, Cholesterol, Graves' Disease

SUMÁRIO

INTRODUÇÃO

Thyroid Eye Disease (TED) is an autoimmune disorder that affects the orbital tissues and is present in approximately 30–40% of individuals diagnosed with Graves' Disease (GD).[1] Various factors contribute to an elevated risk of TED, including thyroid dysfunction, smoking, radioiodine therapy, male gender, advanced age, and specific genetic and demographic characteristics.

The pathogenesis of TED is complex and involves multiple interrelated mechanisms that are not yet fully understood.1 The development of TED begins with the activation of specific orbital fibroblasts, known as preadipocytes, mediated by thyroid receptor antibodies (TRAb). These preadipocytes subsequently differentiate into adipocytes, which increases the expression of thyrotropin receptors.[1-3] Simultaneously, cytokines such as interferon-gamma and tumor necrosis factor (TNF) stimulate a distinct subset of orbital fibroblasts that express the Thy-1 antigen, resulting in elevated hyaluronan production.[4]

Furthermore, the activation of the insulin-like growth factor receptor (IGF1-R) on orbital fibroblasts plays a critical role by triggering the release of chemokines, notably interleukin-16 and RANTES. These chemokines facilitate the recruitment of activated T cells and other immune cells into the orbital region. T cells expressing CD154 interact directly with orbital fibroblasts, forming CD40-CD154 complexes. Oxidative stress also represents a key process in TED pathogenesis.[4]

Activation of both receptors simultaneously leads to a synergistic increase in DNA synthesis and cell proliferation compared to the effects of each agonist alone.7 TSH triggers monoubiquitination of insulin receptor substrate (IRS)-2 in thyroid epithelial cells, thereby enhancing IGF-I signaling and its mitogenic activity.8, 9 Both IGF-I and TSH elevate nuclear β-catenin content, thus promoting Wnt-dependent proliferation of thyroid cells.6 IGF-I can independently induce proliferation in rat thyroid cells, suggesting it may also play a significant role as a regulator of thyroid growth compared to TSH.[10]

The symptoms of TED can vary, but they are typically marked by inflammation, bulging eyes, and double vision.[11] Mild cases are more prevalent than severe ones, which may involve the optic nerve and impair vision.[2, 11]

Choosing the proper treatment for TED is personalized based on the disease's activity and severity. The Clinical Activity Score (CAS)[12] and the EUGOGO (European Group on Graves Orbitopathy) classification[13] are tools used for this assessment.

The challenge lies in categorizing and comprehending the characteristics of the population affected by TED. This is crucial in exploring new treatment options for distinct patient groups, especially those with prevalent inflammation. Additionally, it is essential to understand potential risk factors linked to these groups in different populations to assist future research. This study aims to investigate the association between cholesterol levels and TED within the Brazilian population, presenting population characteristics through analyses conducted at two tertiary care centers.

METODOLOGIA

This study undertook a retrospective analysis of clinical and laboratory data from patients who received treatment for Graves' Disease (GD). Data were extracted from medical records at two tertiary centers spanning the years 1999 to 2021.

Patients included in the study were those who maintained a euthyroid state during clinical and laboratory evaluations and had been treated for GD with methimazole.

The presence of TED was assessed clinically using both the Clinical Activity CAS[12] and the EUGOGO[11, 14] classification. The CAS assigns one point for each of the following symptoms: spontaneous retrobulbar pain, pain on upward or lateral gaze, redness of the eyelids or conjunctiva, eyelid swelling, caruncle inflammation, and conjunctival edema (chemosis). A CAS score of three or more points is indicative of active disease. Additionally, the EUGOGO[11, 13] scale was utilized to evaluate disease severity.

In the EUGOGO classification, patients with mild orbitopathy exhibit features that minimally interfere with daily activities and do not necessitate immunosuppressive or surgical intervention. These patients typically present with one or more of the following symptoms: eyelid retraction of less than 2 mm, mild soft tissue involvement, exophthalmos less than 3 mm above the normal range (adjusted for race and sex), transient or absent diplopia, and corneal exposure responsive to lubrication.[11]

Moderate to severe TED includes patients who, while not at immediate risk of vision loss, experience a significant impact on quality of life due to their ocular condition. The severity of these symptoms may warrant immunosuppressive therapy (if active) or surgical intervention (if inactive). Such patients typically present with one or more of the following signs: eyelid retraction of 2 mm or more, moderate to severe soft tissue involvement, exophthalmos of 3 mm or more above the racial and sex-specific norm, and intermittent or constant diplopia.

Patients with sight-threatening TED are those at risk of reduced visual acuity, often associated with thyroid optic neuropathy (DON) and/or corneal breakdown.[12, 13] For this study, these evaluations were conducted by authors RBS,ABPPM and DV.

During the euthyroid state at the time of laboratory evaluation, serum levels of thyrotropin (TSH), free thyroxine (fT4), thyroid receptor antibody (TRAb), thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb), total cholesterol, cholesterol fractions, and triglycerides were measured. TSH, fT4, TgAb, and TPOAb serum concentrations were determined using chemiluminescent assays (DPC Immulite system). The reference ranges were 0.27–4.2 mIU/L for TSH, 0.93–1.7 ng/dL for fT4, >40 IU/mL for TgAb, and >35 IU/mL for TPOAb.

Over the years, different methods were employed for TRAb determinations. From 1980 to 1991, an in-house assay was used, which measured the thyroid-stimulating antibody (TSAb) activity through cyclic AMP stimulation in human thyroid plasma membranes, with a positive TSAb reference of <128%. Between 1992 and 2008, a radio-receptor assay (RSR Ltd) was first used, followed by a second-generation ELISA assay (RSR Ltd) with a normal range of <10 IU/L. More recently, a human monoclonal assay (M22 antibody) from Siemens Immunulite-TSI was adopted, with normal values defined as <0.175 IU/L. To avoid confounding factors, antithyroid antibodies were reported as either positive or negative.15, 16

Smoking status was also evaluated, and ultrasound was used to measure thyroid volume, with a reference range of 6–15 mL for a healthy thyroid gland.

Patients were excluded from the study if they were diagnosed with causes of hyperthyroidism or thyrotoxicosis other than GD, had undergone treatments for hyperthyroidism other than methimazole, had received subsequent radioiodine therapy, or were taking statins or other medications that could affect lipid profiles.

Descriptive analysis was performed by presenting frequency tables for categorical variables and measures of central tendency and dispersion for numerical variables. When appropriate, proportions were compared using the Chi-square test. The Kruskal-Wallis test was applied for comparing numerical measurements across three groups, followed by Dunn's test to identify specific differences when necessary. To compare numerical measurements between two groups, the Mann-Whitney U test was applied. Simple ordinal logistic regression and multiple regression were employed to identify factors associated with disease severity according to the two criteria. The variable selection process followed a stepwise method. A significance level of 5% was

adopted for all statistical tests. All analyses were conducted using the SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTADOS

The initial cohort of patients diagnosed with GD comprised 339 individuals. Of these, 211 patients were treated with methimazole and included in the study. Following the application of inclusion and exclusion criteria, the final cohort was refined to 165 patients. Table 1 presents an analysis of the general characteristics observed within this group (clinical and laboratory aspects in this population).

Comparative analyses were conducted across the groups using categorical data. When comparing groups based on the CAS, Group A consisted of patients with a CAS of 0, Group B included patients with a CAS of 1 or 2, and Group C comprised patients with active disease, defined as a CAS of 3 or more (Table 2). To evaluate the severity of TED according to the EUGOGO classification (Table 3), patients were divided into Group A (no disease/absent), Group B (mild forms), and Group C (moderate to severe forms, including sight-threatening TED).

In euthyroid patients, several variables were analyzed, including gender, body mass index (BMI), smoking status, thyroid antibodies, TSH, free T4, cholesterol levels, and triglycerides. The analysis of the study population revealed a significant association between LDL cholesterol and total cholesterol (TC) levels with TED activity, as measured by the CAS ($p = 0.007$ - OR 1.012/CI 95% 1.003;1.021 and $p = 0.010$ - OR 1.010/ CI 95% 1.002;1.018, respectively) and TED severity according to EUGOGO standards ($p = 0.001$ OR 1.015 CI 95% 1.006;1.024 and $p= 0.004$ OR 1.011 CI 95% 1.004;1.019). The logistic regression model corroborated these findings, as detailed in Tables 4 and 5, when the three groups were compared.

Results from the multiple regression analyses indicated that greater TED activity was significantly associated with higher LDL cholesterol levels ($p = 0.011$ – OR 1.012 CI 95% 1.003;1.021) and smoking status ($p = 0.011$ – OR 3.096 CI 95% 1.296;7394), as demonstrated in Table 4. Furthermore, TED severity was significantly correlated with lower HDL cholesterol levels ($p = 0.038$ – OR 0.973 CI 95% 0.948;0.999), elevated LDL cholesterol levels ($p = 0.054$ – OR 1.013 CI 95% 1.004;1.023), and active smoking status ($p = 0.019$ – OR 2.881 CI 95% 1.190;6.971), as shown in Table 5.

Continuing with the comparative analysis among the three groups, a simple logistic regression analysis indicated an association between BMI and CAS,

suggesting that a higher BMI may be linked to an increased CAS score (BMI: p = 0.0484; OR: 1.084). However, this association was not significant in further analysis. Age, in contrast, showed no statistically significant correlation with CAS in either the simple or multivariate analyses. When EUGOGO criteria were applied, age was significant in simple logistic regression analysis (age p= 0.0187, OR: 1.026); however, it was not significant in multiple logistic regression analysis. No association with BMI was identified when evaluating TED according to the EUGOGO criteria.

On the other hand, when analyses were performed comparing the groups with inactive disease (Group B - CAS 1 and 2) and active disease (Group C - CAS ≥ 3), excluding the control group (patients without TED) from the analysis, a significant association between LDL cholesterol and age with TED activity was observed. This was confirmed through simple logistic regression for age (p = 0.04469, OR 1.040, 95% CI 1.001–1.081), as shown in Table 6. However, when evaluated using multiple regression, no variable reached statistical significance at the 5% level.

Additionally, a specific analysis of TED patients classified by EUGOGO criteria was conducted. Groups B (mild forms of TED) and C (moderate to severe forms, including sight-threatening TED) were compared. The analysis revealed a significant association between disease severity and higher levels of LDL cholesterol (p = 0.0062, OR 1.014, 95% CI 1.005–1.033) and total cholesterol (TC) (p = 0.0215, OR 1.014, 95% CI 1.002–1.026). These findings were further supported by the multiple logistic regression model for LDL cholesterol (p = 0.0145, OR 1.017, 95% CI 1.003–1.031). The data from these analyses, based on EUGOGO classification, are presented in Table 7.

CONCLUSÃO

Em conclusão, nosso estudo reforça o vínculo entre níveis elevados de LDL, atividade e severidade da DOT na população brasileira, contribuindo para uma melhor compreensão dos possíveis fatores de risco associados à doença. O papel do estresse oxidativo e da inflamação no início da DOT destaca a necessidade de novas abordagens terapêuticas, incluindo o potencial uso de estatinas como terapia anti-inflamatória adjuvante. No entanto, são necessárias mais pesquisas para validar esses achados e explorar os potenciais benefícios do uso de estatinas no manejo da DOT.

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ANEXOS

Table 1 - General Characteristics of the patients analyzed with Graves' Disease	
Variable	All Data
Clinical Features	
Male/ Female	26 (15.8%)/139 (84.2%)
Age (Mean ± SD)	46.51 ± 14.34
BMI (Mean ± SD)	28.61 ± 5.70
Smoker	
Current	24 (14.9%)
Non Smoker	103 (64.0%)
Former Smoker	34 (21.1%)
Thyroid Evaluation	
TSH mIU/L (Mean ± SD)	1.92 ± 1.22
FT4 ng/dL (Mean ± SD)	1.24 ± 0.68
Thyroid US volume mL (Mean ± SD)	18.47 ± 10.12
TRAb IU/L (Mean ± SD)	7.28 ± 10.35
Positive	99 (62.7%)
TPOAb	
Positive	108 (69.7%)
TgAb	
Positive	65 (42.2%)
Cholesterol Evaluation	
Total Cholesterol (mg/ dL) (Mean ± SD)	192.12 ± 39.56
HDL Cholesterol (mg/ dL) (Mean ± SD)	54.23 ± 14.30
LDL Cholesterol (mg/ dL) (Mean ± SD)	118.27 ± 34.21
Triglycerides Cholesterol (mg/ dL) (Mean ± SD)	106.93 ± 50.78 (N=162)
Group Evaluation	
CAS (categorized)	
Group A – CAS 0	80 (48.5%)
Group B – CAS 1 and 2	56 (33.9%)
Group C – CAS 3 or more	29 (17.6%)

EUGOGO (categorized)		**Active**	**Non Active**
Group A – absent disease	81 (49.1%)	0	81 (100%)
Group B – mild	52 (31.5%)	4 (7.7%)	48 (92.3%)
Group C – moderate to severe/sight-threatening	32 (19.4%)	26 (81.2%)	6 (18.8%)

Table 1 - General characteristics of the patients analyzed with Graves' Disease

BMI (Body Mass Index)
TRAb (Thyrotropin Receptor Antibody)
TPOAb (Thyroid Peroxidase Antibodies)
TgAb (Thyroglobulin Antibodies)
TSH (Thyroid Stimulating Hormone)
FT4 (Free Thyroxine)
US (Ultrasound)
HDL (high-density lipoprotein)
LDL (low-density lipoprotein)
CAS (Clinical Activity Score)

Table 2 - Descriptive analysis and Comparisons Between CAS groups				
Variable	Group A – CAS 0	Group B – CAS 1 and 2	Group C – CAS 3 or more	P Value
General Characteristics				
Male/ Female	11 (13.8%)/69 (86.3%)	8 (14.3%)/48 (85.7%)	7 (24.1%)/22(75.9%)	
Age (Mean ± SD)	44.35 ± 15.16 (N=80)	46.38 ± 11.86 (N=55)	52.72 ± 14.96 (N=29)	0.0166[1]#
BMI (Mean ± SD)	27.10 ± 5.73	29.72 ± 5.69	30.29 ± 4.04	*ns*
Smoker				
Current	7 (8.9%)	9 (16.7%)	8 (28.6%)	0.0225[2]
Non Smoker	58 (73.4%)	34 (63.0%)	11 (39.3%)	
Former Smoker	14 (17.7%)	11 (20.4%)	9 (32.1%)	
Thyroid Evaluation				
TSH mIU/L (Mean ± SD)	1.88 ± 1.10	2.02 ± 1.37	1.82 ± 1.27	*ns*
FT4 ng/dL (Mean ± SD)	1.23 ± 0.34	1.16 ± 0.22	1.40 ± 1.49	*ns*
Thyroid US volume mL (Mean ± SD)	18.20 ± 10.54	18.27 ± 10.07	20.14 ± 8.68	*ns*
TRAb IU/L (Mean ± SD)	7.30 ± 10.49	7.24 ± 11.01	7.33 ± 8.58	*ns*
Positive	52 (65.8%) 30	30 (54.5%)	17 (70.8%)	*ns*
TPOAb				
Positive	57 (73.1%)	33 (62.3%)	18 (75.0%)	*ns*
TgAb				
Positive	36 (46.2%)	20 (37.7%)	9 (39.1%)	*ns*
Cholesterol Evaluation				
Cholesterol (mg/ dL) (Mean ± SD)	185.42 ± 35.72	192.44 ± 42.89	210.43 ± 38.61	0.0095[1]#
HDL (mg/ dL) (Mean ± SD)	56.03 ± 13.27	52.57 ± 13.14	52.52 ± 18.53	*ns*
LDL (mg/ dL) (Mean ± SD)	112.33 ± 28.83	117.91 ± 37.78	135.17 ± 35.99	0.0055[1]

Table 2 - Descriptive analysis and Comparisons Between CAS groups
BMI (Body Mass Index)
TRAb (Thyrotropin Receptor Antibody)
TPOAb (Thyroid Peroxidase Antibodies)
TgAb (Thyroglobulin Antibodies)
TSH (Thyroid Stimulating Hormone)
FT4 (Free Thyroxine)
US (Ultrasound)
HDL (high-density lipoprotein)
LDL (low-density lipoprotein)
CAS (Clinical Activity Score)
differences between (Dunn test): 1 and 3; 2 and 3.
[1] based on Kruskal-Wallis test, # based on Dunn's test / [2] based on Chi-square test

Table 3 - Descriptive analysis and comparisons between EUGOGO groups				
Variable	Group A – Absent	Group B – Mild	Group C – Moderate to severe/sight-threatening	P Value
General Characteristics				
Male/ Female	11 (13.6%)/70 (86.4%)	7 (13.5%) /45 (86.5%)	8 (25.0%)/24 (75.0%)	*ns*
Age (Mean ± SD)	44.30 ± 15.08 (N=81)	47.04 ± 12.88 (N=52)	51.28 ± 13.79 (N=32)	0.0460[1]#
BMI (Mean ± SD)	27.04 ± 5.65	30.00 ± 5.80	29.63 ± 4.52	*ns*
Smoker				
Current	7 (8.8%)	8 (16.3%)	9 (28.1%)	0.0443[2]#
Non Smoker	58 (72.5%)	31 (63.3%)	14 (43.8%)	
Former Smoker	15 (18.8%)	10 (20.4%)	9 (28.1%)	
Thyroid Evaluation				
TSH mIU/L (Mean ± SD)	1.86 ± 1.10	1.95 ± 1.34	1.99 ± 1.34	*ns*
FT4 ng/dL (Mean ± SD)	1.24 ± 0.34	1.14 ± 0.21	1.40 ± 1.42	*ns*
Thyroid US volume mL (Mean ± SD)	18.22 ± 10.47	18.46 ± 10.97	19.39 ± 6.58	*ns*
TRAb IU/L (Mean ± SD)	7.26 ± 10.43	7.94 ± 11.32	6.10 ± 8.24	*ns*
Positive	53 (66.3%)	29 (56.9%)	17 (63.0%)	*ns*
TPOAb				
Positive	58 (73.4%)	32 (65.3%)	18 (66.7%)	*ns*
TgAb				
Positive	36 (45.6%)	19 (38.8%)	10 (38.5%)	*ns*
Cholesterol Evaluation				
Cholesterol (mg/ dL) (Mean ± SD)	185.23 ± 35.53	190.27 ± 42.19	212.97 ± 39.09	0.0025[1]#
HDL (mg/ dL) (Mean ± SD)	56.09 ± 13.20	53.40 ± 13.61	50.91 ± 17.46	0.0436[1]#
LDL (mg/ dL) (Mean ± SD)	112.08 ± 28.74	114.90 ± 35.72	139.25 ± 37.10	0.0006[1]#
Triglycerides (mg/ dL) (Mean ± SD)	101.88 ± 52.58	107.14 ± 52.82	119.25 ± 41.37	0.0393[1]#

Table 3 - Descriptive analysis and comparisons between EUGOGO groups
BMI (Body Mass Index)
TRAb (Thyrotropin Receptor Antibody)
TPOAb (Thyroid Peroxidase Antibodies)
TgAb (Thyroglobulin Antibodies)
TSH (Thyroid Stimulating Hormone)
FT4 (Free Thyroxine)
US (Ultrasound)
HDL (high-density lipoprotein)
LDL (low-density lipoprotein)
differences between (Dunn test): 1 and 3; 2 and 3.

Table 4 - Results of simple and multiple logistic regressions, proportional odds model, for studying the CAS (modeling the group probability CAS groups = Group B CAS 1 or 2 – or Group C – CAS 3 or more)				
Simple Analysis				
Variable	Category	P - Value	OR	CI95%
Age		0.0098	1.028	1.007;1.050
Thyroid US volume mL		*ns*		
BMI		0.0484	1.084	1.001;1.174
TRAb		*ns*		
TRAb	Negative vs Positive	*ns*		
FT4		*ns*		
TSH		*ns*		
Cholesterol		0.0102	1.010	1.002;1.018
HDL		*ns*		
LDL		0.0071	1.012	1.003;1.021
Triglycerides		*ns*		
TPOAb	Negative vs Positive	*ns*		
TgAb	Negative vs Positive	*ns*		
Smoker	Smoker vs Non Smoker	0.0043	3.408	1.469;7.908
Smoker	Former vs Non Smoker	*ns*		

Multiple analysis – stepwise selection process				
Group CAS		Total Frequency		
C (3 or more)		27		
B(CAS = 1 and 2)		52		
A (CAS = 0)		78		
Variable	Category	P - Value	OR	CI95%
LDL		0.0112	1.012	1.003;1.021
Smoker	Smoker vs Non Smoker	0.0110	3.096	1.296;7.394
Smoker	Non Smoker vs Former	0.1011	1.873	0.885;3.966
OR = Odds Ratio/ CI = Confidence Interval 95%				

Table 4 - Results of simple and multiple logistic regressions, proportional odds model, for studying the CAS (modeling the group probability CAS groups = Group B CAS 1 or 2 – or Group C – CAS 3 or more)

BMI (Body Mass Index)
TRAb (Thyrotropin Receptor Antibody)
TPOAb (Thyroid Peroxidase Antibodies)
TgAb (Thyroglobulin Antibodies)
TSH (Thyroid Stimulating Hormone)
FT4 (Free Thyroxine)
US (Ultrasound)
HDL (high-density lipoprotein)
LDL (low-density lipoprotein)
CAS (Clinical Activity Score)

Table 5 - Results of simple and multiple logistic regressions, proportional odds model, for the EUGOGO study (modeling the group probability EUGOGO groups = Group B – Mild - or Group C - Moderate to severe/sight-threatening)				
Simple Analysis				
Variable	Category	P - Value	OR	CI95%
Age		0.0187	1.026	1.004;1.047
Sex	Male vs female	*ns*		
Thyroid US volume mL		*ns*		
BMI		*ns*		
TRAb		*ns*		
TRAb	Negative vs positive	*ns*		
FT4		*ns*		
TSH		*ns*		
Cholesterol		0.0042	1.011	1.004;1.019
HDL		0.0612	0.979	0.958;1.001
LDL		0.0013	1.015	1.006;1.024
Triglycerides		*ns*		
TPOAb	Negative vs Positive	*ns*		
TgAb	Negative vs Positive	*ns*		
Smoker	Smoker vs Non-Smoker	0.0047	3.347	1.448;7.738
Smoker	Former vs Non-Smoker	*ns*		
Multiple analysis – stepwise selection process				
Group EUGOGO		Total Frequency		
C (Moderate To Severe/Sight-threatening)		30		
B (Mild)		45		
A (Absent)		79		
Variable	Category	P - Value	OR	CI95%
HDL		0.0384	0.973	0.948;0.999
LDL		0.0054	1.013	1.004;1.023
Smoker	Smoker vs Non-Smoker	0.0189	2.881	1.190;6.971
Smoker	Non-Smoker vs Former	*ns*		

Table 5 - Results of simple and multiple logistic regressions, proportional odds model, for the EUGOGO study (modeling the group probability EUGOGO groups = Group B – Mild - or Group C - Moderate to severe/sight-threatening)

BMI (Body Mass Index)
TRAb (Thyrotropin Receptor Antibody)
TPOAb (Thyroid Peroxidase Antibodies)
TgAb (Thyroglobulin Antibodies)
TSH (Thyroid Stimulating Hormone)
FT4 (Free Thyroxine)
US (Ultrasound)
HDL (high-density lipoprotein)
LDL (low-density lipoprotein)

Table 6 - Descriptive analysis and Comparisons Between CAS groups B and C			
Variable	Group B – CAS 1 and 2	Group C – CAS 3 or more	P Value
General Characteristics			
Male/ Female	8 (14.5%)/47 (85.5%)	7 (24.1%)/22(75.9%)	
Age (Mean ± SD)	46.50 ± 11.93 (N=54)	52.72 ± 14.96 (N=29)	0.0207[1]
BMI (Mean ± SD)	29.85 ± 5.72	30.29 ± 4.04	*ns*
Smoker			
Current	9 (16.7%)	8 (28.6%)	*ns*
Non Smoker	34 (63.0%)	11 (39.3%)	
Former Smoker	11 (20.4%)	9 (32.1%)	
Thyroid Evaluation			
TSH mIU/L (Mean ± SD)	2.04 ± 1.37	1.82 ± 1.27	*ns*
FT4 ng/dL (Mean ± SD)	1.16 ± 0.22	1.40 ± 1.49	*ns*
Thyroid US volume mL (Mean ± SD)	18.23 ± 10.17	20.14 ± 8.68	*ns*
TRAb IU/L (Mean ± SD)	7.24 ± 11.01	7.33 ± 8.58	*ns*
Positive	29 (53.7%)	17 (70.8%)	*ns*
TPOAb			
Positive	32 (61.5%)	18 (75.0%)	*ns*
TgAb			
Positive	20 (38.5%)	9 (39.1%)	*ns*
Cholesterol Evaluation			
Cholesterol (mg/ dL) (Mean ± SD)	192.85 ± 43.18	210.43 ± 38.61	0.0528[1]
HDL (mg/ dL) (Mean ± SD)	52.42 ± 13.21	52.52 ± 18.53	*ns*
LDL (mg/ dL) (Mean ± SD)	118.38 ± 37.97	135.17 ± 35.99	0.0273[1]
Triglycerides (mg/ dL) (Mean ± SD)	107.68 ± 48.58	119.52 ± 49.02	*ns*

Table 6 - Descriptive analysis and Comparisons Between CAS groups B and C
BMI (Body Mass Index)
TRAb (Thyrotropin Receptor Antibody)
TPOAb (Thyroid Peroxidase Antibodies)
TgAb (Thyroglobulin Antibodies)
TSH (Thyroid Stimulating Hormone)
FT4 (Free Thyroxine)
US (Ultrasound)
HDL (high-density lipoprotein)
LDL (low-density lipoprotein)
CAS (Clinical Activity Score)
[1]based on Mann-Whitney test / ² based on Chi-square test / ³ based on Fisher's exact test

Table 7 - Descriptive analysis and comparisons between EUGOGO groups B and C			
Variable	Group B – Mild	Group C – Moderate to severe/sight-threatening	P Value
General Characteristics			
Male/ Female	7 (13.5%) /45 (86.5%)	8 (25.0%)/24 (75.0%)	*ns*
Age (Mean ± SD)	47.04 ± 12.88 (N=52)	51.28 ± 13.79 (N=32)	*ns*
BMI (Mean ± SD)	30.00 ± 5.80	29.63 ± 4.52	*ns*
Smoker			
Current	8 (16.3%)	9 (28.1%)	*ns*
Non Smoker	31 (63.3%)	14 (43.8%)	
Former Smoker	10 (20.4%)	9 (28.1%)	
Thyroid Evaluation			
TSH mIU/L (Mean ± SD)	1.95 ± 1.34	1.99 ± 1.34	*ns*
FT4 ng/dL (Mean ± SD)	1.14 ± 0.21	1.40 ± 1.42	*ns*
Thyroid US volume mL (Mean ± SD)	18.46 ± 10.97	19.39 ± 6.58	*ns*
TRAb IU/L (Mean ± SD)	7.94 ± 11.32	6.10 ± 8.24	*ns*
Positive	29 (56.9%)	17 (63.0%)	*ns*
TPOAb			
Positive	32 (65.3%)	18 (66.7%)	*ns*
TgAb			
Positive	19 (38.8%)	10 (38.5%)	*ns*
Cholesterol Evaluation			
Cholesterol (mg/ dL) (Mean ± SD)	190.27 ± 42.19	212.97 ± 39.09	0.0132[1]
HDL (mg/ dL) (Mean ± SD)	53.40 ± 13.61	50.91 ± 17.46	*ns*
LDL (mg/ dL) (Mean ± SD)	114.90 ± 35.72	139.25 ± 37.10	0.0024[1]
Triglycerides (mg/ dL) (Mean ± SD)	107.14 ± 52.82	119.25 ± 41.37	*ns*

Table 7 - Descriptive analysis and comparisons between EUGOGO groups B and C
BMI (Body Mass Index)
TRAb (Thyrotropin Receptor Antibody)
TPOAb (Thyroid Peroxidase Antibodies)
TgAb (Thyroglobulin Antibodies)
TSH (Thyroid Stimulating Hormone)
FT4 (Free Thyroxine)
US (Ultrasound)
HDL (high-density lipoprotein)
LDL (low-density lipoprotein)
[1] based on Mann-Whitney test / [2] based on Chi-square test / [3] based on Fisher's exact test

A introdução, objetivos, metologia, resultados e discussão foram abordados no artigo em questão publicado: Cardo, C., Bernardo Santos, R., Pinotti Pedro Miklos, A. B., Barbosa Jaconis, S., Romaldini, J. H., & Villagelin, D. (2025). The relationship between cholesterol levels and thyroid eye disease. European Thyroid Journal, 14(1), e240133. https://doi.org/10.1530/ETJ-24-0133, e autorizados pela revista em anexo neste arquivo.

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3. Liberação do CEP

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PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: O uso crônico de metimazol e a remissão da doença de Graves
Pesquisador: Valéria Bahdur Chueire
Área Temática:
Versão: 3
CAAE: 39062520.8.0000.5481
Instituição Proponente: Sociedade Campineira de Educação e Instrução
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.478.480

Apresentação do Projeto:
INTRODUÇÃO:
A Doença de Graves (DG) foi descrita pela primeira vez em 1835, por um médico irlandês chamado Robert James Graves. Ele a caracterizou como uma doença que causava aumento e hiperatividade da tireoide e que normalmente vinha acompanhada de anormalidades oculares. Futuramente, compreendeu-se a fisiopatologia autoimune da doença, com o reconhecimento do anticorpo anti-receptor TSH (TRAb) e a gama de fatores que estão relacionados com o desenvolvimento da doença. A Doença de Graves é a principal causa de hipertireoidismo, responsável por 60 a 80% dos casos, sendo mais incidente em pacientes do gênero feminino na faixa de 20 a 40 anos, com prevalente predisposição genética, de causa multifatorial. É uma doença autoimune, sendo caracterizada por hipertireoidismo, orbitopatia, bócio e, mais raramente, mixedema pré-tibial ou dermopatia tireoidiana. Seu diagnóstico é realizado a partir da análise de um TSH suprimido e T4 livre aumentado, caracterizando o hipertireoidismo, podendo-se dosar também o TRAb, que é critério diagnóstico para Doença de Graves. Além dos exames laboratoriais, o bócio difuso, a orbitopatia aliados ao quadro clínico de distúrbios metabólicos originados pela elevação dos hormônios tireoidianos auxiliam para a confirmação do diagnóstico em questão. A abordagem terapêutica pode se dar de três formas: as tionamidas, objetivo de análise do trabalho, radioiodoterapia e/ou cirurgia. Além desses, pôde-se associar o uso de betabloqueadores para alívio sintomático do quadro clínico do hipertireoidismo. Dentre as Tionamidas, destacasse o

Endereço: Rua Professor Doutor Euryclides de Jesus Zerbini, 1516
Bairro: Parque Rural Fazenda Santa Cândida **CEP:** 13.087-571
UF: SP **Município:** CAMPINAS
Telefone: (19)3343-6777 **Fax:** (19)3343-6777 **E-mail:** comitedeetica@puc-campinas.edu.br