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TIREOIDE
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**PRÊMIO JOVEM
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1. PRÊMIO JOVEM CIENTISTA TRANSLACIONAL • TRABALHO VENCEDOR • TRANSLACIONAL

BIOLOGIA CELULAR DA TIREOIDE

2847 MICRORNA EXPRESSION PROFILE IN PEDIATRIC DIFFERENTIATED THYROID CARCINOMA: INTEGRATED NGS ANALYSIS AND VALIDATION IN A BRAZILIAN COHORT

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Introduction: Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy in children and adolescents. Although its mutational landscape has been partially characterized, large-scale data on microRNA (miRNA) expression in pediatric patients remain scarce, particularly in Brazil. Because miRNAs regulate multiple oncogenic pathways, mapping miRNA dysregulation may reveal biomarkers of tumor aggressiveness beyond known genetic alterations. **Objective:** To identify differentially expressed miRNAs in pediatric papillary thyroid carcinoma using next-generation sequencing (NGS) and to validate both NGS-identified and previously reported miRNAs by RT-qPCR, exploring their association with adverse clinicopathological features. **Methods:** We conducted a retrospective study of patients ≤ 18 years who underwent thyroidectomy at a tertiary referral center. NGS was performed in eight FFPE samples (four tumors and four adjacent normal thyroid tissues, non-paired), and differential expression was analyzed with false discovery rate adjustment. Candidate miRNAs were selected according to statistical significance and biological plausibility, and additional miRNAs previously implicated in thyroid carcinogenesis were included for validation. RT-qPCR was subsequently performed in an independent cohort of 23 paired tumor and normal thyroid samples. Associations between miRNA expression and histopathological markers of aggressiveness were evaluated. **Results:** NGS revealed a distinct miRNA dysregulation signature in tumor tissue, from which five candidates were prioritized for validation. RT-qPCR confirmed differential expression of all selected miRNAs. Overexpression of miR-146b-5p and miR-222-3p was associated with lymph node metastasis ($p = 0.02$ and $p = 0.05$), and miR-146b-5p levels correlated with the number of metastatic lymph nodes ($p = 0.02$). Overexpression of miR-133, identified in the discovery phase, was associated with vascular invasion ($p = 0.017$) and macroscopic extrathyroidal extension ($p = 0.032$). **Conclusion:** This study reports the first systematic analysis of miRNA expression in pediatric DTC in a Brazilian cohort, integrating NGS discovery with RT-qPCR validation. Associations of miR-146b-5p, miR-222-3p, and miR-133 overexpression with markers of aggressive disease support their potential role as biomarkers for future risk stratification and personalized management in children and adolescents with DTC. **Keywords:** miRNA; RT-qPCR; pediatric papillary thyroid carcinoma.

2. PRÊMIO JOVEM CIENTISTA CLÍNICO • TRABALHO VENCEDOR • CLÍNICO

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2841 POSTOPERATIVE UNSTIMULATED THYROGLOBULIN ACCURATELY PREDICTS OUTCOMES IN INTERMEDIATE-RISK DIFFERENTIATED THYROID CANCER: A RETROSPECTIVE COHORT STUDY

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Introduction: Intermediate-risk differentiated thyroid cancer (DTC) patients represent a heterogeneous group, with recurrence rates ranging from 5% to 30%. This variability poses challenges for therapeutic decision-making, highlighting the need for more accurate prognostic biomarkers. **Objective:** Although postoperative stimulated thyroglobulin (STg) is a well-established predictive marker, the prognostic role of unstimulated thyroglobulin (UTg) remains underexplored. This study aims to evaluate the prognostic value of postoperative UTg in patients with intermediate-risk DTC. **Methods:** This retrospective cohort study was conducted between 2015 and 2026 at three Brazilian tertiary hospitals. Clinical, pathological, and laboratory data were collected at baseline and one-year follow-up. Outcomes were classified as favorable (excellent or indeterminate response) or unfavorable (biochemical or structural incomplete response). ROC curves determined cutoff values for predicting outcomes. Patients with positive anti-thyroglobulin antibodies or incomplete data were excluded. **Results:** Of 1,299 DTC patients, 312 (24%) were intermediate-risk; 63 met the inclusion criteria. Most participants were female (76%), with a median age of 49.6 years. Papillary carcinoma was present in 98%, and 62% were classified as intermediate-high risk. At one-year follow-up, 52% achieved excellent response, while 6.3% had biochemical incomplete and 13% structural incomplete response. Higher levels of both UTg ($p = 0.03$) and STg ($p = 0.03$) were significant predictors of unfavorable outcomes. UTg emerged as an independent predictor (OR: 2.77; 95% CI: 1.37–8.96; $p = 0.026$). A UTg cutoff of 0.92 ng/mL distinguished outcomes with 75% sensitivity, 98.2% specificity, and 85.7% accuracy. In paired ROC curve analysis, STg showed a slightly higher AUC (0.864 vs. 0.818), but this difference was not statistically significant ($p = 0.517$). **Conclusion:** Postoperative UTg is a strong prognostic marker in intermediate-risk DTC patients, and a cutoff value of 0.92 ng/mL demonstrates high accuracy in distinguishing treatment responses. Its predictive performance was statistically comparable to that of STg, offering a practical and accessible alternative with reduced side effects. **Keywords:** thyroid neoplasms; thyroglobulin; prognosis.



3. PRÊMIO JOVEM CIENTISTA BÁSICO • TRABALHO VENCEDOR • BÁSICO

NÓDULOS E CÂNCER DE TIREOIDE

2759 OLD DRUG, NEW TARGET: THE ANTITUMOR EFFECT OF NIFUROXAZIDE ON ANAPLASTIC THYROID CANCER

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Introduction: Anaplastic thyroid cancer (ATC) is the most aggressive form of thyroid cancer (TC), with the lowest survival rate. Therapeutic options are limited and involve inhibitors of the MAPK and PI3K signaling pathways. However, most ATCs develop resistance primarily through activation of the JAK/STAT3 pathway as an escape mechanism. This pathway is implicated in tumor development and progression. Nifuroxazide (NFZ), an antibiotic used since 1966, has demonstrated antitumor activity, attributed to its JAK2 inhibitory effects. **Objective:** To investigate the antitumor activity of NFZ, alone or in combination with BRAF and PI3K inhibitors, as well as three derivatives, and to elucidate their mechanisms of action in ATC cells. **Methods:** Non-tumoral thyroid cells (Nthy-ori 3.1), ATC cells (HTH83 and KTC-2), three STAT3 knockout (KO) clones, and CRISPR control cells were used. Drug effects were assessed through cell viability, colony formation, migration, and invasion assays. Epithelial-mesenchymal transition (EMT) gene expression was analyzed by real-time PCR. Cell death and reactive oxygen species (ROS) generation were assessed by flow cytometry. Modulation of the JAK/STAT3, MAPK, and PI3K pathways was assessed by Western blotting. Combination treatments were performed using the BRAF inhibitor (Vemurafenib) and PI3K inhibitor (LY294002). **Results:** NFZ and its derivatives reduced cell viability and colony-forming ability in ATC cells and induced cell death through apoptosis and necrosis. In HTH83, ROS generation contributed to cell death. NFZ also decreased pSTAT3, pERK and pAKT levels, suppressed migration and invasion, and modulated EMT by increasing E-cadherin mRNA expression in ATC cells. Notably, in STAT3-KO cells, NFZ reduced cell viability, colony formation and decreased pERK and pAKT. The NFZ at IC50 combined with BRAF or PI3K inhibitors at IC25 reduced ATC cell viability to a level similar to the inhibitors IC50 alone, indicating synergism. **Conclusion:** NFZ reduced tumorigenic properties in ATC cells through modulation of multiple signaling pathways, including JAK/STAT3, MAPK, and PI3K. This is the first study to demonstrate that NFZ exerts broader signaling modulation beyond JAK/STAT3. Its derivatives also exhibited significant antitumor activity. These findings highlight the therapeutic potential of NFZ repurposing, particularly in combination with targeted inhibitors, which may reduce adverse effects and delay the development of drug resistance. **Keywords:** nifuroxazide; anaplastic thyroid cancer; JAK/STAT3.

4. PRÊMIO JOVEM CIENTISTA • MENÇÕES HONROSAS TRANSLACIONAL

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2750 ASSOCIATION OF THR92ALA-DIO2 POLYMORPHISM AND AGGRESSIVE PHENOTYPE IN PAPILLARY THYROID CARCINOMA

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Introduction: Papillary thyroid carcinoma (PTC) treatment includes total thyroidectomy, radioiodine therapy, and TSH suppression with levothyroxine (T4). The effectiveness of TSH suppression depends on peripheral T4-to-T3 conversion mediated by type 2 deiodinase (DIO2). The Thr92Ala-DIO2 polymorphism (rs225014) has been associated with altered intracellular T3 availability and impaired tissue responsiveness to TSH suppression, but its oncological impact in PTC remains unclear. **Objective:** To investigate the association between Thr92Ala-DIO2 genotypes and clinicopathological features, hormonal profile and oncological outcomes in PTC patients. **Methods:** A total of 147 patients submitted to total thyroidectomy for PTC and followed longitudinally at a tertiary cancer center were evaluated. Thr92Ala-DIO2 genotyping was performed in leukocyte DNA using qRT-PCR and Sanger sequencing. Clinicopathological data, hormonal measurements and oncological outcomes were extracted from medical records and compared across genotypes. Serum total TT3, TT4, FT4 and TSH were assessed under levothyroxine therapy. **Results:** Thr92Ala-DIO2 polymorphism was present in 66.7% of patients: 49/147 (33.3%) Thr/Thr, 73/147 (49.7%) Thr/Ala, and 25/147 (17.0%) Ala/Ala. Carriers of Thr92Ala-DIO2 variant presented larger primary tumors ($p = 0.007$) and higher rates of lymph node metastases at diagnosis ($p = 0.027$), suggesting a more aggressive initial tumor presentation. While TT3, TT4, FT4, and TSH levels did not differ among genotypes, Thr92Ala-DIO2 carriers, whose TSH levels were ≥ 0.5 mUI/L, required significantly higher levothyroxine dose per kilogram ($p = 0.008$). The Thr92Ala-DIO2 polymorphism was associated with increased risk of disease recurrence or persistence (OR: 2.5; 95% CI: 1.2-5.1; $p = 0.015$) and incomplete response to therapy (OR: 3.5; 95% CI: 1.2-9.7; $p = 0.018$). However, in multivariate analysis, this association was not independent and was largely mediated by lymph node and distant metastases at diagnosis. **Conclusion:** The Thr92Ala-DIO2 polymorphism is associated with more aggressive initial presentation and poorer oncological outcomes in PTC. The increased levothyroxine requirements in Thr92Ala-DIO2 carriers support the hypothesis that impaired intracellular thyroid hormone metabolism may influence tumor behavior. **Keywords:** thyroid cancer; type 2 deiodinase; polymorphism.



DISFUNÇÕES TIREOIDIANAS

2754 NEW GENETIC INSIGHTS INTO THYROID DYSGENESIS REVEAL FOXE1-RISK VARIANTS AND DUOX2-RELATED EPITHELIAL-MESENCHYMAL DISTURBANCE

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Introduction: Congenital hypothyroidism is the most common cause of preventable intellectual disability, and thyroid dysgenesis (TD) accounts for 80%–85% of cases. Pathogenic mutations are rarely identified, and the genetic cause is confirmed in only 2%–5% of patients. **Objective:** To investigate informative genetic alterations in TD patient's exome and to perform their potential functional impact. **Methods:** At all, 71 TD patients were included, 35 were underwent whole exome sequencing (WES) and the other 36 along with 128 Brazilian non-TD controls through Sanger sequencing. Public databases were used for genotyping analysis. For functional study, *DUOX2*-variants were generated by site-directed mutagenesis. Hydrogen peroxide generation, epithelial-mesenchymal transition (EMT) gene expression and 3D spheroids formation were evaluated. Also, three-dimensional protein modeling and interaction patterns were predicted. **Results:** The WES analysis did not define a consistent pattern of altered genes in TD. However, a high frequency of polymorphisms in *FOXE1* and five rare *DUOX2* variants were detected. The minor allele A of the functional polymorphism rs1867277 was associated with TD (OR: 2.11, 95% CI: 1.3–3.46). Similarly, the minor allele 14^{Ala} of rs71369530 was associated with TD (OR: 1.78, 95% CI: 1.1–2.88) individually and combination with rs1867277 (OR: 2.9, 95% CI: 1.25–6.72). Variants within the genetic block at 9q22 showed individual association with TD. Functional analyses of rare *DUOX2*-variants demonstrated disruption of epithelial-mesenchymal transition-related gene expression, while no changes were observed in 3D spheroid formation, and only one variant reduced hydrogen peroxide generation. Altered *DUOX2*-*DUOX2* interaction patterns were identified by 3D protein modeling in all *DUOX2*-variants compared to wild-type prediction. **Conclusion:** In conclusion, we showed for the first time that rs1867277 A allele, either individually or in combination with rs71369530 14^{Ala} is a risk factor for TD. Also, this study provides new evidence supporting a potential role for *DUOX2*-variants in TD by disrupting EMT and impairing *DUOX2* and its own maturation factor *DUOX2* interaction in thyroid embryonic period. Our findings are sustained by polygenic disease model of TD, further tests being necessary to further clarify these mechanisms. **Keywords:** congenital hypothyroidism; thyroid dysgenesis; *FOXE1* and *DUOX2*.

NÓDULOS E CÂNCER DE TIREOIDE

2793 CIRCULATING MICRORNAS PROVIDE INCREMENTAL PROGNOSTIC INFORMATION BEYOND CONVENTIONAL STAGING IN PAPILLARY THYROID CARCINOMA

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Introduction: Genomic profiling of papillary thyroid carcinoma (PTC) has identified tumor microRNA (miR) signatures associated with loss of differentiation, tumor progression, and metastatic potential. Although most PTCs follow an indolent course with low disease-specific mortality, a clinically relevant subset develops distant metastases (DM) and disease-related death. Circulating microRNAs may reflect tumor biology and identify patients with clinically aggressive disease beyond conventional staging systems. **Objective:** To identify circulating miRs associated with metastatic disease and disease-specific mortality in PTC. **Methods:** Plasma miR expression was quantified by RT-qPCR in 129 PTC patients treated with total thyroidectomy and additional therapies as indicated. In the discovery phase (9 excellent response [ER] vs. 9 structural incomplete response [SIR: 3 with locoregional (LR) and 6 with distant metastases (DM)]), 754 miRs were screened and 14 candidates were selected through unsupervised hierarchical clustering. In the validation cohort, differential expression was confirmed by comparing 32 SIR patients (14 LR, 18 DM) and 29 ER. The predictive value of confirmed miRs for recurrence in 50 patients with biochemical incomplete or indeterminate response (BIR/IND), progression in DM, and disease-specific mortality was evaluated using logistic regression adjusted for AJCC staging and Kaplan-Meier analyses. **Results:** Four circulating miRs distinguished structural disease from ER. miR-484 was significantly overexpressed in DM ($p = 0.014$), whereas let-7c-5p ($p = 0.009$) and miR-146b-5p ($p = 0.006$) were significantly reduced in DM. miR-221-3p was reduced in locoregional disease ($p = 0.005$). miR-484 was overexpressed in DM compared to LR disease ($p = 0.016$). Importantly, lower circulating levels of let-7c-5p ($p = 0.016$) and miR-146b-5p ($p = 0.045$) independently predicted disease-specific mortality after AJCC adjustment. Patients in the lowest tercile of let-7c-5p had significantly worse survival (log-rank $p = 0.039$). None of the four miRs predicted recurrence among BIR/IND or progression among established DM. **Conclusion:** Circulating miRNA profiling identifies a molecular signature of metastatic PTC and independently predicts disease-specific death. Reduced let-7c-5p expression emerges as a promising non-invasive biomarker of aggressive, life-threatening disease, providing incremental prognostic information beyond conventional staging systems and supporting prospective validation. **Keywords:** microRNA; prognosis; thyroid cancer.



NÓDULOS E CÂNCER DE TIREOIDE

2846 BEYOND NIS EXPRESSION: ALTERED TRAFFICKING MACHINERY LIMITS IODIDE UPTAKE IN THYROID CANCER

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Introduction: The subcellular localization of the sodium-iodide symporter (NIS) at the plasma membrane (PM) is essential for its activity. In thyroid tumors, altered NIS expression and/or its retention in the cytoplasm are frequently observed. Recent evidence further indicates that NIS interacts with several cytoplasmic and PM proteins involved in its trafficking to the cell surface. **Objective:** To evaluate the expression of genes encoding candidate proteins that may interfere with the subcellular localization of NIS in normal and tumoral thyrocytes. **Methods:** Total RNA was extracted from normal human thyrocytes (Nthy-ori 3-1) and tumoral thyrocytes (TPC1, BCPAP, and KTC2), and the expression of genes encoding proteins involved in NIS trafficking, including cytoplasmic (ARF4, COPA) and PM (EZR) proteins that interact with NIS, was evaluated by qPCR. The results were compared with genomic and transcriptomic data from TCGA datasets. In addition, cell transfection assays were performed using the pcDNA3.1-HA-NIS vector, and NIS function was evaluated by non-radioactive iodide uptake assays. Reactive oxygen species (ROS) production was assessed by flow cytometry. **Results:** Compared with Nthyori cells, COPA expression, a protein with a central role in vesicle-mediated transport, was reduced in BRAF-mutant cells, but not in TPC1 cells. EZR expression, which contributes to NIS anchoring and retention at the PM, was reduced in BCPAP and KTC2 cells, but increased in TPC1 cells. In turn, ARF4 expression, which interacts with the cytoplasmic C-terminal region of NIS and promotes its trafficking to the PM, was decreased in TPC1 and BCPAP cells. Similar patterns were observed in the comparison between tumor and normal samples from TCGA. Interestingly, although NIS overexpression increased iodide uptake in all cell lines relative to controls, this effect was not proportional to SLC5A5 mRNA levels, suggesting impaired NIS translocation to the PM in tumor cells. Finally, NIS overexpression altered ROS production in all cell lines analyzed. **Conclusion:** NIS overexpression alone is not sufficient to restore its function in thyroid tumor cells. Defects in the machinery that controls NIS trafficking to the PM may represent a major barrier to iodide uptake in thyroid tumors and a potential target for restoring radioiodine responsiveness. In addition, the differences observed across distinct tumor backgrounds suggest that NIS trafficking is dependent on the tumor molecular context. **Keywords:** NIS; intracellular trafficking; thyroid cancer.

CLÍNICO

NÓDULOS E CÂNCER DE TIREOIDE

2781 PROGNOSTIC HETEROGENEITY WITHIN RADIOIODINE-REFRACTORY METASTATIC THYROID CARCINOMA

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Introduction: Standard management of differentiated (DTC) and poorly differentiated thyroid carcinoma (PDTC) with distant metastases includes surgery, radioiodine (RAI) therapy, and TSH suppression. However, a substantial proportion of patients develop radioiodine-refractory disease. Although multiple criteria define RAI refractoriness, their relative prognostic significance remains unclear. **Objective:** To evaluate progression-free survival (PFS) and disease-specific survival (DSS) according to RAI responsiveness and across distinct RAI-refractoriness criteria. **Methods:** Among 1,496 patients with DTC/PDTC, 147 with distant metastases that received treatment administration of RAI were included. Patients were classified as RAI-responsive (n = 42) or RAI-refractory according to five predefined criteria: (1) absence of uptake on post-therapy whole-body scintigraphy (RxWBS-; n = 49); (2) structural progression within 12 months despite RAI uptake (progression < 12 months RxWBS+; n = 6); (3) uptake in some but not all metastatic lesions (n = 18); (4) cumulative RAI activity ≥ 600 mCi without remission despite uptake (n = 21); and (5) absence of uptake on diagnostic WBS (DxWBS-; n = 11). PFS and DSS were estimated using Kaplan-Meier analysis and multivariable Cox regression adjusted for major clinicopathological variables. **Results:** RAI-refractory disease was identified in 71% and was associated with higher progression (71% vs. 21%, p < 0.001) and cancer-specific mortality (29.5% vs. 7.1%, p = 0.004). PFS and DSS were significantly longer in RAI-responsive patients (log rank p < 0.001 and p = 0.05). RAI refractoriness independently increased risk of progression (HR 4.8, p < 0.001) and cancer-specific death (HR 4.3, p = 0.03). Among refractory subgroups, progression < 12 months despite RAI uptake showed the poorest outcomes (median PFS 0.9 years; median DSS 1.6 years). Although PFS and DSS differed significantly across criteria (log-rank p < 0.001), multivariable analysis identified only this subgroup as independently associated with adverse outcomes, conferring a 3.8-fold higher risk of progression and 6.4-fold higher risk of cancer-specific death compared with RxWBS-. **Conclusion:** RAI refractoriness is an independent predictor of progression and mortality in metastatic DTC/PDTC. Marked heterogeneity exists within refractoriness definitions and early progression despite RAI-uptake represents a particularly high-risk sub-group. Refining criteria may improve risk stratification and guide timing of systemic therapy. **Keywords:** metastatic thyroid carcinoma; prognosis; radioiodine therapy.



EPIDEMIOLOGIA

2791 COLLABORATIVE NETWORK FOR CLINICAL THYROID EYE DISEASE (CONNECT TED STUDY GROUP): CLINICAL FEATURES OF BRAZILIAN PATIENTS WITH THYROID EYE DISEASE

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Introduction: Thyroid eye disease (TED) is a rare, debilitating autoimmune disorder. Data on TED in Latin American populations remains limited. This multicenter study aimed to characterize the clinical features and treatment patterns of TED in Brazil. **Objective:** Evaluate the current epidemiological and clinical characteristics of TED in Brazil. **Methods:** This retrospective multicenter study included 606 patients with Graves' disease and TED from 13 Brazilian tertiary hospitals. Disease activity and severity were assessed using the Clinical Activity Score (CAS) and the European Group on Graves' Orbitopathy (EUGOGO) classification. Associations between epidemiological features and clinical outcomes were analyzed. **Results:** In the overall cohort, the mean age at diagnosis was 44 ± 15 years; 78% of patients were female, and 10% were current smokers. Median thyroid function at baseline was TSH $0.10 \mu\text{IU/mL}$ ($0.01-1.87$) and FT4 1.39 ng/dL ($1.05-2.22$). TED activity at baseline showed a mean CAS of 0.9 ± 1.5 . According to the EUGOGO classification, 36% of patients had mild disease, 16% had moderate-to-severe disease, and 3% had sight-threatening disease. 45% of patients had no signs of TED. Significant regional differences were observed in the mean age at diagnosis: North (N) 48 ± 14 years; Northeast (NE) 44 ± 14 years; Midwest (MW) 38 ± 14 years; Southeast (SE) 45 ± 14 years; and South (S) 37 ± 14 years ($p < 0.005$). Mean TED activity also varied by region, with mean CAS values of 1.2 ± 0.1 in the N, 1.3 ± 0.2 in the NE, 1.8 ± 0.9 in the MW, 0.6 ± 1.4 in the SE, and 1.0 ± 2.2 in the S ($p < 0.005$). According to the EUGOGO classification, patients from SE and S exhibited milder disease than those from other regions ($p < 0.005$). Regarding treatment, 57% of patients with a TED diagnosis received at least one therapeutic intervention. Among treated patients, 89% received lubricating eye drops, 12% received selenium supplementation, 53% received intravenous (IV) corticosteroids, 8% underwent orbital radiotherapy (RT), and only one patient received immunobiologic therapy. 18% of patients treated with IV steroids required an additional treatment for TED; with 13% undergoing RT, 2% receiving immunobiologic therapy, 1% undergoing orbital decompression, and 1% using mycophenolate. **Conclusion:** Our results demonstrate marked regional heterogeneity in TED presentation and treatment, providing a robust evidence base to direct public health policies aimed at expanding access to specialized care and improving outcomes. **Keywords:** thyroid eye disease; TED; thyroid eye disease management.



NÓDULOS E CÂNCER DE TIREOIDE

2807 RISK OF MALIGNANCY ACCORDING TO NUCLEAR ATYPIA, CLINICAL AND ULTRASONOGRAPHIC FEATURES IN INDETERMINATE THYROID NODULES

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Introduction: Thyroid nodules with indeterminate cytology, classified as categories III and IV under the Bethesda System for Reporting Thyroid Cytopathology, pose a clinical challenge due to their variable malignancy risk. Detailed cytological assessment, particularly nuclear atypia, may refine risk stratification and guide management. **Objective:** To evaluate the risk of malignancy in indeterminate thyroid nodules according to nuclear atypia, clinical variables, and ultrasonographic features. **Methods:** Prospective study conducted at two tertiary referral hospitals (January 2019–January 2026). A total of 123 nodules (121 patients) with Bethesda III or IV cytology were included in the sample. Histopathology was available for 83 nodules and served as the reference standard. Atypia was classified as nuclear, architectural, combined nuclear and architectural, oncocytic, or nuclear changes not related to papillary carcinoma. A positive test was defined as isolated or combined nuclear atypia. Clinical, biochemical, and ultrasonographic variables were analyzed, including risk stratification by the ACR TI-RADS. **Results:** Mean age was 54.6 ± 15.1 years, and 77.7% were female. Among nodules, 51.2% were Bethesda III and 48.8% Bethesda IV. Of the 83 nodules with definitive diagnosis, the malignancy rate was 30.1%. Nuclear atypia (isolated or combined) was present in 18 of 22 malignant nodules and was strongly associated with malignancy (OR 37.8; 95% CI 9.08–157.3; $p < 0.001$). Diagnostic performance was robust, with sensitivity 81.8%, specificity 89.4%, positive predictive value 78.3%, negative predictive value 91.3%, and accuracy 87.0%. Male sex increased malignancy risk (OR 3.06; 95% CI 1.04–9.04; $p = 0.038$). No significant association was observed between malignancy and age ($p = 0.63$), BMI ($p = 0.59$), TSH levels ($p = 0.82$), or nodule size ($p = 0.087$). A stepwise increase in malignancy rates was observed across ACR TI-RADS categories: 18.8% in TR3, 30.2% in TR4, and 40.9% in TR5 ($p = 0.026$). **Conclusion:** In indeterminate thyroid nodules, nuclear atypia is a powerful predictor of malignancy with high diagnostic accuracy. Integration of refined cytological assessment with clinical and ultrasonographic risk stratification may substantially improve individualized surgical decision-making. These findings support a multimodal approach to risk stratification in contemporary endocrine practice. **Keywords:** indeterminate thyroid nodules; nuclear atypia; malignancy risk.

NÓDULOS E CÂNCER DE TIREOIDE

2816 ATA 2025 VS. 2015 RISK STRATIFICATION FOR DIFFERENTIATED THYROID CANCER: COMPARABLE PREDICTIVE ACCURACY AND IMPROVED CLINICAL STRATIFICATION IN A REAL-WORLD COHORT

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Introduction: Risk stratification in differentiated thyroid carcinoma (DTC) guides management. Following the 2015 model, the 2025 American Thyroid Association (ATA) guidelines introduced risk subcategories to improve prognostic accuracy and therapeutic prediction. **Objective:** To compare risk stratification and prognostic performance between ATA 2015 and 2025 guidelines in a real-world cohort. **Methods:** We retrospectively evaluated 224 DTC patients at a public center in Northeastern Brazil. Patients stratified by ATA 2015 criteria were reclassified under 2025 guidelines to assess category shifts, recurrence rates and therapeutic response. The primary outcome was structural recurrence (lymph node and/or distant metastases). **Results:** Participants were predominantly female (89.7%) and mixed-race (92%), with a mean age of 45.5 ± 14.7 years and 94.2% papillary carcinoma (mean follow-up: 8.7 ± 5.0 years). ATA 2015 distribution (39.7% Low, 37.1% Intermediate, 23.2% High) shifted under 2025 criteria to 36.6% Low, 18.8% Intermediate-Low, 33.0% Intermediate-High, and 11.6% High. ATA 2015 Intermediate patients ($n = 83$) were mainly redistributed into Intermediate-Low (31.3%) and Intermediate-High (49.3%). Notably, 51.9% of the 2015 High Risk group migrated to Intermediate-High, while 16.8% of the 2015 Low Risk group moved to Intermediate-Low. Discrimination was good for both systems (AUC: 0.726 for ATA 2015 vs. 0.759 for ATA 2025; $p = 0.337$). However, ATA 2025 provided an incremental clinical gradient for lymph nodal (7.3%, 11.9%, 25.7%, 50.0%) and distant recurrences (1.2%, 2.4%, 9.5%, 38.5%) from Low to High risk, respectively, reflecting a refined High Risk phenotype. Conversely, ATA 2015 recurrence rates jumped from Low (9%) to Intermediate (18%) and High (49%). Excellent response prevailed in 2025 Low (75.6%), Intermediate-Low (69.0%), and Intermediate-High (66.0%), whereas 50% of the High Risk group had structural incomplete response. Overall, 78.1% received radioiodine (RAI), including 57.3% of Low and 76.2% of Intermediate-Low groups. **Conclusion:** Although predictive accuracy was comparable, ATA 2025 guidelines improve clinical stratification through an incremental recurrence gradient and enhanced discrimination of high-risk patients. High RAI use in lower-risk categories suggests potential overtreatment. These findings support ATA 2025 applicability in this real-world cohort. **Keywords:** thyroid neoplasms; risk assessment; prognosis.



BÁSICO

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2743 TYPE 3 DEIODINASE DRIVES FIBROSIS AND METABOLIC PATHWAY REPROGRAMMING IN MASLD

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Introduction: Altered thyroid hormone metabolism driven by increased type 3 deiodinase (DIO3) contributes to metabolic dysfunction-associated steatotic liver disease (MASLD). Reduced thyroid hormone activity, specifically lower T3 levels, is expected to diminish mitochondrial function and shift cellular metabolism toward glycolysis, consistent with decreased T3-mediated mitochondrial stimulation. **Objective:** The primary aim was to determine whether this newly identified enrichment of DIO3 within hepatic stellate cells drives a shift toward aerobic glycolysis in MASLD, linking enzyme distribution to mitochondrial dysfunction and metabolic reprogramming. **Materials and methods:** Adult male Sprague-Dawley rats were assigned to four groups for 16 weeks: control, MASLD (high-fat, choline-deficient diet), MASLD + N-acetylcysteine (NAC), and MASLD + L-ornithine L-aspartate (LOLA). Gene expression of glycolytic and mitochondrial markers (HK2, PFKF, PKM2, LDHA, ATP5A) was analyzed by RT-qPCR to capture early glycolytic shifts. Protein levels of GDH, α -KGDH, and acetyl-CoA carboxylase were evaluated by western blotting to assess changes in key metabolic enzymes related to mitochondrial function. Hepatic intracellular triiodothyronine (T3) levels were quantified, and DIO3 localization was assessed by RNAscope and immunofluorescence to directly link enzyme presence with specific hepatic cell populations. **Results:** MASLD animals showed increased ammonia levels, redox imbalance, and upregulation of TR β and DIO3, all partially improved by NAC and LOLA. DIO3 colocalized predominantly with hepatic stellate cells, marking a first demonstration of this cellular localization. MASLD livers exhibited increased expression of glycolytic enzymes and reduced ATP5A expression, indicating enhanced glycolysis and impaired mitochondrial function. GDH, α -KGDH, and acetyl-CoA carboxylase activities were increased, and intracellular T3 levels were reduced. **Conclusion:** A previously unrecognized enrichment of DIO3 in hepatic stellate cells represents a novel finding, highlighting a potential cellular specificity that may underlie key metabolic changes. NAC and LOLA partially reversed metabolic alterations, highlighting potential therapeutic targets. **Keywords:** MASLD; thyroid hormone; deiodinase.

NÓDULOS E CÂNCER DE TIREOIDE

2825 THE EFFECT OF EZH2 INHIBITION ON THE INFLAMMATORY LANDSCAPE OF ANAPLASTIC THYROID CANCER

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Introduction: Anaplastic thyroid cancer (ATC) is a rare but highly lethal malignancy. Beyond its mutational landscape, epigenetic dysregulation and inflammatory signaling are important drivers of anaplastic transformation and tumor microenvironment (TME) remodeling. We previously demonstrated that the EZH2/PRC2 complex acts as an epigenetic repressor promoting thyroid cancer dedifferentiation, and its inhibition restored differentiated features and reduced cell migration, invasion, and tumor growth *in vivo*, alongside decreased recruitment of cancer-associated fibroblasts (CAFs). Despite these findings, the role of EZH2 in regulating inflammatory signatures and TME architecture remains to be explored. **Objective:** To characterize the inflammatory gene signatures and transcriptional profile of EZH2 CRISPR-inhibited SW1736 ATC cells. **Methods:** RNA-seq was performed on EZH2-inhibited SW1736-CIE cells (Illumina NextSeq 2000; paired-end 2 $\times$ 100 bp), yielding ~42 million reads. Differentially expressed genes (DEGs) were analyzed for functional enrichment using Enrichr, with a focus on TME and inflammatory signatures. To assess clinical relevance, GEPIA2 was used to correlate inflammatory gene expression with thyroid cancer patient survival (TCGA database). In addition, macrophage infiltration was assessed via F4/80 immunohistochemistry in xenograft tumors derived from SW1736-CIE and control cells (CEUA protocol 2023150720). **Results:** EZH2 inhibition in SW1736 cells significantly downregulated inflammatory programs, specifically those mediating the production and response of cytokines, interleukins, chemokines, and TNF. Furthermore, gene sets regulating macrophage differentiation were suppressed. In xenograft models, SW1736-CIE tumors exhibited reduced F4/80 staining, which positively correlated with lower CAF infiltration. Comparative analysis confirmed that established ATC-inflammatory markers were consistently suppressed in SW1736-CIE cells. Notably, high expression of *IL13RA2*, *CXCL3*, *CXCL8*, and *PTX3* significantly correlated with reduced survival in thyroid cancer patients within the TCGA database. **Conclusion:** EZH2 promotes pro-inflammatory signaling that drives anaplastic transformation. Its inhibition reverses these aggressive hallmarks, yielding antitumoral effects *in vitro* and *in vivo* by reshaping the TME through reduced CAF and macrophage recruitment. These results suggest EZH2 as a regulator of the inflammatory landscape in advanced thyroid tumors. **Keywords:** EZH2/PRC2; anaplastic thyroid cancer; tumor inflammation.



iodo

2840 MILD IODINE DEFICIENCY DURING PREGNANCY DISRUPTS THE MATERNAL HPT AXIS AND INDUCES SEX-SPECIFIC THYROID ALTERATIONS IN NEONATAL OFFSPRING

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Introduction: Iodine is essential for thyroid hormone synthesis and proper embryonic development. Although the consequences of severe iodine deficiency are well established, the effects of mild iodine deficiency (MID) during pregnancy on the maternal hypothalamus-pituitary-thyroid (HPT) axis function and on offspring thyroid function remain poorly understood. **Objective:** To investigate the effects of MID during pregnancy on molecular parameters of the maternal HPT axis and on neonatal thyroid function. **Methods:** Female mice were subjected to an iodine-deficient diet and received drinking water supplemented with sodium iodide at either normal iodine (NI; 0.2 mg/L) or mild iodine deficiency (MID; 0.08 mg/L) conditions throughout gestation. Mothers and neonates were euthanized on postnatal day 1. Maternal tissues (hypothalamus, pituitary, and thyroid) and neonatal thyroid glands were collected. Gene and protein expression were assessed by qPCR and Western blotting. Serum total T4 levels were measured through ELISA. **Results:** MID increased the expression of thyroid differentiation markers (*Foxe1*, *Pax8*, *Tpo*, *Tshr*, *Nis*), consistent with the increased protein content of NIS and TPO in the maternal thyroid gland. Despite these changes, serum total T4 levels did not differ significantly between MID and NI animals. Likewise, maternal hypothalamic *Trb* and pituitary *Tshb* expression remained unchanged between groups. In contrast, *Gh* and prolactin expression were reduced in the pituitary of MID dams compared with NI. Importantly, MID exposure reduced litter size compared with the NI group. Furthermore, neonatal body weight was significantly lower in the MID group, particularly among males. Notably, exposure to the MID diet elicited sexually dimorphic changes in thyroid gene expression in neonates. In female neonates, the thyroid showed increased *Tpo* expression and a trend toward increased *Nis* expression. In contrast, male neonates exhibited a more pronounced response, with significantly increased thyroid expression of *Tg*, *Tshr*, *Nis*, and *Tpo*. **Conclusion:** MID during pregnancy triggers compensatory activation of the maternal thyroid while maintaining circulating T4 levels. However, it is associated with reduced litter size, lower neonatal body weight, and early sexually dimorphic alterations in neonatal thyroid gene expression. These findings highlight that even MID during gestation can affect maternal thyroid regulation and early thyroid programming in the offspring. **Keywords:** mild iodine deficiency; thyroid function; pregnancy.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2848 PUTATIVE ATTENUATION OF HEPATIC STEATOSIS IN EXPERIMENTAL TYPE 1 DIABETES MELLITUS BY T3 MODULATION OF MIR-207, MIR-375-3P AND THEIR TARGETS

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Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by chronic hyperglycemia. Studies from our laboratory have demonstrated that alloxan-induced T1DM leads to hypothyroidism in rats and both may contribute to the development and progression of hepatic steatosis. It is well established that triiodothyronine (T3) increases mitochondrial fatty acid β -oxidation and reduces hepatic steatosis, by genomic mechanism through THR β . T3 has also been shown to modulate the expression of microRNAs (miRNA) and their messenger RNA (mRNA) targets in many cells and organs. The aim of this study was to evaluate whether T3 modulates hepatic steatosis in T1DM rats through post-transcriptional mechanisms involving microRNAs and their target mRNAs. To address this, liver samples were collected from three groups of rats: control, alloxan-induced T1DM, and T1DM treated with T3 (0.15 μ g/kg BW) for 28 days. Total miRNAs were extracted using a column-based method and analyzed using a miRNA PCR array panel containing 84 miRNAs implicated in DM to identify differentially expressed candidates. This screening revealed that miR-107-3p, miR-207, and miR-375-3p, previously associated with hepatic steatosis, were upregulated in diabetic animals and reduced after T3 treatment. These miRNAs were subsequently validated by qPCR using new liver samples from the same experimental groups. Subsequently, three mRNAs were selected to investigate potential post-transcriptional interactions with these miRNAs by qPCR: carnitine palmitoyltransferase 1A – CPT1A, which facilitates fatty acid oxidation decreasing steatosis, hepatocyte nuclear factor 4 α – HNF4 α , whose activation reduces hepatic steatosis, and AKT2, whose deletion induces hepatic steatosis. The gene expression analysis showed an increased HNF4 α and AKT2 mRNA expression in T3-treated animals compared to untreated diabetic control, and no alteration in CPT1A mRNA content. These results indicate that T3 treatment may exert an inhibitory regulatory effect on miR-207 and miR-375-3p expression. Given that both act by repressing the expression of their target genes, we conclude that T3 may contribute to the upregulation of their corresponding mRNAs, namely HNF4 α and AKT2, which are known to decrease hepatic steatosis. Together, these findings suggest a potential post-transcriptional regulatory mechanism underlying T3 action, attenuating hepatic steatosis in parallel to its known positive genomic action on this hepatic disease. **Keywords:** hepatic steatosis; triiodothyronine; microRNA



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METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2739 HYPOTHYROIDISM ALTERS NEUROMUSCULAR JUNCTION REMODELING AND SKELETAL MUSCLE FUNCTION IN YOUNG MICE

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Introduction: Thyroid hormones regulate muscle homeostasis, myogenesis, and neuromuscular junction (NMJ) organization. Aging is associated with an increased prevalence of hypothyroidism, affecting up to 15% of individuals over 65 years, and with a higher incidence of age-related myopathies. However, the interaction between these conditions remains poorly understood. **Objective:** Investigate the impact of hypothyroidism on sarcopenia development. **Methods:** Male C57BL/6 mice were assigned to control (C) and hypothyroid (H) groups, including young (2 months) and aged (18 months) animals. Hypothyroidism was induced by a standard diet supplemented with 0.15% propylthiouracil for four months. Following euthanasia, the tibialis anterior muscle and plasma was collected. Data were expressed as mean $\pm$ standard deviation and analyzed by Two-way ANOVA (CEUA — UFRJ a16/2302520). Results: Plasma hormone levels confirmed successful hypothyroidism induction: a 50% reduction in T4 in the young group only, and a 40-fold increase in TSH in both age groups. At months 2 and 3 of treatment, hypothyroidism reduced forelimb grip strength (C: 122 ± 4 gf, H: 104 ± 4 gf, $p = 0.009$; $n = 8-12$) and locomotor activity (C: 1176 ± 367 cm, H: 895 ± 360 cm, $p = 0.01$; $n = 25-27$) exclusively in young mice and also decreased tibialis anterior mass in this group (C: 2.8 ± 0.3 mg/mm, H: 2.4 ± 0.2 mg/mm, $p = 0.006$; $n = 12-14$). AChR mRNA, the NMJ postsynaptic receptor, was increased in young (C: 1.0 ± 0.3 , H: 3.29 ± 1.4 , $p = 0.0003$; $n = 9-10$) and aged mice (C: 1.5 ± 0.5 , H: 3.8 ± 1.3 , $p = 0.001$; $n = 6-10$), whereas MuSK, which regulates AChR clustering and stabilization, was reduced in young (C: 1.0 ± 0.2 , H: 0.6 ± 0.08 , $p = 0.0007$; $n = 9$) and aged animals (C: 1.3 ± 0.2 , H: 0.9 ± 0.2 , $p = 0.01$; $n = 6-10$). In addition, BDNF, involved in NMJ maintenance, was reduced only in young mice (C: 1.0 ± 0.38 , H: 0.21 ± 0.02 , $p = 0.0007$; $n = 10$), while AChE, responsible for acetylcholine degradation, was unchanged at both ages. Together, these findings indicate impaired postsynaptic organization and ineffective compensatory NJM remodeling, consistent with a destabilization phenotype without changes in acetylcholine degradation. **Conclusion:** Our results demonstrate that hypothyroidism induces transient muscle strength deficits and sustained muscle mass and locomotor activity impairments, restricted to young mice, suggesting a sarcopenia-like phenotype. In addition, hypothyroidism impairs motor endplate remodeling in the tibialis anterior muscle. **Keywords:** hypothyroidism; sarcopenia; aging.

NÓDULOS E CÂNCER DE TIREOIDE

2755 JAK/STAT3 PATHWAY CONTRIBUTES TO THE MAINTENANCE OF CANCER STEM-LIKE CELLS FEATURES IN ANAPLASTIC THYROID CARCINOMA

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Introduction: Anaplastic thyroid carcinoma (ATC) is the most aggressive thyroid cancer (TC), with patient's survival of 6–25 months due to rapidly progression, resistance acquisition, and limited therapeutic options. Cancer stem-like cells (CSCs) have been related to self-renewal and transformation, enriched in ATC compared to other TC subtypes. Activation of JAK/STAT3 pathway has been correlated with ATC poor survival, as well as with the presence of CSCs. Nifuroxazide (NFZ) has been shown to inhibit JAK/STAT pathway in some metastatic cancer models, however its role remains unexplored in ATC. **Objective:** To functionally characterize CSCs properties in ATC and to evaluate the NFZ activity as JAK/STAT3 pathway inhibitor on stemness. **Methods:** ATC cell lines KTC-2, HTH83 and 8305c and non-tumoral cell line Nthy-ori 3-1 were used. KTC-2 and HTH83 *STAT3* knockout (KO) were also applied. Cell proliferation, cell cycle, cell viability, and colony formation were assessed. ALDH activity and fluorescence-activated cell sorting were performed by flow cytometry using ALDEFLUOR reagent. The expression of nine CSCs markers was analyzed by real-time PCR and sphere formation assay were conducted. Autophagy analysis was evaluated by western blot. **Results:** Higher ALDH activity was observed in all ATC cells compared to Nthy-ori 3-1, along with increased expression of several CSCs biomarkers and enhanced sphere formation capacity. Following cell sorting, HTH83 ALDH⁺ cells showed increased expression of most CSCs biomarkers, including a twofold increase in *ALDH1A3* expression. Functionally, ALDH1 inhibition with DEAB reduced proliferation, cell cycle progression, viability, and clonogenicity in KTC-2, with no effects in HTH83. In HTH83, *STAT3* KO decreased sphere formation and CSCs biomarkers expressions. In all ATC cell lines, NFZ reduced ALDH activity, sphere formation and CSCs biomarkers expression, although with lineage-specific patterns. NFZ decreased ALDH activity in KTC-2 and HTH83 *STAT3* KO cell lines. Additionally, NFZ also induced autophagy in KTC-2, even in the presence of autophagic flux inhibitor. **Conclusion:** These results indicate that ATC cell lines display CSCs properties that can be attenuated by NFZ. The JAK/STAT3 pathway contributes to the maintenance of cancer stem-like cell features, particularly in HTH83 cell line. Targeting CSCs markers and ALDH activity, in combination with JAK/STAT3 inhibition, may represent a promising therapeutic strategy for ATC. **Keywords:** anaplastic thyroid carcinoma; cancer stem-like cells; JAK/STAT3 pathway.



NÓDULOS E CÂNCER DE TIREOIDE

2760 THE JAK/STAT3 SIGNALING PATHWAY: NEW INSIGHTS INTO SIGNAL PATHWAYS CROSSTALK IN ANAPLASTIC THYROID CANCER

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Introduction: Signaling pathways are closely associated with cancer development and progression. In anaplastic thyroid carcinoma (ATC), the most aggressive form of thyroid cancer, the main treatment strategies involve inhibition of the MAPK and PI3K pathways. However, therapeutic resistance frequently emerges. The JAK/STAT3 pathway, also associated with proliferation and survival, has emerged as an escape mechanism driving therapeutic resistance, and crosstalk among these pathways has been reported. **Objective:** To investigate the effect of STAT3 knockout (STAT3-KO) on tumor characteristics of anaplastic thyroid carcinoma cells and its influence on the MAPK and PI3K signaling pathways. **Methods:** ATC cells (HTH83 and KTC-2), three STAT3-KO clones, and CRISPR control cells were used. Cell viability, colony formation, and proliferation assays were performed to evaluate the effect of STAT3 knockout. Modulation of the JAK/STAT3, MAPK, and PI3K signaling pathways was assessed by Western blotting. Epithelial-mesenchymal transition (EMT) gene expression was analyzed by real-time PCR. **Results:** STAT3 deletion increased ERK and AKT phosphorylation in KTC-2 and HTH83 cell lines and increased cell viability only in the KTC-2 cell line. However, it decreased cell proliferation in all knockout cell lines when compared to their respective control and non-deleted cell lines. Furthermore, STAT3-KO differentially modulated EMT-associated gene expression, decreasing vimentin mRNA levels in HTH83 cells while increasing them in KTC-2 cells. Finally, colony formation capacity was not altered in STAT3 knockout cell lines. **Conclusion:** The increased ERK and AKT phosphorylation observed following STAT3 deletion indicates compensatory pathway activation, reinforcing the concept that JAK/STAT3 signaling functions as an adaptive escape mechanism in the context of MAPK and PI3K signaling inhibition. Notably, despite enhanced ERK and AKT activation, STAT3 deletion reduced cell proliferation, suggesting that MAPK and PI3K signaling alone is insufficient to sustain the full proliferative phenotype of ATC cells and highlighting a role of STAT3 in tumor cell growth. Although STAT3 activation following MAPK and PI3K inhibition previously supported the existence of functional crosstalk, this is the first study to demonstrate that selective STAT3 inhibition in ATC cells reciprocally enhances MAPK and PI3K activation, revealing a bidirectional regulatory interplay within this signaling network. **Keywords:** JAK/STAT3; crosstalk pathways; anaplastic thyroid cancer.

NÓDULOS E CÂNCER DE TIREOIDE

2776 DIAGNOSTIC PERFORMANCE OF A MICRORNA AND DNA-BASED MOLECULAR CLASSIFIER (MIR-THYPE FULL) IN PEDIATRIC INDETERMINATE CYTOLOGY THYROID NODULES

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Introduction: Thyroid nodules are common in adults (~25%) but relatively rare in the pediatric population (~1.5% in individuals < 18 years). Despite their lower prevalence, pediatric thyroid nodules carry a significantly higher risk of malignancy (RoM), particularly in indeterminate cytology categories. For Bethesda III nodules, the RoM ranges from 50%–75% in children *versus* 10%–30% in adults, and for Bethesda IV nodules, from 75%–93% *versus* 25%–40%, respectively. Although molecular testing may be recommended and may be beneficial in these cases, currently available molecular tests in Latin America have not been validated for pediatric use. **Objective:** To evaluate the diagnostic performance of the microRNA and DNA-based molecular test mir-THYPE full in pediatric thyroid nodules with indeterminate cytology. **Methods:** The study was multicentric and included FNA smear slides from 23 pediatric thyroid nodules (14 Bethesda III and 9 Bethesda IV) previously submitted to the mir-THYPE full molecular test. The assay combines microRNA expression profiling, detection of point mutations (BRAF V600E and TERT promoter C228T/C250T), and gene fusions (PAX8/PPARγ, RET/PTC1 and RET/PTC3) using the qPCR technique. Histopathological diagnosis was used as the reference standard to assess diagnostic performance. **Results:** Among the 23 pediatric nodules analyzed, 19 were correctly classified by the molecular test (82.6% overall accuracy). The assay demonstrated 100% sensitivity and 69.2% specificity. Fourteen samples were classified as positive for malignancy, of which 10 were histologically confirmed as malignant (71.4% positive predictive value). All malignant cases corresponded to papillary thyroid carcinomas/microcarcinomas, including one BRAF V600E positive sample. Nine samples were classified as negative for malignancy, all of which were confirmed as benign (100% negative predictive value). No gene fusions were detected. The disease prevalence was 43.5%, consistent with the 39% reported in the literature for similar pediatric cohorts. **Conclusion:** This multicentric study showed preliminary findings to support the feasibility and promising diagnostic performance of the mir-THYPE full molecular test in pediatric thyroid nodules with indeterminate cytology. Future validation in a larger cohort aims to further refine performance metrics and to strengthen the evidence for its use in risk stratification, supporting more individualized surgical decision-making in these patients. **Keywords:** pediatric thyroid nodule; molecular testing; microRNA.

NÓDULOS E CÂNCER DE TIREOIDE

2777 PROGNOSTIC VALUE OF BRAF V600E ALLELE FREQUENCY IN AGGRESSIVE CLINICOPATHOLOGICAL FEATURES OF PAPILLARY THYROID CARCINOMA

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Introduction: Papillary thyroid carcinoma (PTC) generally presents with an indolent course and favorable prognosis. Nevertheless, a subset of tumors displays aggressive clinicopathological characteristics associated with worse outcomes. The allele frequency (AF) of the BRAF V600E mutation has recently been investigated as a quantitative marker potentially associated with aggressive features, including intermediate/high American Thyroid Association recurrence risk (ATA RR), lymph node metastasis (LNM), extrathyroidal invasion (EI) and angiolymphatic invasion (AI). **Objective:** To investigate the prognostic relevance of BRAF V600E mutation allele frequency in relation to aggressive clinicopathological features in PTC. **Methods:** A total of 116 PTC samples previously evaluated by detailed histopathological examination for ATA RR, LNM, EI, and AI were utilized in this study. BRAF V600E mutation status and AF were determined using qPCR. Receiver operating characteristic (ROC) curve analysis was performed to establish an optimal AF cut-off value to stratify cases into three categories: BRAF-negative, BRAF-positive with AF below the cut-off, and BRAF-positive with AF above the cut-off. **Results:** From the 116 PTC cases, 46 (46/116 — 39.6%) were positive for the BRAF V600E mutation. Both the presence of the BRAF V600E mutation and increasing AF were significantly associated with intermediate/high ATA RR ($p < 0.001$), LNM ($p < 0.001$), and EI ($p = 0.030$). ROC analysis identified 16.90% as the optimal AF cut-off. For ATA RR, risk increased across the three categories: 10.0%, 38.5% and 63.6%, respectively. Similarly, LNM rates rose: 13.0%, 27.3% and 61.9%. For EI, the frequency increased from 3.6% in BRAF-negative or AF below the cut-off to 18.2% in cases with AF above the cut-off. **Conclusion:** Quantification of BRAF V600E mutation AF can provide relevant prognostic information regarding ATA RR, LNM, and EI in PTC. Incorporating AF into initial evaluation may enhance risk stratification and support more individualized clinical management of the patients. **Keywords:** papillary thyroid cancer; BRAF; allele frequency.

DISFUNÇÕES TIREOIDIANAS

2795 EFFECTS OF LEVOTHYROXINE TREATMENT ON BODY COMPOSITION VARIABLES IN CLINICAL AND SUBCLINICAL HYPOTHYROIDISM: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Hypothyroidism reduces metabolic rate and alters body composition leading to an increase in body weight (BW) and body mass index (BMI). The current treatment with Levothyroxine (LT4) restores the hormonal levels; however, its efficacy in reversing these specific anthropometric alterations remains debated. Herein, we have evaluated the effects of LT4 on body composition in adults with clinical (CH) and subclinical (SCH) hypothyroidism through a systematic review and meta-analysis. The review protocol was registered on PROSPERO (CRD42024589156) and followed PRISMA guidelines. Studies involving CH or SCH adults treated with LT4 monotherapy until achieving normal hormonal levels were searched in PubMed, Embase, Scopus, Web of Science, and Cochrane databases. Eligible studies reported pre- and post-treatment data on BMI, BW, fat mass (FM), and lean mass (LM). Each variable was analyzed according to treatment duration, sex distribution, and pre- and post-treatment TSH levels. Thirty-five studies were included (22 CH; 15 SCH), comprising 1,116 individuals with hypothyroidism (672 CH; 444 SCH). In CH, LT4 reduced BMI in the overall analysis (Standardized mean difference [SMD] -0.18; 95% confidence interval [CI] -0.29, -0.8; mean difference [MD] -0.68 kg/m²). When stratified by treatment duration, moderate BMI reductions were observed after 12 months of L-T4 treatment (SMD -0.57; CI -0.99, -0.16; MD -2.30 kg/m²). LT4 reduced BW in CH (SMD -0.25; CI -0.38, -0.21; MD -2.14 kg), primarily driven by short-term treatment (<3 months; SMD -0.39; CI -0.60, -0.19; MD -4.39 kg); it did not change FM (SMD 0.03; CI -0.13, 0.20), and led to a small reduction in LM (SMD -0.25; CI -0.47, -0.02), an effect influenced by the TSH levels pre- and post-treatment [greater reductions in LM were observed when pre-treatment TSH was >50 mIU/L (SMD -0.39; CI -0.70, -0.09) and when post-treatment TSH ranged 2.1–5.0 mIU/L (SMD -0.38; CI -0.67, -0.09)]. In contrast, LT4 showed no significant effects on BMI, BW, FM, or LM of SCH, regardless of overall or subgroup analysis. Besides the reestablishment of hormonal thyroid axis, LT4 monotherapy triggers small reductions in BMI and BW, accompanied by a decrease in LM rather than FM in CH, while it appears insufficient to improve body composition in SCH. Thus, our data suggest that novel therapeutic approaches for CH and SCH treatment are needed, focusing on the metabolic and peripheral aspects of such thyroid disorders. **Keywords:** body weight; hypothyroidism; adiposity.



NÓDULOS E CÂNCER DE TIREOIDE

2805 LOW-RISK THYROID CANCER UNDER ATA 2025: DE-ESCALATION AND SAFE FOLLOW-UP DISCONTINUATION IN A PUBLIC HEALTHCARE CENTER IN NORTHEASTERN BRAZIL

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Introduction: Differentiated thyroid carcinoma (DTC) is typically an indolent malignancy with excellent prognosis. However, prolonged surveillance and historically aggressive management strategies have increased healthcare burden, particularly in settings with limited access to specialized care. The 2025 American Thyroid Association (ATA) guidelines promotes treatment de-escalation and supports safe discontinuation of long-term follow-up in low-risk patients with sustained excellent response. **Objective:** To evaluate response to therapy, and long-term outcomes of patients classified as low risk of recurrence according to the ATA 2025 guidelines. **Methods:** We conducted a retrospective cohort study of 225 patients with DTC followed at a tertiary referral center. Patients were reclassified according to the ATA 2025 risk stratification system, and those categorized as low risk were evaluated for clinicopathological characteristics, response to therapy, and long-term outcomes based on the ATA 2025 response-to-therapy classification. **Results:** Of 225 patients, 82 (36.4%) were classified as low risk of recurrence. The mean age was 46.9 ± 17.6 years; 84% were female, and 90.2% self-identified as Black or mixed-race. Most tumors (85.4%) were papillary thyroid carcinoma, including 41.4% microcarcinomas. Total thyroidectomy was performed in 88% of patients, and 57.3% received radioiodine as initial therapy. After a mean follow-up of 9.1 ± 5.6 years, 93.9% achieved a favorable response (excellent or indeterminate). During this period, 8.5% developed lymph node metastases and 2.4% developed distant metastases. No patient required a second radioiodine treatment, and only 6% underwent additional surgery, at a mean of 3.5 ± 2.9 years after initial treatment. Among those observed for more than 10 years, 89.6% achieved an excellent response and were eligible for discharge from specialized care. **Conclusion:** Patients classified as low risk of recurrence demonstrate excellent long-term outcomes, with a very low rate of unfavorable response and minimal need for additional intervention. These findings support the safety of follow-up discontinuation after sustained excellent response and suggest that many patients may have been overtreated under previous paradigms. In a public healthcare center from Northeastern Brazil, structured de-escalation may improve equitable access to specialized care without compromising oncologic safety. **Keywords:** thyroid neoplasm; risk assessment; treatment outcome.

DISFUNÇÕES TIREOIDIANAS

2845 PCBs DIFFERENTIALLY MODULATE MOLECULAR AND FUNCTIONAL PATHWAYS IN NORMAL AND TUMORAL HUMAN THYROCYTES

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Introduction: Our previous data indicated that polychlorinated biphenyls (PCBs) alter differentiation markers in rat thyrocytes through epigenetic mechanisms and dysregulation of signaling pathways. **Objective:** To evaluate the impact of PCB exposure on molecular and functional parameters of normal and tumoral human thyrocytes. **Methods:** Normal thyrocytes (Nthy-ori 3-1) and tumoral thyrocytes (TPC1 and BCPAP) were treated or not for 24 h with a PCB mixture (Aroclor 1254: 10^{-7} to 10^{-11} M). Gene expression and signaling pathway activation were evaluated by qPCR and Western blotting, respectively. NIS function was assessed by a non-radioactive iodide uptake assay. Cell viability was evaluated by the MTT assay, oxidative stress by fluorescence assays, and cell migration by wound-healing assays. **Results:** PCB exposure increased the migratory activity of BCPAP cells, which showed increased gene expression of VIM, SNAIL, and ZEB1, along with reduced E-CAD expression. In contrast, Nthy-ori cells showed reduced migration, increased expression of E-CAD, TWIST, and ZEB1, and decreased VIM expression. In TPC1 cells, PCBs did not alter migration but increased the expression of E-CAD, TWIST, and ZEB1. Additionally, in Nthy-ori and TPC1 cells, PCBs exposure reduced gene expression of DNMTs, HDACs, EP300, and KDM5c, and increased HAT1, which is consistent with enhanced transcriptional activity in thyrocytes, whereas the opposite pattern was observed in BCPAP cells. Regarding cell proliferation, PCB exposure reduced cell viability in Nthy-ori cells, but increased it in TPC1 cells, while no changes in this parameter were observed in BCPAP cells. Concerning the expression of the pro-apoptotic and necroptotic markers BAX and RIPK1, respectively, their expression was reduced in Nthy-ori and TPC1 cells and increased in BCPAP cells. Interestingly, PCB treatment reduced ERK phosphorylation in TPC1 and BCPAP cells, increased AKT phosphorylation in Nthy-ori cells, and increased CREB phosphorylation in BCPAP cells. Finally, PCB exposure increased iodide uptake and reduced ROS production in all three cell lines. **Conclusion:** PCB exposure induces distinct and cell-type-dependent effects in normal and tumoral human thyrocytes. These findings indicate that PCBs may differentially influence tumor-related phenotypes according to the molecular background of thyroid cells, highlighting their potential role in thyroid dysfunction and tumor progression. **Keywords:** PCBs; thyroid cancer; endocrine disruptors.



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HOT TOPICS



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NÓDULOS E CÂNCER DE TIREOIDE

2804 CAN WE SAFELY AVOID RADIODINE THERAPY IN PAPILLARY THYROID CARCINOMA WITH LYMPH NODE METASTASIS AFTER THERAPEUTIC NECK DISSECTION?

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Introduction: Patients with papillary thyroid carcinoma (PTC) undergoing total thyroidectomy (TT) who present lymph node metastasis can have a higher risk of structural disease recurrence. The therapeutic neck dissection provides a recurrence-free advantage. The usefulness of pre-therapy stimulated thyroglobulin (sTg) and diagnostic whole-body scan (WBS) as prognostic predictors at initial treatment is not fully established. **Objective:** To assess the prognostic value of pre-therapy sTg and diagnostic WBS in predicting recurrence and treatment response in PTC patients with lymph node metastasis after total thyroidectomy and therapeutic neck dissection. **Methods:** This retrospective study included 221 PTC patients with PTC who underwent TT, central and/or therapeutic neck dissection (CND/LND), and RAI treatment between October 2003 and August 2024. All of them did diagnostic WBS before RAI therapy (DxWBS). The primary outcome (structural recurrence and treatment response) was evaluated in patients grouped by negative uptake DxWBS, sTg < 1 ng/mL, and negative anti-Tg (DxWBS/sTg-), or uptake outside the thyroid bed DxWBS and/or sTg ≥ 1 ng/mL, and/or positive anti-Tg (DxWBS/sTg+). Nineteen patients who had distant metastases at initial treatment were excluded from the analysis. **Results:** Of the 202 patients, 71 (35.2%) were submitted to CND and 131 (64.8%) to LND. Recurrence or persistence occurred in 16.9% of CND and 25.2% of LND. 43 patients presented with DxWBS/sTg- (23% CND, 19.8% LND), only 1 patient had uptake outside the thyroid bed after RAI treatment, which was a false positive result (ovarian cyst uptake). While 27/159 (17%, p = 0.011) patients who presented DxWBS/sTg+ had uptake outside the thyroid bed after RAI treatment. One year after RAI treatment, biochemical or structural incomplete response to therapy was significantly higher in the DxWBS/sTg+ group (29.9%) than 1/42 (2.4%, p < 0.001) DxWBS/sTg- group. Patients with DxWBS/sTg+ were more likely to present persistent or recurrent structural disease compared to the DxWBS/sTg-, 26.4% vs. 7%, respectively. **Conclusion:** Patients undergoing TT with therapeutic neck dissection who present with DxWBS without uptake outside the thyroid bed and sTg < 1 ng/mL have a low risk of recurrence. The absence of iodine-avid metastatic lesions in the WBS after RAI therapy in this group of patients suggests that we can spare them from RAI therapy after the initial surgical approach. **Keywords:** papillary thyroid carcinoma; lymph node metastasis; prognosis.



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**APRESENTAÇÕES –
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HIPERTIREOIDISMO EM FOCO: NOVOS OLHARES SOBRE A DOENÇA DE GRAVES

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2814 DETERMINANTS OF QUALITY OF LIFE IN EUTHYROID GRAVES' DISEASE: THE ROLE OF THE TT3/TT4 RATIO, AGE, AND GENDER

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Introduction: Graves' disease (GD) is the leading cause of hyperthyroidism worldwide. Restoring and maintaining euthyroidism is essential for improving quality of life (QoL). However, data regarding the impact of circulating T3 and T4 levels. **Objective:** To investigate the association between the TT3/TT4 ratio and QoL in euthyroid patients with GD, and to examine the independent contribution of demographic factors, particularly age and gender, to QoL impairment. **Materials and methods:** This study included patients with GD who were in a sustained euthyroid state and were either receiving antithyroid drugs (ATD), had been treated with radioactive iodine followed by levothyroxine replacement, or were in disease remission. QoL outcomes were assessed using the ThyPRO-39 questionnaire. **Results:** The study included 185 patients with a mean age of 54 ± 14 years; 88% were female; 15% of patients had a history of tobacco use (current or prior). Regarding treatment status, 54% were receiving ATD, 26.5% had undergone RAI followed by levothyroxine replacement, and 19.5% were in remission. Thyroid eye disease (TED) was absent in 82% of patients, 17% had mild TED and 1% had moderate-to-severe TED. Regarding thyroid biomarkers, mean TSH was 2.43 ± 2.58 mIU/L, mean FT4 was 1.25 ± 0.32 ng/dL, mean TT4 was 10.37 ± 6.27 µg/dL, mean FT3 was 3.25 ± 0.76 pg/mL, and mean TT3 was 1.17 ± 0.49 ng/dL. The mean TT3/TT4 ratio was 0.12 ± 0.05 , and the mean FT3/FT4 ratio was 2.70 ± 0.84 . Evaluation of the impact of the TT3/TT4 ratio on QoL demonstrated that a higher ratio was associated with worse overall QoL, increased depressive symptoms, and greater impairment in daily life ($p < 0.005$). Age also played a significant role in QoL impairment, with older age associated with greater impact on appearance, social life, emotional susceptibility, and overall QoL ($p < 0.005$). Gender significantly influenced QoL outcomes. Female patients presented worse scores compared to male patients in multiple domains, including hypothyroid symptoms, goiter symptoms, hyperthyroid symptoms, eye symptoms, tiredness, cognitive complaints, emotional susceptibility, social life impact, appearance, and overall QoL impact ($p < 0.005$). **Conclusion:** Our findings suggest that the TT3/TT4 ratio, age, and gender play significant roles in QoL impairment among euthyroid patients with GD. While certain QoL domains appear more strongly influenced by epidemiological factors such as age and gender, others are more closely associated with the balance between TT3 and TT4. **Keywords:** Grave's disease; quality of life; hormone levels.

CÂNCER DE TIREOIDE — DA BANCADA AOS NOVOS TRATAMENTOS

BIOLOGIA CELULAR DA TIREOIDE

2817 METFORMIN AS AN ANTITUMOR AGENT IN ANAPLASTIC THYROID CARCINOMA: EFFECTS IN 2D AND 3D MODELS AND ELUCIDATION OF THE MECHANISM OF ACTION

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Introduction: Anaplastic thyroid carcinoma (ATC) is a rare but extremely aggressive cancer with a median survival of 6 to 25 months. Despite advances in new therapies, tumors often remain refractory to radioiodine or develop resistance, and patients show significant side effects. Metformin, a first-line drug for type 2 diabetes, has shown antitumor properties, primarily mediated by AMPK activation and mTOR inhibition. Recent studies suggest that metformin may also modulate the JAK/STAT3 pathway, implicated in tumor progression and drug resistance; however, its role in ATC remains largely unexplored. Three-dimensional (3D) models have emerged as valuable tools for preclinical drug evaluation due to their ability to recapitulate the tumor microenvironment. **Objective:** To evaluate the antitumor effect of metformin in two-dimensional (2D) and 3D models of ATC and to investigate its mechanism of action involving the JAK/STAT3, MAPK, and PI3K/AKT pathways. **Methods:** ATC cell lines (KTC2 and HTH83), their respective STAT3-knockout clones generated by CRISPR-Cas9 (KS3-D2, HS3-A6, HS3-B5), and non-tumor thyroid cells (Nthy-Ori3.1) were employed. Cell viability was assessed using PrestoBlue in 2D and 3D cultures. 3D spheroids were generated by hanging drop and analyzed visually and by ImageJ. Activation of STAT3, AKT, and ERK was evaluated by Western blot. Epithelial-mesenchymal transition (EMT) gene expression was assessed by RT-qPCR, and clonogenic survival was evaluated. Patient-derived primary cultures were also tested. **Results:** Metformin significantly reduced viability in all 2D cultures, with tumor cells showing greater sensitivity than non-tumor cells. In all 3D models, metformin reduced viability, albeit at higher concentrations, with reduced spheroid size and increased cell dissemination. Metformin decreased p-STAT3, total STAT3, p-ERK, total ERK, and p-AKT expression and modulated EMT genes. In HTH83 STAT3-knockout cells, metformin reduced viability, but not in KTC2-derived clones, suggesting context-dependent mechanisms. Colony formation assays confirmed these findings. Metformin also reduced cell viability of patient-derived primary culture. **Conclusion:** These results confirm the cytotoxic activity of metformin in 2D and 3D ATC models and patient-derived cultures, reinforcing its potential as a safe, affordable repurposed drug, and with a mechanism of action involving, at least in part, the modulation of the JAK/STAT MAPK and PI3k/AKT pathways. **Keywords:** anaplastic thyroid carcinoma (ATC); pathway JAK/STAT3; metformin.



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BIOLOGIA CELULAR DA TIREOIDE

2736 BISPHENOL A TRIGGERS CELL-TYPE-SPECIFIC DYSREGULATION OF METABOLIC AND STRESS-RESPONSE PATHWAYS IN THYROID MODELS

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Introduction: Bisphenol A (BPA) is a widespread environmental contaminant that disrupts endocrine function, including thyroid signaling. However, its effects on thyroid cell biology at the transcriptomic level remain unclear. This study aimed to analyze the specific transcriptional responses induced by BPA exposure in thyroid cell lines with distinct phenotypes. **Objective:** The primary objective of this study was to characterize and compare the transcriptomic profiles of a non-tumoral control thyroid cell line (Nthy-ori 3-1) and two papillary thyroid carcinoma cell lines (TPC-1 and BCPAP) following exposure to BPA. Aimed to identify differentially expressed genes (DEGs), common and unique response pathways, and assess the effects of exposure time and dosage. **Methods:** Total RNA was extracted from cell lines exposed to BPA at concentrations of 0.8 and 1.0 µg/mL for 24 and 48 h. Transcriptomic analysis was performed using RNA-seq to identify DEGs. **Results:** Transcriptomic analysis revealed highly cell line-specific responses. BCPAP cells were the most sensitive, with 6,048 DEGs, followed by TPC-1 (2,701) and Nthy-ori 3-1 (2,393). The strongest effect occurred at 24 h with 1.0 µg/mL BPA, followed by a marked attenuation at 48 h, suggesting adaptive tolerance. Filtering for robust, protein-coding DEGs refined the lists to 974 (BCPAP), 25 (TPC-1), and 3 (Nthy-ori). Only one gene, *MT-ATP8* (mitochondrial ATP synthase), was common to all three cell lines, showing opposing regulatory patterns. Pathway enrichment revealed distinct biological impacts: downregulated protein synthesis in Nthy-ori 3-1; modulation of growth-related signaling pathways and later ribosomal biogenesis in TPC-1 cells, and profound disruption of amino acid metabolism, translational machinery, and mitochondrial energy/antioxidant pathways in BCPAP cells. **Conclusion:** BPA exposure triggers complex, time- and dose-dependent transcriptomic alterations that are fundamentally distinct between normal and neoplastic thyroid cells. The BCPAP cell line exhibited exceptional sensitivity, with a broad disruption of core metabolic and stress response pathways. The observed attenuation of responses over time suggests dynamic cellular adaptation, underscoring the cell-context-dependent toxicity of BPA and its potential to interfere with critical metabolic and signaling networks in thyroid cells. **Keywords:** bisphenol A; transcriptomic analysis; thyroid carcinogenesis.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2737 ATORVASTATIN AND RIFAXIMIN PREVENT ALTERATIONS IN HEPATIC THYROID HORMONE METABOLISM IN HEPATOCELLULAR CARCINOMA

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Introduction: Metabolic-associated steatotic liver disease (MASLD) is one of the leading causes of hepatocellular carcinoma (HCC) worldwide. **Objective:** This study aimed to evaluate alterations in thyroid hormone metabolism and tumor progression in an *in vivo* HCC model. **Materials and methods:** Sprague-Dawley rats received diethylnitrosamine (135 mg/L) in drinking water for 16 weeks combined with a high-fat diet to induce HCC. Animals were treated with atorvastatin (AT, 5 mg/kg) or rifaximin (RIFA, 5 mL/kg). Tumoral and adjacent non-tumoral liver tissues were analyzed for markers of fibrosis, hypoxia, tumor progression, and thyroid hormone metabolism. **Results:** Animals with HCC showed an 88% increase in TGFB1 expression in tumoral areas compared with adjacent normal tissue. Treatment with AT or RIFA reduced TGFB1 expression by 10% and 30%, respectively. Fibrotic area was reduced by 30% in RIFA-treated animals compared with the HCC group, whereas AT did not induce a significant reduction. Hypoxia-inducible factor 1 (HIF1) expression increased by 200% in tumor areas; AT and RIFA reduced HIF1 expression by 75% and 50%, respectively. Deiodinase type 3 (DIO3) expression increased by 50% in tumoral tissue, while deiodinase type 1 (DIO1) expression remained unchanged. **Conclusion:** Tumor progression and dedifferentiation were attenuated by AT or RIFA treatment in this *in vivo* HCC model. Thyroid hormone metabolism was altered through increased DIO3 expression, suggesting local inactivation of thyroid hormones within tumoral tissue. These findings indicate that modulation of thyroid hormone metabolism may be associated with tumor aggressiveness and disease progression in MASLD-related HCC. **Keywords:** deiodinase; thyroid hormones; hepatocellular carcinoma.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2738 EARLY CARDIAC ALTERATIONS ASSOCIATED WITH THYROID HORMONE METABOLISM IN A MODEL OF METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Introduction: Metabolic associated steatotic liver disease (MASLD) is linked to several disturbances, including thyroid hormone signaling. However, its impact on cardiac thyroid hormone metabolism and functional remodeling remains poorly characterized.

Objective: Investigate cardiac thyroid hormone metabolism in MASLD, with a focus on the cellular distribution of type 3 deiodinase (DIO3) and its association with early cardiac alterations. **Methods:** Adult male Sprague-Dawley rats (n = 20) were assigned to a control group fed a standard diet or to a MASLD group fed a choline-deficient, high-fat diet for 16 weeks. Cardiac structure and function were evaluated by echocardiography. DIO3 mRNA expression was analyzed by RNAscope and quantitative PCR. Macrophage infiltration was assessed by immunofluorescence using the F4/80 marker, and myocardial T3 levels were measured in cardiac tissue. **Results:** Animals with MASLD exhibited impaired cardiac function, characterized by reduced ejection fraction (p = 0.0034) and increased fractional shortening (p = 0.0049), suggesting early compensatory remodeling. Fibrotic areas were detected in 44% of MASLD hearts, accompanied by heterogeneous macrophage infiltration. DIO3 mRNA showed limited colocalization with macrophages (2%–10%), whereas the majority of the signal (approximately 80%) was localized in cardiomyocytes, confirmed by RNAscope and colocalization with MYH6-positive cells. MASLD hearts also displayed increased expression of hypoxia-related markers, including a 150% rise in HIF expression, along with elevated PPAR- α levels, consistent with enhanced DIO3 expression. **Conclusion:** MASLD induces early cardiac functional and molecular alterations, associated with alterations in thyroid hormone metabolism. Increased cardiomyocyte DIO3 expression may represent an adaptive response during the initial stages of the disease, potentially contributing to local thyroid hormone inactivation and early cardiac remodeling. **Keywords:** MASLD; thyroid hormone metabolism; heart.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2741 DYSFUNCTION ON HEPATIC GLYCOLYTIC, MITOCHONDRIAL, AND THYROID HORMONE METABOLISM IN HEPATOCELLULAR CARCINOMA: EFFECTS OF ATORVASTATIN AND RIFAXIMIN

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Introduction: Metabolic reprogramming is a hallmark of hepatocellular carcinoma (HCC), particularly in the context of metabolic-associated steatotic liver disease (MASLD). Dysregulation of hepatic glycolytic, mitochondrial, and thyroid hormone metabolism contributes to tumor development and progression. **Objective:** This study aimed to evaluate alterations in hepatic energy metabolism related to intracellular triiodothyronine (T3) levels during HCC development and to investigate the effects of atorvastatin and rifaximin in an experimental *in vivo* model. **Materials and methods:** HCC was induced in Sprague-Dawley rats by administration of diethylnitrosamine (135 mg/L) in drinking water for 16 weeks combined with a high-fat diet. Animals were treated with atorvastatin (5 mg/kg) or rifaximin (5 mL/kg). Tumor and adjacent non-tumor liver tissues were analyzed for the expression of genes involved in glycolytic and mitochondrial metabolism, including hexokinase 2 (HK2), phosphofructokinase platelet type (PFKP), pyruvate kinase M2 (PKM2), lactate dehydrogenase A (LDHA), and ATP synthase subunit alpha (ATP5A) using real-time quantitative PCR. The activities of glutamate dehydrogenase (GDH), α -ketoglutarate dehydrogenase (α -KGDH), and acetyl-CoA carboxylase were evaluated by western blotting. Hepatic tissue T3 levels were quantified. **Results:** Tumor liver tissue exhibited increased expression of glycolytic enzymes HK2, PFKP, PKM2, and LDHA, indicating a metabolic shift toward enhanced glycolysis, while altered ATP5A expression suggested impaired mitochondrial oxidative phosphorylation. The activities of GDH, α -KGDH, and acetyl-CoA carboxylase were increased, reflecting metabolic adaptations related to mitochondrial function and lipogenic pathways. Intracellular T3 levels were markedly reduced in the HCC group compared with the control (–66.6%). Treatment with atorvastatin partially restored T3 levels (–57.0% vs. control), whereas rifaximin showed a more modest effect (–63.3% vs. control). **Conclusion:** Hepatocellular carcinoma in this model is associated with dysfunction of hepatic metabolism, characterized by enhanced glycolysis, mitochondrial impairment, and reduced intracellular T3 availability. Atorvastatin and rifaximin partially attenuated these metabolic disturbances, with distinct effects on hepatic T3 levels, highlighting thyroid hormone modulation as potential therapeutic strategies in MASLD-related HCC. **Keywords:** hepatocellular carcinoma; hepatic glycolytic; triiodothyronine.



BIOLOGIA CELULAR DA TIREOIDE

2756 LOSS OF FUNCTION OF PIK3C3 VIA DELETERIOUS VARIANTS AND DOWNREGULATION MAY DRIVE THYROID CARCINOGENESIS THROUGH AUTOPHAGY DISRUPTION

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The pathogenesis of thyroid cancer is associated with dysregulation in autophagy, a highly conserved intracellular degradation pathway essential for cellular homeostasis. PIK3C3, a component of the PI3K complex, is crucial for the initiation and maturation of autophagosomes and plays a central role in autophagy regulation. Dysregulation of this complex can compromise genomic stability and immune responses, thereby promoting tumorigenesis. Despite the role of PIK3C3 in autophagy and cancer, the structural impact of its missense variants on protein stability and their potential association with thyroid cancer susceptibility remain poorly understood. This *in silico* aimed to characterize missense polymorphisms in PIK3C3, predict their structural and functional effects on the encoded protein, and evaluate their potential influence on thyroid carcinogenesis. Polymorphisms were retrieved from dbSNP and UniProt. Missense variants were prioritized using a consensus pathogenicity approach, PredictSNP (MAPP, PhD-SNP, PolyPhen, and SIFT), SNPs&GO, PMUT, and Fathmm. Protein stability and evolutionary conservation were assessed on I-Mutant2.0, MuPro, IStable, and ConSurf. Structural alterations were modeled with the HOPE platform. Gene-disease associations and differential expression were validated with Comparative Toxicogenomics Database (CTD), COSMIC, and UALCAN (TCGA data). Among the 933 SNPs identified in PIK3C3, four variants: rs375875992 (S12G), rs200762676 (G185R), rs140733016 (L367S), and rs140244450 (L366M), were classified as deleterious by all algorithms, with predicted significant impacts on protein function and thermodynamic stability. These variants involve substitutions within highly conserved functional domains, potentially disrupting local folding and protein conformation through mechanisms such as aberrant flexibility and compromised hydrophobic interactions. Furthermore, PIK3C3 expression was significantly downregulated in primary tumors compared to normal tissues ($p < 0.01$), with even more pronounced downregulation in aggressive histological subtypes, including papillary and anaplastic thyroid carcinomas ($p < 0.001$ vs. normal tissue). Deleterious PIK3C3 variants may compromise protein function, suggesting a loss-of-function mechanism in autophagy. Its dysfunction may promote cellular damage and mutations, thereby favoring tumorigenesis. These findings highlight potential avenues for developing prognostic biomarkers for thyroid cancer susceptibility. **Keywords:** thyroid cancer; PIK3C3; autophagy.

NÓDULOS E CÂNCER DE TIREOIDE

2757 INTEGRATIVE BIOINFORMATICS AND GENOMIC ANALYSIS IDENTIFIES ICAM1, MADCAM1, AND ITGAM AS NOVEL RISK STRATIFICATION BIOMARKERS IN THYROID NODULAR DISEASE

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Introduction: The substantial biological heterogeneity of thyroid cancer, particularly in follicular-patterned lesions, complicates diagnosis and risk stratification. Genetic variability in the pathways governing cell adhesion, immune interactions, and matrix remodeling may underpin this heterogeneity and influence tumor behavior. **Objective:** To integrate bioinformatics and genetic analyses to evaluate polymorphisms in genes encoding immunoglobulin superfamily adhesion molecules, integrins, junctional proteins, matrix metalloproteinases, and extracellular matrix-associated proteins, and to assess their association with thyroid cancer. **Methods:** An integrated bioinformatics approach was used to screen 407,812 polymorphisms across 22 candidate genes, including immunoglobulin superfamily members, integrins, junctional proteins, and matrix metalloproteinases, prioritizing 133 variants with a high predicted functional impact. Eight single nucleotide polymorphisms (SNPs) with high predicted functional impact were selected for further genotyping in a cohort of 648 individuals, including patients with benign ($n = 152$) and malignant ($n = 171$) thyroid nodules and healthy controls ($n = 325$). Associations with histological subtypes and clinicopathological features were also analyzed. **Results:** Three polymorphisms showed significant clinical associations. *ICAM1* rs5498 was associated with follicular thyroid carcinoma (FTC) compared to controls ($p = 0.023$) and goiter ($p = 0.038$). *MADCAM1* rs3745925 robustly distinguished follicular adenoma (FA) from controls ($p = 0.002$) and papillary thyroid carcinoma (PTC) ($p < 0.001$) and differentiated FTC from goiter ($p = 0.041$) and PTC ($p = 0.043$). *ITGAM* rs1143683 differentiated FA from FTC ($p = 0.029$) and, along with *ITGAL* rs2230433 and *ICAM1* rs5498, was significantly associated with tumor multifocality ($p = 0.043$, $p < 0.001$, and $p < 0.0001$, respectively). Variants in *ITGA4*, *ITGAL*, and *MMP9* showed no significant associations. **Conclusion:** This study demonstrates the power of combining computational prediction with clinical validation to identify functionally relevant genetic variants. The significant associations of *ICAM1*, *MADCAM1*, and *ITGAM* polymorphisms with specific thyroid tumor subtypes and multifocality support their role in the molecular heterogeneity of thyroid diseases. These variants may serve as auxiliary biomarkers to improve risk stratification and characterization, particularly for diagnostically challenging follicular-patterned lesions. **Keywords:** thyroid cancer; bioinformatics; cell adhesion molecules.



BIOLOGIA CELULAR DA TIREOIDE

2761 DELETERIOUS NTAN1 POLYMORPHISMS DESTABILIZE KEY PROTEIN SITES, IMPLICATING THE N-DEGRON PATHWAY IN THYROID CANCER PATHOGENESIS

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Introduction: The N-terminal asparagine amidase gene (NTAN1) is a core component of the N-degron pathway that regulates protein quality control through targeted proteolysis. Large-scale cancer genomic data, including TCGA datasets, show that NTAN1 harbors somatic alterations, such as deletions, substitutions, and frameshifts, in multiple tumor types. NTAN1 expression has been associated with the prognosis of some malignancies, including glioma and renal cancer. Recent studies have also linked NTAN1 to immune-related and metabolic pathways, suggesting a broader role in cancer-associated cellular regulation. However, the contribution of NTAN1 genetic polymorphisms to thyroid cancer susceptibility and progression remains unclear. **Objective:** To characterize the functional impact of NTAN1 single nucleotide polymorphisms (SNPs) and evaluate their potential as biomarkers for thyroid cancer susceptibility and progression. **Methods:** Using dbSNP and Ensembl, 10,470 NTAN1 variants were screened using 20 bioinformatic tools, including PredictSNP2.0, PredictSNP1.0, MuPRO, NetSurf, ConSurf, NetPhos, and NetOGlyc. After applying a minor allele frequency (MAF) filter > 0.1 and removing duplicates, 37 SNPs (70 alterations) were retained. Regulatory and missense variants were prioritized for the functional analysis. **Results:** Three regulatory SNPs (rs11075253, rs1135999-A/C, and rs2280017) were classified as 50.0% deleterious, indicating potential effects on NTAN1 expression. The missense variant rs1136001 (H283Y/D/A) was predicted to be neutral but reduced protein stability (MuPRO $\Delta\Delta G = -0.8407$ to -1.1843) and induced a novel interaction with PHE286. For rs1135999, the A>C (S287A) and A>G (S287P) substitutions were predicted to be 50.0% and 33.3% deleterious, respectively, both decreasing stability. Residue 287 is an exposed site predicted to undergo protein kinase C phosphorylation and O-glycosylation. Overall, the five NTAN1 polymorphisms showed deleterious effects on protein stability and regulatory function. **Conclusion:** Common NTAN1 polymorphisms affecting exposed residues and post-translational modification sites may destabilize the protein and disrupt N-degron-mediated proteostasis. These findings support the relevance of NTAN1 polymorphism analysis in thyroid cancer and nominate specific variants as candidate biomarkers for risk stratification and prognosis, warranting further clinical validation. **Keywords:** bioinformatics; biomarkers; thyroid cancer.

BIOLOGIA CELULAR DA TIREOIDE

2762 BIOINFORMATICS ASSESSMENT OF FN1 AND LILRB4 MISSENSE VARIANTS AND THEIR POTENTIAL ROLE IN THYROID CANCER IMMUNOREGULATION

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Introduction: Thyroid cancer is the most common endocrine malignancy and predominantly comprises papillary thyroid carcinoma (PTC). Although the prognosis is generally favorable, aggressive and metastatic diseases are often linked to immune evasion mechanisms within the tumor microenvironment. Fibronectin 1 (FN1), an extracellular matrix glycoprotein overexpressed in tumors, acts as a physiological ligand for the immunoinhibitory receptor LILRB4, expressed on myeloid cells, establishing a stromal immune checkpoint that suppresses antitumor responses. However, the functional impact of the genetic variants of FN1 and LILRB4 on this axis in thyroid cancer remains largely unexplored. **Objective:** This *in silico* study aimed to characterize missense polymorphisms in FN1 and LILRB4 and evaluate their predicted structural and functional impacts on the encoded proteins, as well as their potential influence on the FN1-LILRB4 immunoregulatory axis in thyroid cancer. **Methods:** Missense variants were sourced from the dbSNP database, and protein sequences were obtained from UniProt. Bioinformatics analyses utilized robust functional and pathogenicity prediction tools (SIFT, PolyPhen-2, SNP&GO, and PhD-SNP). Protein stability changes for prioritized variants were assessed using I-Mutant2.0 and MUpro. **Results:** We identified 2,991 FN1 and 655 LILRB4 variants. In FN1, 47 deleterious single nucleotide polymorphisms (SNPs) were predicted, of which 31 (65.96%) showed reduced protein stability and high pathogenicity scores (MutPred > 0.80). Key variants rs554742541 (C135R), rs1181638652 (C225W), rs1553667072 (C123R), rs1064795155 (C231W), and rs1553658926 (C260G) were located at highly conserved sites critical for protein function. For LILRB4, 42 deleterious SNPs were identified. Although MutPred2 indicated generally low pathogenicity scores (< 0.60), 33 variants (78.57%) were predicted to reduce protein stability and impair protein function. Variants rs759117240 (W106S), rs1003078720 (P130R), and rs1417713355 (Y96H), located in conserved regions, showed a significant predicted impact on protein function. **Conclusion:** Deleterious missense variants in FN1 and LILRB4 with predicted destabilizing effects on protein structure and function were identified, providing a foundational genetic framework for investigating the FN1-LILRB4 axis as a modulator of immune evasion in thyroid cancer. Further experimental validation is required to confirm the biological and clinical relevance of these variants. **Keywords:** bioinformatics; fibronectin 1; immunoregulation.



NÓDULOS E CÂNCER DE TIREOIDE

2764 TRANSCRIPTOMIC ANALYSIS REVEALS PRO-ONCOGENIC EFFECTS OF ROUNDUP® AT REGULATORY DOSES IN THYROID CELLS

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Roundup® is one of the most widely used herbicides worldwide and is known for its endocrine-disrupting properties. Epidemiological and experimental evidence has associated exposure to this compound with adverse health effects, including modulation of processes related to carcinogenesis. However, the molecular mechanisms by which different doses of glyphosate-based herbicides affect thyroid cells remain largely unknown. This study aimed to investigate the effects of Roundup® Original DI on the transcriptomic profiles and molecular pathways of thyroid cell lines using RNA sequencing (RNA-Seq), focusing on doses established as safe by the Brazilian Health Regulatory Agency (Anvisa), including the Acceptable Occupational Exposure Level (AOEL) and Acceptable Daily Intake (ADI). The non-tumorigenic thyroid Nthy-ori 3-1 and papillary thyroid carcinoma TPC-1 cell lines were exposed to Roundup® at 65, 160 (AOEL), and 830 µg/L (ADI) for 24 and 48 h, with all experiments performed in triplicate. After RNA-Seq, differentially expressed genes (DEGs) were identified *versus* untreated controls. Functional enrichment analysis was performed, with significance set at $p < 0.05$. In the Nthy-ori 3-1 cell line, exposure to Roundup® for 24 h resulted in 169, 138, and 203 DEGs at concentrations of 65, 160, and 830 µg/L, respectively, with a predominance of downregulated genes. After 48 hours, fewer DEGs were detected (71, 97, and 99, respectively), accompanied by a relative increase in upregulated genes. The enriched pathways included Gα12/13, IL-17, and NF1-dependent RAS signaling. In TPC-1 cells, 254, 310, and 215 DEGs were identified after 24 h, predominantly upregulated, particularly at the 160 µg/L concentration. After 48 h of exposure, 72, 245, and 98 DEGs were observed. Functional enrichment revealed modulation of pathways related to the Molecular Mechanisms of Cancer, STAT3 signaling, IL-6 signaling, wound healing, and p38 MAPK signaling. The AOEL dose induced the highest number of unique genes and modulated pathways at both time points. These findings demonstrate that Roundup® induces significant transcriptomic alterations in thyroid cells, affecting pathways associated with inflammation, DNA repair, and oncogenic signaling. Notably, a dose of 160 µg/L promoted the most pronounced pro-oncogenic transcriptional changes in malignant cells, suggesting that exposure levels currently regarded as safe may influence the molecular mechanisms underlying tumor progression. **Keywords:** glyphosate-based herbicide; RNA-Seq; thyroid cancer.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2765 HYPOTHYROIDISM DISRUPTS THE DAILY OSCILLATIONS OF THYROTROPIN (TSH) SERUM CONCENTRATION IN MALE RATS

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Thyrotropin (TSH) is a central component of the thyroid axis, and its serum levels oscillate throughout the day, influenced by the central circadian clock localized in the suprachiasmatic nucleus (SCN) of the hypothalamus. Hypothyroidism alters the expression of clock genes in the SCN and in the anterior pituitary gland; however, its consequence for the daily TSH oscillation is unknown. Our study aimed to evaluate the effects of hypothyroidism on daily TSH synthesis and secretion. For this, Wistar male rats were divided into Control (C) and Hypothyroid (Tx) groups. Hypothyroidism was induced by thyroidectomy and addition of 0.03% methimazole + 4.5 mM CaCl₂ in the drinking water for 24 days. Following, the animals were euthanized every 3 h over 24 h. The anterior pituitary and trunk serum were collected. *Tshb* mRNA content was evaluated by RT-qPCR and TSH serum levels were determined by MILLIPLEX assay. Results were tested for normality and homoscedasticity. The effect of time for each experimental group was analyzed by Kruskal-Wallis test. Data that presented daily variations of each group were submitted to cosine curve fitting with a 24-h periodicity. Student's t-test was applied to compare the differences between mesor, amplitude and acrophase among C and Tx. Two-way ANOVA was used to determine effects of time, treatment and interaction between these factors. Pairwise comparisons between C and Tx groups were tested by Bonferroni's multiple comparisons at each time point. The null hypothesis was rejected when $P < 0.05$. Pituitary *Tshb* mRNA content was increased in Tx rats throughout the day, as expected, and no significant daily variations were observed in C and Tx groups. Two-Way ANOVA revealed effects for treatment on the contents of *Tshb* mRNA in the pituitary. TSH serum levels exhibited a 24-h period oscillatory pattern (circadian) in both groups. Hypothyroidism increased the mesor, a rhythm-adjusted mean, and amplitude of TSH levels, as well as advanced its acrophase (time of day when the peak of TSH level is observed). Treatment and time main effects and interaction between those factors were detected by Two-way ANOVA. These results show that hypothyroidism alters the pattern of daily oscillations of TSH levels. Further studies are needed to evaluate whether the current T4 replacement protocol for hypothyroidism treatment can reestablish the temporal dynamics of the thyroid axis in addition to the hormonal levels of thyroid axis components. **Keywords:** thyrotropin; hypothyroidism; daily patterns.



METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2767 TYPE 3 DEIODINASE IS ACTIVATED IN THE BRAIN IN AN ANIMAL MODEL OF MASLD

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Introduction: Thyroid hormones are essential for cerebral energy metabolism. Alterations in type 3 deiodinase (D3) activity may reduce brain T3 availability under conditions of metabolic disease. **Objective:** To evaluate D3 induction and its effects on brain metabolism in an animal model of metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** Adult male Sprague-Dawley rats (n = 20) were randomly assigned to a control group receiving a standard diet (2.93 kcal/g) or a choline-deficient high-fat diet (HFCD; 4.3 kcal/g). After 18 weeks of ad libitum feeding, MASLD was established. Animals were euthanized, and brain tissues were collected. Oxidative stress markers, D3 expression and protein levels, T3-responsive genes, endoplasmic reticulum (ER) stress markers, mitochondrial function, and mitochondrial biogenesis were evaluated. Blood ammonia levels were measured. **Results:** MASLD animals exhibited significantly elevated blood ammonia levels. Brain tissue analysis revealed increased protein carbonyls and TBARS, along with reduced sulphydryl and glutathione levels, indicating oxidative stress. Notably, oxidative damage such as elevated TBARS can disrupt astrocyte-neuron metabolic coupling by impairing lactate shuttling, potentially reducing neuronal ATP supply and impacting brain energetics. D3 expression was markedly induced via ERK signaling, accompanied by reduced expression of T3-regulated genes, consistent with decreased cerebral T3 availability. Increased ER stress and reduced mitochondrial biogenesis (P = 0.001) were observed. Mitochondrial respiration was impaired, with 28% reduction in State 3 and 18% in State 4 respiration in MASLD brains compared to controls. This quantifiable decline highlights a bioenergetic bottleneck at both ADP-stimulated and basal respiratory states, likely reflecting the combined effects of hyperammonemia and thyroid hormone inactivation. **Conclusion:** D3 activation in the MASLD brain reduces T3 availability and disrupts cerebral energy metabolism, potentially contributing to neurological dysfunction associated with liver disease. **Keywords:** MASLD; thyroid hormone; deiodinase.

BIOLOGIA CELULAR DA TIREOIDE

2768 STRUCTURAL AND FUNCTIONAL IMPACTS OF SOD2 MISSENSE VARIANTS ON MITOCHONDRIAL ANTIOXIDANT DEFENSE AND IMMUNE REGULATION IN GRAVES' DISEASE

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Introduction: Oxidative stress is key in the pathogenesis of Graves' disease (GD), an autoimmune disorder in which the thyroid is susceptible to injury owing to physiological ROS dependence for hormone biosynthesis. Manganese superoxide dismutase (MnSOD), encoded by SOD2, is the primary mitochondrial antioxidant enzyme that detoxifies superoxide radicals. However, the effects of missense variants on GD remain poorly characterized. **Objective:** To assess structural and functional impacts of deleterious SOD2 variants and their role in GD-related oxidative and immune pathways. **Methods:** Four previously prioritized missense SNPs (L84F, S27R, L38Q, and V142F) were assessed using multiple *in silico* platforms. MutPred2 was used to evaluate the structural stability and post-translational modification sites with high-confidence thresholds (p < 0.05). The HOPE server provided three-dimensional structural comparisons between wild-type and mutant residues by analyzing size, charge, hydrophobicity, and spatial arrangement. STRING v12.0 (confidence > 0.900) was used to map protein-protein interaction networks to identify connections with immune regulation and mitochondrial function. **Results:** MutPred2 revealed significant structural disruptions in all variants, with L38Q (rs375884951) showing the loss of allosteric sites at I42 (p = 0.03), gain of catalytic sites at E39 (p = 0.02), altered transmembrane structure (p = 0.02), and reduced solvent accessibility (p = 0.0096). V142F (rs376398472) exhibited loss of allosteric (p = 0.008) and catalytic sites (p = 0.004). HOPE confirmed the reduced solvent accessibility, altered hydrophobicity, and disrupted interatomic interactions. I-Mutant 2.0 and MUpro analyses indicated decreased protein stability for most variants ($\Delta\Delta G < 0$), with L38Q showing the most pronounced destabilization ($\Delta\Delta G = -2.29$ kcal/mol). STRING analysis identified novel high-confidence interactions with KAT2A, FOXO3, PPARGC1A, CAT, SOD1, and GPX7, linking SOD2 to mitochondrial homeostasis, FOXO-mediated oxidative stress transcription, apoptosis regulation, and immune response pathways that are critically involved in GD pathogenesis. Reactome pathway analysis confirmed significant enrichment (FDR ≤ 0.05) of detoxification of reactive oxygen species and cellular responses to stress. **Conclusion:** L38Q and V142F may impair mitochondrial antioxidant defense and modulate immune signaling via KAT2A, contributing to GD pathogenesis. Clinical validation will clarify their prognostic value. **Keywords:** Graves' disease; oxidative stress; SOD2.



BIOLOGIA CELULAR DA TIREOIDE

2772 IN SILICO ANALYSIS OF DELETERIOUS SNPS IN THE G6PD GENE AND THEIR IMPLICATIONS FOR MORPHOLOGY, FUNCTION, AND PROTEIN INTERACTIONS IN THYROID TUMORIGENESIS

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Introduction: Oxidative stress is a central factor in thyroid carcinogenesis, as these cells handle reactive species such as H₂O₂. The enzyme Glucose-6-Phosphate Dehydrogenase (G6PD) is vital for maintaining redox balance by synthesizing NADPH, an essential cofactor for antioxidant systems. Single nucleotide polymorphisms (SNPs) that impair G6PD function may promote metabolic reprogramming and genomic instability, favoring the development of thyroid cancer (TC). **Objective:** To identify deleterious SNPs in the G6PD gene and assess their impacts on stability, function, and protein interaction network, aiming to understand how such variants may promote the tumor microenvironment. **Methods:** SNPs retrieved from dbSNP (NCBI) were analyzed in isoforms A and B (UniProt IDs: P11413-3 and P11413). The impact of the substitutions on the properties of G6PD SNPs was analyzed using the predictions from the tools SIFT, PredictSNP1.0, PolyPhen-2, Provean, SNPs&GO, PMUT, and PANTHER. Protein stability was assessed using I-Mutant 2.0 and MUpro. Protein interaction network was investigated using the STRING tool (confidence level 0.900). **Results:** Among the 517 SNPs analyzed in both isoforms, 64 variants (12%) were classified as deleterious in both SIFT and PredictSNP 1.0. After functional analysis, 39 variants were considered deleterious based on the consensus of 5 tools. All variants showed $\Delta\Delta G$ values < 0 , ranging from -2.9 to -0.1 kcal/mol, indicating that these mutations may affect protein stability. Among the 39 critical variants, 10 were categorized as Class I (severe deficiency) and 6 as Class II (moderate deficiency). The interactome analysis revealed that G6PD interacts with crucial proteins such as TP53, LDHA, and GAPDH. The reduced enzymatic activity of G6PD could compromise cell cycle regulation, energy metabolism, and DNA repair via these interactions. **Conclusion:** This study identifies SNPs in the G6PD gene with high potential to destabilize the enzyme. The detection of 16 variants from Classes I and II, integrated into an interaction network with essential proteins, suggests that G6PD deficiency acts not only as an isolated metabolic error but as a driver of genomic instability and glycolytic reprogramming in the thyroid. These findings position the deleterious G6PD SNPs as potential genetic markers of susceptibility to thyroid cancer, offering new insights into how the host's redox genetic background modulates the aggressiveness of the tumor microenvironment. **Keywords:** oxidative stress; thyroid cancer; bioinformatics.

NÓDULOS E CÂNCER DE TIREOIDE

2773 THE RELATIONSHIP BETWEEN IN VITRO FERTILIZATION (IVF) AND THE RISK OF THYROID CANCER IN WOMEN: A SYSTEMATIC REVIEW

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Introduction: *In vitro* fertilization (IVF) involves controlled ovarian stimulation, resulting in supraphysiological hormone levels. Given that thyroid cancer is the most common endocrine malignancy in women, concerns have emerged regarding a possible association between fertility treatments and thyroid carcinogenesis. **Objective:** To investigate the relationship between IVF exposure and the risk of thyroid cancer through a systematic review. **Methods:** A systematic review was conducted using the PubMed, Scopus, Web of Science, Embase, Google Scholar, and Virtual Health Library (VHL) databases. Original cohort and case-control studies were included, whereas case reports and studies published before 1978 were excluded. Data extraction and critical appraisal focused on the eight principal cohort studies. **Results:** Eight cohort studies were included from an initial pool of 160 articles. The findings were heterogeneous. Large-scale registry studies identified potential risk signals: Lindquist et al. (2022) reported an overall hazard ratio (HR) of 1.63 (95% CI: 1.07–2.48), while Reigstad et al. (2017) found an HR of 1.53 (95% CI: 1.01–2.31), which increased to 2.19 among nulliparous women. Drug-specific associations were inconsistent; Hannibal et al. (2008) observed increased risks associated with clomiphene (RR = 2.28) and progesterone (RR = 10.14), whereas other studies failed to confirm these findings. **Conclusion:** Current evidence does not support a definitive causal relationship between IVF and thyroid cancer in the general population but cannot exclude an increased risk in specific subgroups. Long-term surveillance appears warranted, particularly for nulliparous women undergoing multiple IVF cycles. **Keywords:** *In vitro* fertilization; thyroid neoplasms; systematic review.



BIOLOGIA CELULAR DA TIREOIDE

2775 CELL-TYPE SPECIFIC EFFECTS OF ROUNDUP ON THE INVASIVE POTENTIAL OF THYROID MALIGNANCIES

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Introduction: The rising global incidence of thyroid cancer may be partially attributed to environmental factors, particularly endocrine-disrupting chemicals (EDCs). These compounds can interfere with thyroid hormone signaling, a pathway that regulates key cellular processes, such as migration and invasion. Glyphosate-based herbicides, including commercial formulations like Roundup, are among the most widely used agrochemicals worldwide and have been classified as probably carcinogenic to humans by the International Agency for Research on Cancer. Nevertheless, the potential effects of Roundup on thyroid tumor biology remain poorly understood, especially at environmentally relevant and human-permissible exposure levels. **Objective:** To evaluate the effects of Roundup Original DI on the migration and invasion of thyroid follicular cells. **Methods:** A non-tumor thyroid cell (Nthy-ori 3-1), papillary thyroid carcinoma-derived TPC-1 and BCPAP, and an anaplastic cell line (8505C) were exposed to increasing concentrations of Roundup (6.5–6500 µg/L). Migration and invasion were assessed using Transwell assays with uncoated and extracellular matrix-coated inserts. **Results:** Migratory behavior was predominantly determined by intrinsic cellular characteristics, with tumor-derived cells showing intrinsically higher migration than normal thyroid cells. Overall, Roundup concentration did not significantly affect cell migration ($p = 0.9255$). When examining individual cell lines, a significant increase was observed exclusively in TPC-1 cells at 65 µg/L ($p = 0.0195$ vs. control). In the invasion assays, repeated-measures ANOVA demonstrated significant effects of cell type ($p = 0.0073$) and Roundup concentration ($p = 0.0384$), without interaction between factors. Tumor cell lines, particularly 8505C, showed higher invasive capacity than Nthy-ori 3-1, especially at 6.5–160 µg/L. Although individual comparisons were not consistently significant after correction, a trend toward increased invasion at low concentrations was noted. **Conclusion:** Roundup did not uniformly alter cell migration but modulated invasive behavior in a cell type- and concentration-dependent manner. Tumor cells exhibit intrinsically greater migratory and invasive capacities than normal thyroid cells. The subtle effects observed at low concentrations warrant further investigation into the potential impact of glyphosate-based formulations on thyroid cancer progression at environmentally relevant levels. **Keywords:** endocrine disruptors; tumor progression; agrochemicals.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2788 EVALUATION OF THYROID HORMONE METABOLISM IN LIVER TISSUE IN PATIENTS WITH METABOLIC STEATOTIC LIVER DISEASE (MASLD) UNDERGOING BARIATRIC SURGERY

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Metabolic steatotic liver disease (MASLD) represents the most prevalent form of chronic liver disease, encompassing a spectrum of alterations for which effective treatments are still unknown. Thyroid hormone (TH) metabolism interferes with the progression to advanced stages of the disease. In this context, we hypothesize that the pro-inflammatory state induced by obesity contributes to disruptions in TH metabolism in the liver. Our study aims to demonstrate the alterations in TH in patients with MASLD undergoing bariatric surgery, correlating them with markers of oxidative stress, and evaluating whether hepatic parameters of the Krebs cycle, endoplasmic reticulum, D3 expression, and mitochondrial function are altered. We included thirty-five patients with a mean age of 44.24 ± 12.11 years, along with a control group of non-obese individuals of the same age undergoing elective surgery. Sixty percent of the participants were male, with a mean weight of 132.93 ± 34.36 kg and a BMI of 48.30 ± 11.16 . Total cholesterol levels were measured at $171.30 \text{ mg/dL} \pm 36.44 \text{ mg/dL}$, triglycerides at 108.23 mg/dL , HDL at $51.05 \text{ mg/dL} \pm 34.56 \text{ mg/dL}$, and glucose at $110.25 \text{ mg/dL} \pm 31.36 \text{ mg/dL}$, and seven patients had severe macrovesicular steatosis. Sixteen patients had normal T3 levels ($96 \pm 14 \text{ ng/dL}$), while fourteen had low T3 syndrome ($54 \pm 8 \text{ ng/dL}$), that is, practically half of the patients in this study. When evaluating D1 and D3 metabolism, MASLD patients exhibited high D3 levels, with expression up to 15 times higher than in controls and a 70-fold increase in the immunofluorescence assay. Notably, carbonyl and TBARS levels increased by 45%, while sulfhydryl and GSH levels decreased by 30% and 40%, respectively, confirming an altered redox state. Furthermore, when analyzing mitochondrial dysfunction, we observed significant alterations in cellular hypoxia, biogenesis, and uncoupling protein in endoplasmic reticulum stress. In conjunction, alterations in Krebs cycle enzymes and complex IV impact the urea cycle and respiratory chain. These results demonstrate that TH metabolism and energy production are disrupted in the steatotic liver of these patients. In conclusion, we suggest that a more proactive approach is essential to improve hepatic metabolic function in MASLD from the time of diagnosis. **Keywords:** liver; MASLD; thyroid hormone.



REGULAÇÃO DA FUNÇÃO TIREOIDIANA

2801 PERIPUBERTAL TO ADULTHOOD EXPOSURE TO LOW DOSE OF GLYPHOSATE-BASED HERBICIDE (GBH) DISRUPTS THYROID GLOBAL PROTEIN EXPRESSION IN RATS

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GBH is widely used in weed control associated with the planting of transgenic seeds, and it is still the main pesticide used in Brazil. In previous studies, we observed that peripubertal exposure leads to morphological changes in the adult thyroid, as well as modulation of the hypothalamus-pituitary-thyroid axis and the expression of thyroid hormone-responsive genes in the heart and liver. In this study, we further investigated the effects of low doses of GBH on thyroid function through global (untargeted) identification of proteins by high-resolution mass spectrometry (nanoLC/MS-MS Orbitrap, ThermoFisher) in the thyroids of rats exposed from weaning until 90 days of age to 0.5 mg GBH/kg BW/day. A total of 7,651 proteins were identified, of which 96 were differentially expressed by GBH, 64 upregulated and 32 downregulated. When performing the interactome analysis, we observed that most of these proteins form interconnected functional connections, so that the increase and/or decrease in their expression could affect the functions in which they are involved. Among the most upregulated proteins, we highlight Calm3 (Calmodulin-1), which directly connects to Map2k1 (Dual specificity mitogen-activated protein kinase 1), Ezr (Ezrin), Tpm1 (Tropomyosin alpha-1 chain), Src (Proto-oncogene tyrosine-protein kinase Src), Ctnnb1 (Catenin beta-1), Myl6 (Myosin light polypeptide 6), and Hspa9 (Stress-70 protein). These proteins are related to Mapk activation, regulation of early endosome to late endosome transport, and disordered domain-specific binding. Overall, they act in the formation of thyroid follicles and the epithelial-mesenchymal transition, influencing carcinogenesis, such as papillary thyroid and anaplastic carcinoma. Among the most downregulated proteins, we highlight Eif6 (Eukaryotic translation initiation factor 6), which directly connects to 40S ribosomal protein S2 (Rps2) and 60S ribosomal proteins: L18 (Rpl18), L26 (Rpl26), L15 (Rpl15), L32 (Rpl32), which are related to ribosomal structure, and thus interfere with the regulation of the translation machinery. They play a role in thyroid gland function and development, and relationships with the development of papillary thyroid carcinoma are also described. In conclusion, perinatal exposure to GBH causes significant dysregulation in the expression of thyroid proteins that may compromise its function and interfere with tumorigenesis process. **Keywords:** glyphosate-based herbicide (GBH); thyroid proteomics; tumorigenesis.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2809 VITAMIN D IS NECESSARY FOR OVARIAN THYROID HORMONE SIGNALING IN MICE

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Introduction: Thyroid hormones act throughout all stages of folliculogenesis and contribute to ovarian endocrine function. Vitamin D has been proposed as a supportive strategy for women with reduced fertility, although the effects of supplementation remain incompletely characterized. Additionally, the crosstalk between vitamin D and thyroid hormone signaling in the ovary remains unclear. **Objective:** Investigate the effect of Vitamin D status on the thyroid transcriptional profile in mouse ovaries. **Methods:** Female C57BL/6 mice were divided into three groups with different variations in vitamin D intake (n° A20/22-153-16, CEUA/UFRJ): CONTROL (1,000 IU/kg vitamin D3, “C”), SUPPLEMENTED (10,000 IU/kg vitamin D3, “S”), and DEFICIENT (0 IU/kg vitamin D3, “D”), the diet was offered for 31 days. The euthanasia was in the last day of treatment, and the ovaries were collected for gene expression analysis by RT-qPCR (N = 8 per group). Data were expressed as mean ± standard deviation and analyzed by One-way ANOVA. **Results:** First, we investigated thyroid hormone transport in the ovary, and we did not observe differences in the gene expression encoding Mct8, Mct10, Lat1, Lat2, and Oatp1c1 in both groups. Next we analyzed the deiodinase gene expression. Dio1 and Dio2 were unchanged, whereas Dio3 increased in the deficient group compared with the control (p = 0.04) and supplemented groups (p = 0.03; C: 1.0 ± 0.1, S: 0.9 ± 0.1, D: 1.4 ± 0.1), suggesting a decrease in triiodothyronine availability in the deficient group. To better understand the signaling pathway, we next analyzed the thyroid hormone receptor expression and three responsive genes upregulated by thyroid hormone. The Thra1 expression decreased only in the supplemented group (p = 0.04; C: 1.0 ± 0.1, S: 0.8 ± 0.1, D: 1.0 ± 0.1). Thrb1 was reduced in both deficient (p = 0.03) and supplemented groups (p = 0.01; C: 1.0 ± 0.1, S: 0.6 ± 0.1, D: 0.7 ± 0.1). Among T3-responsive genes, Thrsp did not differ, while Hr was reduced in deficient (p = 0.03) and supplemented groups (p = 0.02; C: 1.0 ± 0.2, S: 0.7 ± 0.1, D: 0.7 ± 0.1), and Actb decreased in the supplemented group (p = 0.002; C: 1.0 ± 0.1, S: 0.7 ± 0.1, D: 0.8 ± 0.1). The Thrsp gene is downregulated by vitamin D, which can partially explain our data. **Conclusion:** Our findings suggest a potential crosstalk between vitamin D and thyroid hormone pathways. Both deficient and supplemented conditions were associated with reduced thyroid hormone signaling pathways in the ovary. **Keywords:** thyroid hormone signaling; vitamin D; ovarian folliculogenesis.



EPIDEMIOLOGIA

2810 FACTORS ASSOCIATED WITH ADVANCED STAGING OF THYROID CANCER IN BAHIA: A STUDY WITH DATASUS DATA FROM 2020 TO 2025

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Introduction: Thyroid cancer is the most frequent endocrine malignancy and has shown an increasing incidence in recent decades, including in Brazil. Despite its favorable prognosis, delayed diagnosis and treatment can compromise clinical outcomes. Within the Unified Health System (SUS), Law n° 12,732/2012 mandates that treatment begin within 60 days of diagnosis; however, regional inequalities persist. Staging is a primary prognostic factor that guides therapeutic choice and is also influenced by sociodemographic characteristics such as sex and age. **Objective:** To analyze the profile of thyroid cancer cases in Bahia between 2020 and 2025 according to sex, staging, therapeutic modality, and time to treatment initiation, based on Datasus data. **Methods:** This is an observational, cross-sectional, and quantitative epidemiological study using secondary data from the Datasus Oncology Panel. Records of malignant thyroid neoplasms (ICD-10 C73) in Bahia from 2020 to 2025 were included. The variables analyzed were sex, age group, staging, therapeutic modality, and time to treatment initiation. Associations between categorical variables were evaluated using the chi-square test with a significance level of 5%. **Results:** A total of 3,755 cases were identified during the period. A female predominance was observed in all years, with a female-to-male ratio of 5:1. Regarding staging, “unknown” or “not applicable” accounted for more than 80% of the records; nevertheless, 40 advanced cases were identified 17 Stage III and 23 Stage IV. The comparison between age (<55 vs. ≥55 years) and advanced staging showed a significant association ($\chi^2 = 4,2$; $p = 0,04$), indicating a higher proportion of stages III/IV in individuals aged ≥ 55. Radiotherapy predominated in Stage III cases, while chemotherapy was most frequent in Stage IV; surgery remained the absolute predominant treatment (96%) overall. Regarding the time to treatment initiation, there was a significant lack of information. Among cases with valid information, approximately 72% began therapy on the same day or within 30 days of diagnosis. **Conclusion:** Thyroid cancer in Bahia showed a predominance in females and a significant association between advanced staging and therapeutic modality. The high number of records with missing information limited broader analyses; however, the data highlight consistent clinical patterns and point to the need for improvements in the quality of health records. **Keywords:** thyroid neoplasms; thyroid gland; epidemiology.

NÓDULOS E CÂNCER DE TIREOIDE

2812 NON-RADIOACTIVE IODIDE UPTAKE SCREENING IDENTIFIES LYSICAMINE AS A POTENTIAL REDIFFERENTIATION AGENT IN THYROID CANCER CELLS

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Introduction: During the progression of thyroid cancer (TC), tissue dedifferentiation and loss of radioiodine uptake are observed due to decreased NIS expression or cytoplasmic retention. NIS is a plasma membrane protein responsible for the active transport of iodide into thyroid follicular cells. The clinical management of radioiodine-refractory thyroid cancers remains a challenge. Restoring radioiodine sensitivity has emerged as a therapeutic strategy, particularly for more aggressive forms of thyroid tumors. **Objective:** This study aimed to screen compounds that enhance iodide uptake in human thyroid cell lines using a non-radioactive assay. **Methods:** A non-tumoral (NThyOri 3.1) cell line with ectopic human NIS expression was generated by transfection with a plasmid encoding the NIS gene using Lipofectamine. A stable clone was selected with geneticin and used to standardize the iodide uptake assay. NThyOri 3.1, HTH83, and KTC2 anaplastic thyroid cancer (ATC) cell lines were employed for drug screening. Redifferentiation gene expression was assessed using real-time PCR. ERK and PI3K inhibitors were used as positive controls. **Results:** A stable clone (NB6) was selected, exhibiting a high-fold increase in NIS expression. The non-radioactive iodide uptake assay was standardized using NB6 cells and PI3K and ERK inhibitors, resulting in increases of 81%, 46%, and 52% in iodide uptake, respectively, compared with non-transfected NThyOri 3.1. Among the tested drugs, lysicamine increased iodide uptake at 1,5X IC50 in NThy-ori 3-1 and HTH83 cells, by 65% and 110%, respectively. The expression of NIS, TG, and TPO was increased in lysicamine-exposed cells; however, PAX8 expression was reduced. **Conclusion:** Lysicamine promoted iodide uptake and upregulated key thyroid differentiation markers in both non-tumoral and anaplastic thyroid cancer cells, highlighting its potential as a novel redifferentiation agent. By enhancing NIS expression and function, lysicamine may represent a promising strategy to restore radioiodine responsiveness in aggressive thyroid tumors. Further studies are needed to clarify the molecular mechanisms involved in these effects. **Keywords:** anaplastic thyroid cancer; radiiodine uptake; NIS.

EPIDEMIOLOGIA

2813 CHALLENGES IN POST-SURGICAL HYPOPARATHYROIDISM SURVEILLANCE USING ADMINISTRATIVE DATA: AN ANALYSIS OF THE HEALTH CARE NETWORK IN BAHIA (2015–2025)

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Introduction: Iatrogenic hypoparathyroidism is a significant complication of total thyroidectomy and may require long-term calcitriol replacement in persistent cases. Within the Brazilian Unified Health System (SUS), monitoring this outcome is challenging due to the concurrent use of calcitriol in chronic kidney disease (CKD) and the lack of integration between hospital and outpatient administrative databases. **Objective:** To evaluate the relationship between total thyroidectomy volume and the dispensing of calcitriol 0.25 mcg across municipalities in Bahia, assessing the usefulness of an administrative indicator for indirect surveillance of postoperative hypoparathyroidism. **Methods:** An ecological analytical study using Datasus data from January 2015 to November 2025. Total thyroidectomies were obtained from SIH/SUS and calcitriol dispensing from SIA/SUS. The Care Stock-to-Flow Ratio (CSFR) was defined as the ratio between accumulated capsules dispensed and total surgeries during the study period, serving as an ecological proxy for possible postoperative hypoparathyroidism. To reduce CKD-related indication bias, ASFR was correlated with the hemodialysis rate per 100.000 inhabitants using Spearman's coefficient (ρ). Results: A total of 2.066 thyroidectomies were recorded. Salvador accounted for 64% of procedures (1.323 cases) and showed an intermediate ASFR (4.928 capsules per surgery). Inland municipalities presented higher ASFR values, including Ilhéus (10.576) and Itabuna (8.617), suggesting a geographic mismatch between surgical location and long-term pharmacological follow-up. No significant correlation was observed between hemodialysis burden and ASFR ($\rho = -0.04$; $p > 0.05$), indicating that dialysis-dependent CKD alone does not explain variability in calcitriol dispensing. **Conclusion:** The absence of correlation between ASFR and hemodialysis rates suggests that CKD does not fully account for differences in calcitriol dispensing. These findings point to a possible mismatch between surgical care and subsequent pharmacological follow-up, highlighting limitations of administrative data and the need to incorporate structural variables of the nephrology network to refine surveillance strategies. **Keywords:** thyroidectomy; hypoparathyroidism; calcitriol; chronic kidney disease.

REGULAÇÃO DA FUNÇÃO TIREOIDIANA

2820 ASSESSMENT OF THE IMPACT OF EXPOSURE TO MINING-RELATED CONTAMINANTS ON THYROID FUNCTION — A SYSTEMATIC REVIEW

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Mining activities constitute an important economic sector for the Minas Gerais (MG) state; however, they are associated with the release of several compounds, especially heavy metals, and environmental contamination. The hypothalamic-pituitary-thyroid (HPT) axis is particularly vulnerable to endocrine disruptors (EDCs), and many substances have been shown to impair the thyroid axis homeostasis. In this sense, the chronic exposure to a combination of mining-related contaminants might contribute to the pathogenesis of thyroid disorders. Herein, we aimed to search for the main mining-related contaminants associated with thyroid dysfunction. A systematic review was conducted in PubMed (2010–2025) using MeSH and free-text terms related to endocrine disruptors, thyroid function, heavy metals, contamination, and mining pollutants. The protocol was prospectively registered in PROSPERO (ID 1325504). Experimental and review studies evaluating the effects of heavy metal exposure on thyroid function in humans, animal models, or *in vitro* systems were included. Twenty-nine studies investigating heavy metals and thyroid alterations were identified. Six involved human populations exposed to cadmium (Cd), lead (Pb), mercury (Hg), chromium (Cr), and manganese (Mn), including combined exposures. Observational, cross-sectional, and cohort studies assessed blood or urinary metal levels and serum T3, T4, and TSH. Animal models included amphibians (Cd, Cr, Ag, Cu, Pb), zebrafish (U, Cd, Pb), rats (Cd, Zn, and mixtures), turtles (Hg), and cetaceans (Cd, Fe, Zn, Cu, Se, Hg). Exposures were acute or chronic and frequently occurred during developmental windows. Reported outcomes included morphological alterations, impaired growth, changes in gene expression of components of HPT axis, hormonal imbalance, and oxidative stress. Four *in vitro* studies examined molecular mechanisms of metal toxicity, and five reviews addressed EDC effects on thyroid physiology. Cadmium was the most frequently studied metal, generally assessed in isolation. However, real-world mining-related exposures involve multiple metals across different life stages, representing a more complex scenario than controlled experimental models. Further studies evaluating combined exposures and possible synergistic interactions are needed to better understand the impact of mining-related contaminant on the HPT axis and to support public health strategies for populations living near mining areas. **Keywords:** hypothalamic-pituitary-thyroid axis; endocrine disruptors; heavy metals.



METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2826 TRIIODOTHYRONINE RAPIDLY REMODELS ION HOMEOSTASIS, LIPID METABOLISM, AND GROWTH-FACTOR SIGNALING PROGRAMS IN MCF-7 BREAST CANCER CELLS

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Thyroid hormone signaling has been implicated in cancer-relevant transcriptional and metabolic programs, yet the earliest transcriptome-level responses to triiodothyronine (T3) in breast cancer cells remain incompletely defined. Here, we profiled the acute transcriptional response of ER-positive MCF-7 breast adenocarcinoma cells to T3 (10^{-8} M, 1 h) by strand-specific RNA-seq. Principal component analysis showed complete separation between control and T3-treated samples along PC1 (~81.8% of variance), indicating a robust early response. Differential expression analysis ($|\text{fold change}| \geq 1.5$; $\text{FDR} < 0.05$) identified 95 regulated genes (70 upregulated, 25 downregulated), including strong induction of STC1 and IGFBP5, and modulation of receptor and signaling nodes (EGFR, RET, IL1R1, TNFAIP3). Over-representation analyses highlighted coordinated regulation of (i) ion/metal homeostasis and stress buffering, (ii) lipid and cholesterol handling (*e.g.*, induction of MGLL and STARD5 with repression of phospholipase A2 family members), and (iii) extracellular matrix/adhesion and membrane trafficking/glycosylation programs (*e.g.*, FN1, TNS1, CLTCL1, GCNT2, B3GNT5, GALNT4), consistent with early rewiring of cell-environment communication and receptor-proximal processes. To nominate upstream regulators, we performed transcription factor activity inference using DoRothEA/ULM on gene-level statistics, identifying a set of putative regulatory factors whose predicted activities were consistent with the observed inflammatory and growth-factor pathway remodeling. Collectively, these results define an early T3-responsive transcriptional program in MCF-7 cells that links ionic regulation and lipid remodeling with growth-factor signaling and membrane/ECM communication modules. These findings motivate targeted follow-up to test whether acute T3-driven transcriptional changes alter receptor signaling dynamics, secreted factor profiles, and downstream functional phenotypes relevant to breast cancer progression. **Keywords:** triiodotironina (T3); MCF-7 breast cancer cells; transcriptomic remodelling.

AUTOIMUNIDADE

2829 IMPROVEMENT OF METABOLIC PROFILE AFTER TOTAL THYROIDECTOMY IN A PATIENT WITH GRAVES' DISEASE AND CONGENITAL GENERALIZED LIPODYSTROPHY: A CASE REPORT

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Introduction: Graves' disease induces a hypermetabolic state with important cardiovascular, skeletal, and metabolic consequences. Total thyroidectomy is a definitive treatment; however, its metabolic effects in patients with complex comorbidities remain poorly characterized. Congenital generalized lipodystrophy (CGL) is marked by severe insulin resistance, dyslipidemia, and leptin deficiency, conditions that may be exacerbated by hyperthyroidism. We describe the metabolic evolution after total thyroidectomy in a patient with Graves' disease associated with CGL type 1. **Case report:** A 22-year-old woman with AGPAT2 mutation (CGL type 1; leptin 0.42 ng/mL [3.7–11.1]), uncontrolled diabetes mellitus (HbA1c 14.8%; basal-bolus insulin 8 IU/kg/day), hypertriglyceridemia (363 mg/dL), and BMI 15.5 kg/m² was evaluated. She presented hyperthyroidism due to Graves' disease (TSH < 0.01 mIU/L; free T4 5.66 ng/dL; TRAb 36.1), persistent tachycardia (mean heart rate 119 bpm), and alkaline phosphatase > 1000 U/L. Total thyroidectomy was performed in September 2024. Standard therapy for CGL had not been initiated due to limited access to metreleptin. After 12 months, resolution of the hypermetabolic state and normalization of alkaline phosphatase (67 U/L) were observed, suggesting reduced bone turnover. BMI increased to 18.2 kg/m². Glycemic control improved (HbA1c 14.8% to 8.9%) despite ongoing high insulin requirements (5.9 IU/kg/day). Triglycerides decreased (363 to 185 mg/dL), LDL cholesterol remained controlled (89 mg/dL), and HDL cholesterol persisted low. Postoperative hypothyroidism is under levothyroxine adjustment, and compensated hypoparathyroidism is under follow-up. The patient awaits access to metreleptin therapy. **Conclusion:** Total thyroidectomy promoted significant metabolic improvement, including glycemic, skeletal, cardiovascular, and nutritional parameters, even without specific leptin replacement therapy. Resolution of hyperthyroidism contributed to metabolic stabilization and reduced bone turnover. Multidisciplinary follow-up is essential to optimize postoperative hormonal and metabolic outcomes. **Keywords:** Graves disease; lipodystrophy; hyperthyroidism.



METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2836 EARLY CARDIOMETABOLIC RISK IN CHILDREN AND ADOLESCENTS WITH DOWN SYNDROME: IMPACT OF THYROID DYSFUNCTION ON THE LIPID PROFILE

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Down syndrome (DS), mainly caused by trisomy 21, is the most common chromosomal condition in the pediatric population. Metabolic alterations inherent to DS predispose individuals to endocrine disorders, particularly thyroid dysfunction, which may worsen disturbances in lipid metabolism. Previous studies have reported a higher prevalence of hypothyroidism (clinical and subclinical) in this population, as well as increased rates of hypertriglyceridemia and reduced HDL-cholesterol, forming a lipid profile associated with early cardiovascular risk. This study aimed to evaluate the nutritional status and investigate the association between thyroid dysfunction and lipid profile alterations in children and adolescents with DS followed at a specialized outpatient clinic. This observational cross-sectional clinical study was approved by the Research Ethics Committee. Fifty-three individuals with DS aged over 3 years were included. Serum levels of total cholesterol, HDL, LDL, triglycerides, TSH, and free T4 were measured. Nutritional status was classified using DS-specific growth curves (CDC). Thyroid dysfunctions were defined according to standardized laboratory criteria. Statistical analysis included Chi-square and Fisher's exact tests using SAS version 9.4, considering $p < 0.05$ as statistically significant. The sample included 39 children (<10 years) and 14 adolescents (≥ 10 years), with a predominance of females (54.7%) and eutrophic nutritional status (77.3%). Thyroid dysfunction was identified in 13.2% of participants, with subclinical hypothyroidism being the most frequent form (9.4%). Among individuals with thyroid dysfunction, 14.3% presented global dyslipidemia. No statistically significant association was observed between thyroid dysfunction and LDL levels. However, 28.6% showed reduced HDL and 48.9% elevated triglycerides, indicating relevant metabolic vulnerability. Although thyroid dysfunction frequency was relatively low, a high prevalence of lipid alterations was observed, suggesting early cardiometabolic risk in this population. These findings highlight the importance of systematic monitoring of thyroid function and lipid profile in children and adolescents with DS, regardless of nutritional status, to enable early detection and preventive clinical interventions. **Keywords:** trisomy 21; thyroid; dyslipidemia and cardiometabolic risk.

iodo

2842 LONG-TERM EFFECTS OF MILD IODINE DEFICIENCY DURING GESTATION ON THYROID HORMONE-RELATED GENE EXPRESSION IN THE HEART AND KIDNEY OF ADULT OFFSPRING

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Introduction: Iodine is an essential micronutrient for thyroid hormone (TH) production, particularly during critical stages of development. Previous data from our group showed that mild iodine deficiency (MID) during gestation alters hypothalamic-pituitary-thyroid axis function in offspring into adulthood. However, little is known about the effects of this exposure on the target tissues of thyroid hormone action. **Objective:** This study aimed to evaluate the impact of exposure to a MID diet on the expression of genes involved in TH action and metabolism in the heart and kidneys of male and female offspring during adulthood. **Methods:** Female mice were subjected to an iodine-deficient diet and received drinking water supplemented with sodium iodide under either normal iodine (NI; 0.2 mg/L) or mild iodine deficiency (MID; 0.08 mg/L) conditions throughout gestation. Female and male offspring were euthanized on postnatal day 90, and the heart and kidney were collected for RNA extraction. The expression of genes involved in TH transport (*Mct10*), TH metabolism (*Dio1*, *Dio2*, *Dio3*), and TH action (*Tra*, *Mb*, *Glut4*) was evaluated by qPCR. **Results:** In the hearts of adult female and male offspring, increased Mb mRNA expression and reduced *Dio3* expression were observed. A significant increase in *Tra* expression in the heart was observed only in females. In the kidney, *Dio* expression was significantly reduced in females and showed a trend toward decreased expression in males. Interestingly, renal *Nis* expression was reduced in offspring, suggesting alterations in renal iodine metabolism and reabsorption. **Conclusion:** MID during gestation induces long-term and tissue-specific changes in the expression of genes involved in TH action and metabolism in the heart and kidneys of adult offspring. These findings reveal that even subtle maternal iodine deficiency during critical developmental windows may reprogram peripheral TH signaling in offspring, with potential functional consequences that persist into adulthood. **Keywords:** mild iodine deficiency; pregnancy; heart and kidney disorders.



REGULAÇÃO DA FUNÇÃO TIREOIDIANA

2843 THE PLACENTA AS A TARGET OF ENDOCRINE DISRUPTION: DDE DISRUPTS THYROID HORMONE TRANSPORT, IODIDE HOMEOSTASIS, AND EPIGENETIC REGULATION

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Introduction: Thyroid hormones (TH) are crucial for fetal development and are supplied exclusively by the mother during the first weeks of gestation. The placenta plays an important role in regulating the availability of these hormones to the fetus by mediating both TH and iodide transport. Our group previously demonstrated that DDE (dichlorodiphenyldichloroethylene), the main metabolite of DDT, disrupts the hypothalamic-pituitary-thyroid (HPT) axis by reducing TH levels in offspring. However, the consequences of this exposure during pregnancy on placental TH and iodide transport mechanisms, as well as on the epigenetic regulation underlying these processes, are unknown. **Objective:** To investigate the effects of DDE exposure on the expression of TH and iodide transporters, as well as on the expression of genes involved in the epigenetic regulation of gene expression. **Methods:** Pregnant female mice were exposed or not to DDE (0.1 mg/kg/day) during gestation. On GD16.5, the dams were euthanized, and the placentas were collected. Gene and protein expression were evaluated by qPCR and Western blot, respectively. **Results:** DDE exposure increased the expression of the transporters Lat1 and Lat2 in the placenta, without altering the expression of Oatp4a1 or Mct10. Interestingly, both gene and protein expression of NIS were reduced in the placenta of DDE-exposed animals. In addition, Dio1 expression was decreased, whereas Dio3 expression was increased in the placenta of pregnant mice exposed to DDE. Finally, the expression of enzymes involved in epigenetic processes associated with transcriptional repression (Dnmt1, Dnmt3a, Hdac3, and Kdm5c) significantly increased in the placenta of DDE-exposed animals. **Conclusion:** Maternal exposure to DDE during gestation disrupts key placental mechanisms involved in TH metabolism and iodide handling, besides altering the expression of epigenetic regulators linked to transcriptional repression. Together, these findings suggest that DDE may impair placental control of fetal TH availability through both direct effects on transporter and deiodinase expression and epigenetic reprogramming, highlighting the placenta as a critical target of endocrine disruption during pregnancy. **Keywords:** DDE exposure; placental thyroid hormone transport; epigenetic regulation.

NÓDULOS E CÂNCER DE TIREOIDE

2849 ZEBRAFISH (DANIO RERIO) AS AN POWERFUL ANIMAL MODEL FOR MEDULLARY THYROID CARCINOMA XENOTRANSPLANTATION: APPLICATION IN THE INVESTIGATION OF ONCOGENESIS ASSOCIATED WITH MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2)

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Introduction: Medullary thyroid carcinoma (MTC) is a rare neuroendocrine neoplasm, with approximately 25% of cases associated with hereditary forms, particularly multiple endocrine neoplasia type 2 (MEN2). This syndrome follows an autosomal dominant inheritance pattern and is linked to activating mutations in the *RET* proto-oncogene, especially the p.M918T mutation, which is characteristic of MEN2B. The MZ-CRC-1 cell line, derived from MTC and harboring this mutation, represents a relevant model for investigating tumorigenesis. In this context, Zebrafish (*Danio rerio*) emerges as a strategic experimental platform due to its embryonic transparency, rapid development, and compatibility with human cell xenotransplantation. These features enable direct *in vivo* visualization of tumor growth and metastatic behavior. **Methods:** Zebrafish embryos at 48 hours post-fertilization (hpf) were used as the animal model for xenotransplantation. MZ-CRC-1 cells were trypsinized, quantified, and labeled with a fluorescent dye. After anesthesia with tricaine, the cells were microinjected into the perivitelline space of the embryos. The animals were maintained at 34 °C, a temperature that supports human cell viability without impairing embryonic development. Tumor progression was monitored over a three-day period using fluorescence microscopy, enabling assessment of tumor growth, cellular dissemination, and potential host physiological alterations. Complementary immunofluorescence analyses were performed to further characterize tumor features. **Results:** A total of 178 embryos were microinjected with the MZ-CRC-1 cell line, of which 161 developed tumors, with implantation rates ranging from 59%, 70%, 82%, 83%, and 88%. In the highest-efficiency experiment (88%), 42 embryos were microinjected, and 37 developed tumors; this assay also included 14 HBSS-injected controls and 20 non-injected negative controls. Three days post-injection, tumor analysis classified the 37 tumors as small (35%), medium (38%), and large (27%), with metastases observed in 35% of cases and secondary tumors in 49%, indicating aggressive tumor behavior. Additionally, 10% mortality, 11% bradycardia, 11% edema, and 16% malformations were recorded, alterations associated with tumorigenesis. **Conclusion:** Zebrafish has been established as a robust and highly efficient *in vivo* model for studying MEN2B associated MTC. Its application in xenotransplantation allows rapid and cost-effective observation of key carcinogenic events. **Keywords:** medullary thyroid carcinoma; zebrafish; tumorigenesis.



METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2855 EFFECT OF T3 ON THE HEPATIC LDLR AND PCSK9 EXPRESSION IN RATS INDUCED TO DIABETES MELLITUS BY ALLOXAN

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Previous studies from our group demonstrated that alloxan-induced diabetes mellitus in rats leads to hyperglycemia and increased serum cholesterol levels, as well as to a hypothyroid state increased lipid levels in both conditions may worsen glycemic control and are associated with insulin resistance and cardiovascular complications such as atherosclerosis and hypertension. T3 treatment of diabetic animals improved glycemia, and restored serum cholesterol level. Therefore, identifying genes, proteins, and regulatory pathways through which T3 modulates lipid metabolism in alloxan-induced diabetic animals, is highly relevant. Thus, a transcriptomic analysis by RNAseq was performed in liver of Control-nondiabetic rats (C), Diabetic rats induced by alloxan (D) and D rats treated with T3 - 1.5 µg/100 g body weight, i.p.- (DT3) for 28 days. This analysis revealed about 2,165 differentially expressed genes between D and C groups and 1,709 between DT3 and D groups, many of them associated with lipid metabolism, and showed a reduced LDLR expression in the D group, which was restored in the DT3 group. For PCSK9, transcriptomic data indicated decreased expression in D animals and increased expression in DT3 animals. LDLR and PCSK9 are respectively involved in cholesterol uptake and in the regulation of LDLR degradation through receptor internalization. Based on these findings, gene (RT-qPCR) and protein (Western blotting) validation analyses were performed in liver samples stored at -80 °C from rats subjected to the same conditions reported for transcriptomic analyses. RT-qPCR analysis confirmed a significant reduction of LDLR mRNA in the D group and restoration in the DT3 group, and the same pattern was observed for LDLR protein expression (reduction in D and increase in DT3 group). For PCSK9 mRNA expression, there was no statistically difference between D and DT3, even though T3 treatment reduced PCSK9 protein expression in D rats. We conclude that the increased serum cholesterol levels observed in D rats could be justified by the reduced hepatic LDLR and increased PCSK9 content, resultant of the hypothyroidism that courses with the D, in this experimental model, since T3 treatment was able to restore both proteins to the levels of non-diabetic (C) rats, even in the absence of insulin. This indicates that T3, and not insulin, is the major regulator of the serum cholesterol level in D rats. **Keywords:** triiodothyronine; diabetes mellitus; cholesterol.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2856 INTERACTION BETWEEN INSULIN-DEFICIENT DIABETES MELLITUS AND THYROID FUNCTION IN NON-INSULIN-TREATED DIABETIC DOGS: AN INTEGRATED CLINICAL, PHYSIOLOGICAL, AND ENDOCRINE ANALYSIS

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Thyroid hormones play a central role in the regulation of energy metabolism and endocrine homeostasis. Increasing evidence suggests that metabolic diseases such as insulin-deficient diabetes mellitus (IDDM) may influence thyroid physiology. Experimental studies conducted in murine models in our laboratory previously demonstrated an association between IDDM and reduced thyroid activity, as well as improved glycemic control following administration of triiodothyronine, supporting the hypothesis of endocrine cross-talk between glucose metabolism and the hypothalamic-pituitary-thyroid (HPT) axis. Based on these findings, the present study investigated whether newly diagnosed diabetic dogs exhibit alterations in thyroid function prior to initiation of insulin therapy. Twenty-two dogs were evaluated, including 10 healthy animals (control group) and 12 dogs with newly diagnosed IDDM (IDDM group), all prior to insulin therapy. Complete blood cell count, serum biochemical profile and urinalysis were performed in all individuals as part of the initial clinical evaluation. Thyroid function was assessed in both groups by measuring thyroid-stimulating hormone (TSH), total thyroxine (TT4) and free thyroxine measured by equilibrium dialysis (fT4-ED). Dogs in the IDDM group exhibited metabolic alterations consistent with the diabetic state, including marked hyperglycemia ($p < 0.0001$), increased triglycerides ($p = 0.0384$), elevated alanine aminotransferase ($p = 0.0277$) and alkaline phosphatase ($p = 0.0214$), and increased beta-hydroxybutyrate ($p < 0.005$). Urinalysis demonstrated significant glucosuria ($p = 0.0007$), ketonuria and proteinuria ($p < 0.05$). No significant differences were observed between groups for sodium, potassium, albumin, total cholesterol, as well as for TT4 and TSH levels, even though the latter values were at the lower limit of the normal range. The fT4 levels showed a significant decrease in the female dogs, while in the male dogs the decrease was at the limit of significance. These findings suggest that the diabetic state may influence early regulation of the HPT axis before insulin therapy, supporting literature data that show a potential correlation between diabetes and thyroid diseases, mainly hypothyroidism. Characterizing these alterations in newly diagnosed diabetic dogs may contribute to a better understanding of this endocrine interaction and highlight spontaneous canine diabetes as a relevant translational model for investigating this endocrine cross-talk. **Keywords:** insulin-deficient diabetes mellitus; thyroid function; endocrine-metabolic correlation.



iodo

2857 DIRECT CELLULAR EFFECTS OF IODIDE DEFICIENCY ON THYROID DIFFERENTIATION AND SIGNALING PATHWAYS

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Introduction: Iodine deficiency (ID) is a major global public health concern. The effects of ID on thyroid function have classically been attributed to increased TSH levels triggered by reduced T4 and T3 concentrations. However, the direct impact of iodide availability on thyroid cell gene expression and intracellular signaling remains poorly understood. **Objective:** To investigate the molecular effects of moderate and severe ID on thyroid cell differentiation, signaling pathways, and epigenetic regulation in PCCL3 cells. **Methods:** PCCL3 rat thyroid follicular cells were cultured for seven days under three conditions: control (C: 10^{-8} M NaI), moderate ID (MID: 10^{-9} M NaI), and severe ID (SID: iodide-free medium/PBS). Importantly, TSH concentration remained the same across all experimental groups. To evaluate the involvement of the MAPK/ERK pathway in iodide-induced effects, cells were treated with the inhibitor PD0325901. Gene and protein expression were assessed by qPCR and Western blotting. **Results:** Both SID and MID significantly increased the expression of thyroid differentiation markers, including Slc5a5 (NIS), Tpo, Tg, and Tshr. In addition, the key transcription factors Foxe1 and Pax8, essential for thyroid cell identity, were also upregulated under iodide-deficient conditions. At the protein level, increased NIS expression was confirmed in both the SID and MID groups. ID also altered the expression of enzymes involved in epigenetic regulation, including DNA methyltransferases (Dnmts), histone acetylation and deacetylation enzymes (Hat1, Hdac3), and histone methylation and demethylation enzymes (Kdm5c, Kdm6a, Ezh2). SID and MID also reduced phosphorylated ERK and AMPK content, commonly associated with cell proliferation and dedifferentiation. Notably, ERK inhibition abrogated the upregulation of Slc5a5, Pax8 and Foxe1 induced by ID conditions. **Conclusion:** Our findings demonstrate that ID directly modulates thyroid cell differentiation, epigenetic regulation, and intracellular signaling, even in the absence of TSH alterations. Together, these results indicate that iodide acts not only as a substrate for thyroid hormone synthesis but also as an important regulator of thyroid follicular cell identity and homeostasis. **Keywords:** iodine deficiency; thyroid cell differentiation; epigenetic regulation.

REGULAÇÃO DA FUNÇÃO TIREOIDIANA

2859 CHRONIC EXPOSURE TO ISOLATED OR MIXTURE OF CONTAMINANTS DERIVED FROM MINING ACTIVITIES ALTERS THE THYROID HORMONAL BALANCE IN RATS

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Mining activity represents an important economic sector in Brazil, however, it is associated with the release of heavy metals into the environment, such as cadmium (Cd), lead (Pb), and zinc (Zn), which can contaminate water, soil, and air. These elements have been described as potential endocrine disruptors capable of interfering with hormonal regulation. The hypothalamus-pituitary-thyroid (HPT) axis is particularly sensitive to environmental contaminants, since thyroid hormones play a key role in regulating energy metabolism, development, and systemic homeostasis. In this context, the present study evaluated the effects of isolated and combined exposure to Cd, Pb, and Zn on thyroid hormonal balance in rats. Adult male Wistar Hannover rats (8 weeks old) were distributed into eight experimental groups (n = 5): control, Cd, Pb, Zn, Cd+Pb, Cd+Zn, Pb+Zn and Cd+Pb+Zn. Metals were administered by oral gavage for 30 days at the following doses: Cd (0.05 mg/kg/day), Pb (0.05 mg/kg/day), and Zn (3 mg/kg/day). The Cd+Pb+Zn mixture led to a 66% of mortality over 30 days, thus, this experimental condition was discontinued. At the end of the experiment, animals were euthanized and the serum was obtained. Total triiodothyronine (T3) and thyroxine (T4) serum concentrations were determined by ELISA. Results were tested for normality and homoscedasticity. Data were analyzed using one-way ANOVA followed by Bonferroni's multiple comparisons test. Pairwise analysis showed that the Pb+Zn group showed increased T3 concentrations compared with the Cd and Zn groups while no differences were observed in serum total T4 concentration. The T4/T3 ratio was increased in rats treated with Zn compared to Pb, Pb+Zn and Cd+Pb groups. Our preliminary findings suggest that the exposure to the mining-related metals impair the thyroid hormonal balance possibly by triggering thyroid allostatic-adaptative responses, affecting parameters related to peripheral thyroid hormone conversion and metabolism. **Keywords:** mining activity; hypothalamic-pituitary-thyroid axis; heavy metals, endocrine disruptors.



DISFUNÇÕES TIREOIDIANAS

2863 THYROID STORM IN AN ELDERLY PATIENT WITH MULTIORGAN FAILURE AND THERAPEUTIC LIMITATION

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Introduction: Thyroid storm is a rare, life-threatening endocrine emergency caused by acute exacerbation of thyrotoxicosis with systemic decompensation. Mortality remains high, particularly in elderly patients. Diagnosis is primarily clinical, and the Burch-Wartofsky score is widely used to support early recognition and guide immediate treatment. **Case presentation:** A 75-year-old woman with hypertension, diabetes mellitus, previous ischemic stroke, and prior diagnosis of hypothyroidism was admitted with a 15-day history of anorexia and weight loss, progressing to fever, diaphoresis, diarrhea, tachycardia, hypertension, and altered mental status, associated with muscular rigidity and intermittent tonic spasms. On admission, she was disoriented and hypoactive, with right-sided hemiparesis (previous deficit). Laboratory tests revealed microcytic anemia, hypokalemia, and hypomagnesemia. Brain computed tomography showed no acute abnormalities. She scored 65 points on the Burch-Wartofsky scale, highly suggestive of thyroid storm. Treatment with methimazole, beta-blocker, iodide, and corticosteroids was initiated. During hospitalization, she developed leukocytosis ($26,300/\text{mm}^3$), acute kidney injury (urea 353 mg/dL), pulmonary congestion, respiratory failure requiring intubation, and multiorgan dysfunction. Significant liver enzyme elevation led to methimazole discontinuation. Due to therapeutic limitation and clinical refractoriness, plasmapheresis was performed as rescue therapy. Despite intensive management, the patient died on the sixth hospital day. Thyroid function tests released posthumously confirmed primary thyrotoxicosis (T_3 348.4 ng/dL ; free T_4 5.04 ng/dL ; $\text{TSH} < 0.01 \text{ mIU/L}$). **Conclusion:** Thyroid storm in elderly patients may progress rapidly to multiorgan failure. Early clinical recognition and prompt treatment are essential, although prognosis may remain poor in severe and therapeutically limited cases. **Keywords:** thyroid storm; thyrotoxicosis; hyperthyroidism.

DISFUNÇÕES TIREOIDIANAS

2864 NEUTROPENIA ASSOCIATED WITH METHIMAZOLE USE WITH SURGICAL OUTCOME: CASE REPORT

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Introduction: Hyperthyroidism is frequently treated with antithyroid drugs, such as methimazole. Although generally safe, these drugs can cause rare adverse effects ($0.1\%–0.5\%$), including leukopenia and agranulocytosis. Early recognition is essential to prevent severe events and guide definitive treatment. We report a case of methimazole-induced leukopenia that required thyroidectomy. **Case report:** A 42-year-old female was referred to the endocrinology outpatient clinic for hyperthyroidism due to Graves' disease diagnosed 5 years earlier, with poor treatment adherence. She had used methimazole and propranolol between 2020 and 2022, discontinued the medication, and restarted approximately 6 months ago. At consultation, she reported palpitations, tremors, insomnia, conjunctival hyperemia, ocular proptosis, and 2 months of amenorrhea with an initial inconclusive beta-human chorionic gonadotropin. Laboratory evaluation revealed suppressed thyroid-stimulating hormone ($\text{TSH} < 0.01 \text{ mIU/L}$) and free thyroxine (FT_4) 5.79 ng/dL . Physical examination showed normal heart rate, diffusely enlarged thyroid, and right-predominant proptosis without active ophthalmopathy. Due to possible pregnancy, methimazole was temporarily replaced by propylthiouracil and a new beta-human chorionic gonadotropin test was requested. After one week, with a negative result, methimazole was reintroduced. The patient subsequently developed fever and lumbar pain; labs showed neutropenia (leukocytes $2.900/\text{mm}^3$; neutrophils $1.258/\text{mm}^3$), prompting drug discontinuation. Progressive neutrophil decline ($1.156/\text{mm}^3$) required temporary lithium for hyperthyroidism until surgery. Infection screening revealed no focus; TSH Receptor Antibodies (TRAb) was positive (25 UI/L). She underwent total thyroidectomy and developed postoperative hypoparathyroidism, requiring calcium carbonate and calcitriol, with good clinical recovery. **Conclusion:** Neutropenia associated with methimazole is a rare but potentially severe event. Early recognition allows prompt drug discontinuation and consideration of definitive treatment. This case highlights the importance of clinical and laboratory monitoring in patients on antithyroid drugs to ensure timely management and favorable outcomes. **Keywords:** hyperthyroidism; methimazole; neutropenia

NÓDULOS E CÂNCER DE TIREOIDE

2838 LYMPH NODE RATIO AS A QUANTITATIVE PREDICTOR OF STRUCTURAL RECURRENCE IN DIFFERENTIATED THYROID CARCINOMA: ANALYSIS OF 2,049 PATIENTS WITH NODAL ASSESSMENT

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Introduction: In differentiated thyroid carcinoma (DTC), the current AJCC/TNM staging classifies nodal disease as N1a or N1b based on anatomical compartment involvement, without considering the burden of lymph node metastasis. The lymph node ratio (LNR), defined as the number of metastatic lymph nodes divided by the total number of lymph nodes evaluated, has emerged as a promising quantitative predictor capable of refining prognostic stratification. **Objective:** To evaluate the accuracy of the lymph node ratio in predicting structural recurrence in DTC patients in whom pathological lymph node assessment was available, and to determine an optimal cutoff for clinical application. **Methods:** Retrospective analysis of 2,049 patients who underwent total thyroidectomy for DTC at a tertiary oncology center (2014–2024) and had pathological lymph node evaluation (total lymph nodes assessed > 0). The LNR was calculated as the number of positive lymph nodes divided by the total number of lymph nodes assessed. ROC analysis was performed to determine discriminative accuracy and the optimal cutoff. Multivariate logistic regression was performed, adjusting for pT stage, sex, and age. **Results:** Among 2,049 patients (mean 9.9 lymph nodes evaluated per patient), 64 (3.1%) developed structural recurrence over a median follow-up of 9.7 months. The LNR demonstrated an AUC of 0.710 for predicting recurrence. The optimal cutoff was 0.11 (sensitivity 76.6%, specificity 62.9%). Recurrence rates across LNR strata were: LNR 0% (ratio = 0), 1.2%; LNR 1%–10%, 0.0%; LNR 11%–20%, 5.3%; LNR 21%–50%, 4.6%; and LNR > 50%, 8.1% ($p < 0.001$). By absolute positive lymph node count: 0 nodes, 1.2%; 1–5, 4.1%; and > 6 nodes, 9.1%. On multivariate analysis, LNR > 0.11 was an independent predictor of recurrence (OR: 3.96; 95% CI: 2.22–7.06; $p < 0.001$), along with male sex (OR: 1.87; 95% CI: 1.12–3.13; $p = 0.017$). Advanced pT stage did not reach significance. **Conclusion:** The LNR is a robust quantitative predictor of recurrence in DTC, with an AUC of 0.710 and a clinically applicable cutoff of 11%. Its incorporation into postoperative risk stratification may complement the anatomical N1a/N1b classification and help identify patients requiring closer surveillance. **Keywords:** lymph node metastasis; differentiated thyroid cancer; lymph node ratio.

DISFUNÇÕES TIREOIDIANAS

2740 THYROID EYE DISEASE IN BRAZIL: INSIGHTS FROM A DECADE OF CLINICAL AND LABORATORY FOLLOW-UP IN A SINGLE CENTER

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Introduction: Thyroid Eye Disease (TED) is an autoimmune disorder most commonly associated with Graves' disease (GD), affecting up to 40% of patients. Although moderate-to-severe forms are less frequent, they are associated with significant functional and aesthetic morbidity. TED pathophysiology involves immune-mediated activation of orbital fibroblasts, primarily driven by thyroid-stimulating hormone receptor antibodies (TRAb) and insulin-like growth factor 1 receptor (IGF-1R). **Objective:** To identify clinical and laboratory predictors of onset, progression, and therapeutic response in patients with moderate-to-severe TED. **Methods:** This retrospective cohort study analyzed 36 patients followed from 2015 to 2025 at a Brazilian tertiary referral center. Clinical outcomes were categorized into five groups, with categories I–III considered favorable. Associations between variables and outcomes were evaluated using Wilcoxon, chi-square, or Fisher's exact tests ($p < 0.05$). **Results:** Majority were female (64%), with median age at GD diagnosis of 50 years and TED onset at 55 years. Most cases of TED occurred after (53%) or concurrently (42%) with the diagnosis of hyperthyroidism. Smoking was reported in 40%. At TED onset, 75% were receiving antithyroid drugs. A quarter underwent radioiodine, with 44.5% experiencing disease worsening. Inflammatory resolution was achieved in 94%, and 69% attained favorable outcomes. No associations were found with sex, age, body mass index, smoking status, thyroid volume, comorbidities, or baseline Clinical Activity Score (CAS). Surprisingly, a baseline TRAb greater than 20 times was significantly associated with favorable outcomes. Final CAS was a strong prognostic indicator: patients with CAS ≤ 1 achieved favorable outcomes, whereas none with persistent inflammatory activity did. **Conclusion:** Most patients experienced meaningful clinical improvement and therapeutic response. Contrary to previous reports, higher baseline TRAb levels were associated with better outcomes. These findings highlight the need for individualized and longitudinal management, emphasizing inflammatory control and thyroid function stability. Larger studies are needed to confirm prognostic markers and guide treatment strategies in TED, particularly in Brazil. **Keywords:** thyroid eye disease; hyperthyroidism; Graves disease.

DISFUNÇÕES TIREOIDIANAS

2742 PITUITARY APOPLEXY IN A PATIENT WITH HYPERTHYROIDISM DUE TO TOXIC MULTINODULAR GOITER — A CASE REPORT

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Introduction: Pituitary adenomas account for up to 10% of intracranial tumors. A rare but potentially severe complication is pituitary apoplexy, characterized by acute hemorrhage or infarction within the tumor, with an estimated incidence of 2%–10% among adenomas. This condition may present with sudden headache, visual deficits, and signs of acute pituitary insufficiency. Toxic multinodular goiter is a common cause of thyrotoxicosis in the elderly, responsible for approximately 15%–20% of hyperthyroidism cases, particularly in iodine-deficient regions. **Case report:** An 82-year-old woman presented with gait difficulty preceded by fatigue. Initial suspicion of stroke prompted brain MRI, which revealed a sellar lesion. Laboratory evaluation showed significant hyponatremia (Na 124 mEq/L). Endocrine assessment included pituitary hormone measurements and dedicated sellar MRI, demonstrating a hemorrhagic pituitary macroadenoma consistent with apoplexy. Hormonal evaluation showed gonadotropin deficiency (FSH 2.6; LH 0.95), relative cortisol deficiency (9.8), mildly elevated prolactin (30.2), attributed to stalk compression, and unexpectedly suppressed TSH (<0.01) with normal free T₄ (0.98). Thyroid function tests were repeated, confirming the findings. Thyroid scintigraphy with ^{99m}Tc demonstrated autonomous nodular uptake consistent with toxic multinodular goiter. **Conclusion:** The patient received hydrocortisone replacement, later transitioned to prednisone 10 mg daily. Thyrotoxicosis was treated with methimazole 20 mg, subsequently reduced to 10 mg. The coexistence of toxic multinodular goiter and panhypopituitarism is extremely rare and not part of the classical pathophysiological spectrum of these conditions. Toxic multinodular goiter results from autonomous thyroid hormone production independent of pituitary regulation, leading to TSH suppression via negative feedback. In contrast, panhypopituitarism typically causes central hypothyroidism. No causal association between these entities has been established. When both are present, they should be investigated as independent conditions, as observed in this case. **Keywords:** toxic multinodular goiter; pituitary apoplexy; hyperthyroidism.

DISFUNÇÕES TIREOIDIANAS

2745 POPULATION MATTERS: THE TERT PROMOTER RS2853669 IS RARE IN PAPILLARY THYROID CARCINOMA FROM NORTHEAST BRAZIL

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Introduction: The rs2853669 (–245 T>C) single nucleotide polymorphism (SNP) in the TERT promoter is a functional variant that may influence telomerase expression by altering transcription factor binding. Telomerase activation is involved in cellular immortalization and tumor progression. In papillary thyroid carcinoma (PTC), the C allele frequency ranges from 25% to 40% in European and Asian populations. The polymorphism has been associated with tumor aggressiveness and prognosis, especially when combined with TERT promoter hotspot mutations (C228T, C250T) or BRAF V600E. Data from Latin American populations remain limited, and regional studies are necessary given the genetic heterogeneity of Brazil. **Objective:** To determine the genotypic and allelic frequencies of rs2853669 in patients with PTC treated at a referral oncology hospital in Bahia, Brazil, and to evaluate its association with clinicopathological features and ATA risk stratification. **Methods:** This cross-sectional study included 101 patients with histologically confirmed PTC. Clinical data were obtained from medical records and included age, sex, tumor size, histological variant, extrathyroidal extension, lymph node involvement, and ATA risk classification. Genomic DNA was extracted from tumor samples, and rs2853669 genotyping and TERT promoter mutation analysis were performed using validated molecular methods. Associations were analyzed using appropriate statistical tests ($p < 0.05$). **Results:** The mean age was 48.2 ± 14.5 years, and 91.1% were female. All cases were wild-type for TERT promoter hotspot mutations. The rs2853669 polymorphism was detected in three patients, with genotypic frequencies of 2% (T/C) and 1% (C/C), and allelic frequencies of 98% (T) and 2% (C). No significant association was observed between the C allele and clinicopathological variables. **Conclusion:** The rs2853669 polymorphism showed a very low C allele frequency in patients with papillary thyroid carcinoma from Bahia, Brazil, markedly lower than that reported in European and Asian populations. This difference may reflect population-specific genetic backgrounds and the high ethnic admixture in Brazil. Although the absence of complete BRAF mutation data is a limitation, these findings contribute to the regional molecular characterization of thyroid cancer and highlight the importance of population-based studies to clarify the clinical relevance of TERT promoter variants. **Keywords:** thyroid cancer; TERT; rs2853669.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2746 A MISSING PIECE IN THYROID DYSGENESIS? EXPLORING DIO2 POLYMORPHISMS IN CONGENITAL HYPOTHYROIDISM

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Introduction: Congenital hypothyroidism (CH) is the most common screened neonatal endocrine disorder, with thyroid dysgenesis (TD) causing ~85% of cases. Persistent impairment despite adequate levothyroxine (LT4) suggests serum TSH/T4 may not reflect tissue T3 levels. This is relevant in thyroidectomized patients, where type 2 deiodinase (DIO2) variants affect tissue T3 despite euthyroidism. Since DIO2 converts T4 to T3, polymorphisms like Thr92Ala (rs225014) and ORFa-Gly3Asp (rs12885300) might modulate intracellular signaling in TD, though their role remains unclear. **Objective:** To determine the prevalence of DIO2 rs12885300 and rs225014 polymorphisms in Brazilian children with TD and their association with neonatal biochemical CH severity. **Methods:** This cross-sectional study included 34 children with CH due to TD identified through the Neonatal Screening Program of Apae-Salvador, Brazil. Thyroid dysgenesis phenotypes were confirmed by ultrasound, scintigraphy and thyroglobulin measurement. Neonatal clinical and biochemical data were obtained from screening and early follow-up records, and genotyping of DIO2 polymorphisms was performed using peripheral blood DNA and TaqMan® assays. **Results:** Of the 34 patients, 22 (65%) were female. Thyroid dysgenesis phenotypes included hypoplasia (34%), ectopy (32%), hemiagenesis (17%), and agenesis (17%). The DIO2 ORFa-Gly3Asp polymorphism was identified only in heterozygosity in nine patients (26%) and showed non-significant trends toward lower free and total T4 and higher TSH levels at diagnosis. The DIO2 Thr92Ala polymorphism was present in 27 patients (79%), either in heterozygosity (56%) or homozygosity (28%), with no significant differences in neonatal biochemical parameters. Overall, no significant association was observed between DIO2 variants and neonatal biochemical severity of TD. **Conclusion:** DIO2 polymorphisms were frequent in Brazilian children with TD but showed no impact on initial CH presentation. Correlations with hormone levels were limited to neonatal confirmatory testing. Future studies should assess long-term outcomes (stabilization, L-T4 dose/kg, and biochemical control) not evaluable in this retrospective study. **Keywords:** congenital hypothyroidism; DIO2 polymorphism; thyroid dysgenesis.

DISFUNÇÕES TIREOIDIANAS

2747 SEVERE AUTOIMMUNE HYPOTHYROIDISM PRESENTING WITH GROWTH DECELERATION, DELAYED SKELETAL MATURATION, AND PUBERTAL DELAY IN A 13-YEAR-OLD BOY

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Introduction: In pediatric practice, hypothyroidism may present primarily as growth deceleration, while other manifestations can be subtle or overlooked. Severe, long-standing hypothyroidism is uncommon in children and adolescents, and delayed recognition can compromise linear growth and pubertal progression. **Case presentation:** A 13-year-old male was evaluated for reduced growth velocity, having declined from approximately the 50th percentile to the 3rd percentile. Physical examination showed height 142 cm (Z-score -1.96), body mass index (BMI) 18.6 kg/m² (~P50), xerosis, and a palpable grade 2 goiter. Heart rate was 80 beats per minute, regular. Pubertal assessment demonstrated Tanner stage II with testicular volume 6 mL, pubic hair Tanner II, and a prepubertal penile appearance. Initial thyroid function tests revealed thyroid-stimulating hormone (TSH) 554 µIU/mL (reference 0.23–5.20) with free thyroxine (FT4) 0.16 ng/dL (reference 0.70–1.89), consistent with severe hypothyroidism; repeat testing confirmed TSH 630 µIU/mL, FT4 0.16 ng/dL, and free triiodothyronine (FT3) 1.31 pg/mL (reference 2.00–4.20). Autoimmune etiology was supported by thyroid peroxidase antibodies (TPOAb) > 13,000 IU/mL (positive > 60) and thyroglobulin antibodies (TgAb) 53.5 IU/mL (positive > 4.5). Thyroid ultrasonography showed a hypoechoic and heterogeneous gland with pseudonodules. Additional findings included low insulin-like growth factor 1 (IGF-1) 44.7 ng/mL (reference 133–471), hemoglobin 10.6 g/dL, creatinine 1.17 mg/dL, and negative celiac serology. Bone age was 8 years, markedly delayed relative to chronological age, indicating substantial impact on skeletal maturation. **Conclusion:** This case emphasizes that hypothyroidism must be considered early in the differential diagnosis of growth deceleration, even when classic systemic symptoms are not prominent. Profound TSH elevation, severe FT4 deficiency, positive thyroid autoantibodies, and markedly delayed bone age support prolonged autoimmune hypothyroidism with clinically relevant effects on growth and pubertal development. Timely recognition and appropriate management are critical to reduce the risk of persistent short stature and pubertal disruption. **Keywords:** hypothyroidism; autoimmune; reduced growth velocity.



NÓDULOS E CÂNCER DE TIREOIDE

2752 RADIOIODINE IN ADULTS WITH LOW-RISK DIFFERENTIATED THYROID CANCER: A SYSTEMATIC REVIEW AND META-ANALYSES

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Introduction: The use of postoperative radioactive iodine (RAI) in adults with low-risk differentiated thyroid cancer (DTC) remains debated. We aim to compare outcomes in low-risk DTC patients treated with or without RAI following thyroidectomy. **Methods:** We searched PubMed, Embase, LILACS, and the Cochrane Library for studies involving adults with low-risk DTC (ATA 2015) who underwent total or subtotal thyroidectomy, comparing outcomes between those who received radioiodine and those who did not. Random-effects models were used to combine odds ratios (ORs) with 95% confidence intervals (CIs). We used the Cochrane Q statistic and I² statistic to assess heterogeneity across studies. Statistical analyses were performed using R software and RStudio (version 2024.04.1+748; R Core Team, Viena, Austria). **Results:** Two randomized controlled trials and 13 observational cohorts were included, comprising 6,175 patients, of whom 3,664 (59.3%) received RAI. Excellent response was not statistically significant (OR 1.18; 95% CI 0.70–1.99; I² = 78%; p = 0.54). RAI was not associated with reduced overall recurrence (OR 0.75; 95% CI 0.42–1.36; p = 0.35) or local recurrence (OR 1.11; 95% CI 0.49–2.52; p = 0.80). Distant metastasis was similar between groups (OR 0.45; 95% CI 0.18–1.11; p = 0.08). All-cause mortality did not differ significantly between groups (OR 1.18; 95% CI 0.42–3.37; p = 0.75). **Conclusion:** In adults with low-risk DTC, postoperative RAI was not associated with improved recurrence, metastasis, or mortality outcomes. Our results support current guideline recommendations favoring a selective, individualized approach to RAI use in low-risk disease. **Keywords:** radioactive iodine; differentiated thyroid cancer; thyroidectomy.

AUTOIMUNIDADE

2753 SEVERE TED AFTER TOTAL THYROIDECTOMY: A RARE COMPLICATION

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Introduction: Thyroid eye disease (TED) is a rare manifestation of thyroid autoimmunity closely associated with Graves' disease (GD). Given the close relation between both conditions, surgical approach for GD results in significant TED improvement for most patients. **Case report:** K.C.B., a 46-year-old woman with a history of prior tobacco use, was admitted to the endocrinology service in June 2025 due to mixed hepatitis suspected to be methimazole-induced liver injury (DILI). The patient reported a recent diagnosis of hyperthyroidism and began the use of methimazole 40 milligrams one month prior. Initial evaluation reviewed signs of moderate to severe according to EUGOGO, with Clinical Activity Score (CAS) of 2 points (pts), proptosis 21 mm and 17 mm, eye gap 10 mm and 9 mm (respectively right and left eye) and intermittent diplopia. The biochemical evaluation was consistent with acute hepatitis. Thyroid function showed suppressed TSH: 0.01 μ IU/mL (Ref: 0.27–4.20 uIU/mL) and increased FT4: 1.94 ng/dL (Ref. 0.93–1.7 ng/dL) with positive titles of thyroid receptor antibodies (TRAb): 5.4 IU/L (Ref. < 3.10). Orbital magnetic resonance imaging (MRI) demonstrated thickening of the extraocular muscles, more pronounced on the left, with associated proptosis. Ursodeoxycholic acid at 15 mg/kg/day was prescribed for DILI management with substantial improvement in liver function. Due to the presence of TED and a serious adverse effect to antithyroid drugs, the patient underwent total thyroidectomy (TT) for GD management. After two months, she presented with TED progression, CAS of 6 pts, proptosis of 20 mm and 18 mm, and eyelids of 8 mm and 9 mm, associated with intermittent diplopia, compromised Ishihara test, and strabismus. Orbital MRI showed no optic nerve compression. Laboratory revealed increased TRAb levels (6.68 IU/L) with TSH: 6.4 μ IU/mL and FT4: 0.8 ng/dL. The patients received intravenous steroids with 4.5 g of methylprednisolone for 4 weeks, presenting improvement in TED with CAS of 2 pts, reduction in proptosis of 5 mm and 2 mm in the right and left eye, respectively. However, treatment was interrupted due to a second onset of hepatitis. At present, she remains with persistently elevated TRAb 6.78 IU/L and active TED awaiting surgical orbital decompression. **Conclusion:** This case reports a rare exacerbation of TED after TT, outlining that although deeply connected in a physiopathological manner, TED and GD may behave differently to the same therapy. **Keywords:** thyroid eye disease; Graves' disease; autoimmunity.



AUTOIMUNIDADE

2758 CLINICAL-LABORATORY, THERAPEUTIC, AND LONGITUDINAL PROFILES OF THYROID EYE DISEASE IN A BRAZILIAN TERTIARY CENTER AND DEVELOPMENT OF A STANDARDIZED INSTRUMENT FOR LONGITUDINAL FOLLOW-UP

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Introduction: Thyroid eye disease (TED) has a heterogeneous clinical course with frequent dissociation between inflammatory activity and disease severity, which hampers longitudinal assessment, particularly in the context of non-standardized clinical records. **Objective:** To describe the clinical-laboratory, therapeutic, and longitudinal profiles of patients with TED followed at a tertiary referral center and to develop a standardized data collection instrument. **Methods:** This retrospective observational study included 40 patients with TED followed at an endocrinology service in Goiás, Brazil. Demographic variables, comorbidities, characteristics of the underlying thyroid disease, inflammatory activity assessed by the Clinical Activity Score (CAS), clinical severity according to EUGOGO criteria, radiological findings, treatments and evolution were analyzed. **Results:** The study showed a predominance of female patients, with a mean age of 43.2 ± 13.7 years, consistent with previous reports. High prevalences of overweight/obesity and dyslipidemia were observed, and 25% of patients were smokers. Hyperthyroidism was the predominant thyroid functional status (72.5%), with variable TRAB levels at diagnosis (11.2 ± 14.2 times the upper limit of normal). Higher inflammatory activity was significantly associated with greater clinical severity, with moderate-to-severe forms predominating in the active group (68.4% vs. 4.8%; $p < 0.001$), with no significant association with other analyzed variables. Mixed and myogenic radiological patterns were most frequent, without correlation with CAS. Intravenous glucocorticoid pulse therapy showed a significant association with TED activity and severity, confirming its central role in moderate-to-severe cases, with sustained clinical response during follow-up. The analysis revealed substantial incompleteness and heterogeneity of medical records, leading to the development of a standardized data collection instrument comprising baseline and follow-up forms, longitudinal tables for evolution, and a structured quality-of-life questionnaire, designed based on identified gaps of the research and refined through expert consensus. **Conclusion:** In addition to characterizing TED profiles, this study identifies relevant limitations in retrospective data collection and proposes a standardized instrument as a central outcome, with potential to improve longitudinal care, reduce information loss, and enhance therapeutic decision-making. **Keywords:** Graves orbitopathy; thyroid eye disease; data collection.

DISFUNÇÕES TIREOIDIANAS

2766 TREATMENT TRAJECTORIES AND REMISSION RATES IN GRAVES' DISEASE

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Introduction: The effectiveness of antithyroid drugs (ATD), radioactive iodine (RAI), and surgery for the treatment of Graves' hyperthyroidism is well established. However, there is limited real-world evidence regarding long-term treatment trajectories, including remission rates, need for additional therapies, and progression to definitive treatments requiring levothyroxine replacement. **Objective:** To characterize treatment trajectories and long-term clinical outcomes in patients with Graves' disease managed at a tertiary care center. **Methods:** This retrospective cohort study included patients with Graves' disease followed at a tertiary care center. Clinical records were reviewed to determine initial treatment modality, subsequent therapies, remission rates, recurrence, demographic characteristics, and comorbidities. **Results:** A total of 196 patients were included, with a mean follow-up of 1246 days (interquartile range 714–1356). Most patients were female (94%), and 14% had a history of tobacco use. Median TSH at baseline was $2.57 \mu\text{IU/mL}$ (0.01–2.69), median FT4 was 1.75 ng/dL (1.12–2.01), and median thyroid volume was 27.84 mL (10.1–31.1). Antithyroid drugs were the initial therapy in 83.7% of patients, while 13.3% received RAI and 3.1% underwent surgery as initial treatment. Among patients initially treated with ATD, 4.9% subsequently received RAI and 0.6% underwent total thyroidectomy. Among patients initially treated with RAI, 3.8% required additional ATD therapy and 3.8% underwent surgery. Among patients who experienced relapse, 50% were treated with RAI and 50% received a second course of ATD. At 12 months, 185 patients remained in follow-up: 73.5% were receiving ATD, 16.8% had received RAI, 2.7% had undergone surgery, and 7.0% were in remission. At 24 months, among 136 patients, 73.5% remained on ATD, 17.7% had received RAI, 2.7% had undergone surgery, and 7.1% were in remission. At 36 months, among 101 patients, 74.3% were receiving ATD, 17.8% had received RAI, 2.0% had undergone surgery, and 5.9% were in remission. **Conclusion:** This real-world cohort demonstrates a clear preference for antithyroid drugs as both initial and long-term therapy for Graves' disease. In patients with disease relapse, both RAI and repeat ATD therapy were commonly used, with comparable utilization patterns. Remission rates remained relatively low over long-term follow-up, highlighting the chronic nature of Graves' disease and the need for individualized treatment strategies. **Keywords:** Grave's disease; hyperthyroidism; Grave's disease treatment.

NÓDULOS E CÂNCER DE TIREOIDE

2769 REDIFFERENTIATION THERAPY IN RADIOIODINE-REFRACTORY THYROID CANCER: FIRST BRAZILIAN REAL-WORLD EXPERIENCE

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Introduction: Redifferentiation therapy (RDT) using targeted kinase inhibitors has emerged as a strategy to restore radioiodine (RAI) uptake in radioiodine-refractory differentiated thyroid carcinoma (RAIR-DTC), challenging the concept of irreversible refractoriness. Real-world data remain scarce, particularly in Latin America. We report the first Brazilian clinical experience with RDT in routine practice. **Methods:** This observational, longitudinal retrospective study included eight patients with RAIR-DTC treated since 2024 with a single course of RDT using selective MEK, BRAF, or RET inhibitors. The primary endpoint was restoration of RAI uptake. Secondary endpoints included disease control rate (DCR) after therapeutic RAI and safety profile. **Results:** Patients' ages ranged from 11 to 76 years (male:female ratio 1:1). Four patients harbored BRAF^{V600E} mutations, one had MKRN1::BRAF fusion, one had NRAS^{Q61R} mutation, and two had RET fusions (CCDC6::RET and NCOA4::RET). The RDT strategy included: (i) BRAF^{V600E} inhibitors in three patients; (ii) MEK inhibitor monotherapy in two patients (including one with BRAF fusion); (iii) combined BRAF and MEK inhibition in one patient; and (iv) selective RET inhibitors in two patients. Following RDT, most patients demonstrated restoration of iodine uptake on diagnostic and post-therapy scans. Median administered RAI activity was 150 mCi. Objective response rate and progression-free survival will be presented at the meeting. The most frequent adverse events were acneiform rash, mucositis, and paronychia, consistent with known toxicity profiles. **Conclusion:** In this first Brazilian real-world series, RDT restored RAI uptake in patients previously considered refractory, enabling renewed therapeutic use of RAI. These findings reinforce that refractoriness may be reversible in molecularly selected patients and support prospective studies to better define optimal candidates and long-term outcomes. **Keywords:** thyroid cancer; redifferentiation therapy; radioiodine-refractory.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2770 DOES DECLINING FREE T3 DRIVE SARCOPENIA? EVIDENCE FROM A COMMUNITY-BASED COHORT OF ELDERLY WOMEN

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Introduction: Aging is associated with progressive changes in body composition, including reduced lean mass and increased adiposity, contributing to sarcopenia and sarcopenic obesity. Serum free triiodothyronine (fT3) levels also decline with age, reflecting reduced peripheral thyroid hormone conversion. Given the role of thyroid hormones in muscle metabolism, fT3 has been proposed as a potential modulator of muscle mass and function. However, data in community-dwelling elderly women remain limited and inconsistent. **Objective:** To evaluate the association between serum fT3 levels and appendicular lean mass (ALM), weight-adjusted skeletal muscle index (wSMI), and functional performance in elderly women. **Methods:** This cross-sectional study included community-dwelling elderly women. Participants underwent clinical evaluation, anthropometric measurements, and functional assessments (handgrip strength and gait speed). Body composition was measured by dual-energy X-ray absorptiometry (DXA). Serum TSH, fT4, and fT3 were assessed by chemiluminescence. Low muscle mass was defined using established ALM and wSMI cutoffs. Group comparisons were performed using appropriate parametric or non-parametric tests. **Results:** Forty-two women were included (mean age 69.1 ± 4.8 years). The median fT3 levels were 2.69 pg/mL (IQR: 2.4-2.9). The prevalence of low muscle mass was 23.8% by ALM and 45.2% by wSMI. Women classified as low wSMI exhibited significantly higher BMI, waist circumference, and fat mass index, as well as lower gait speed compared to those with normal wSMI. No significant association was found between serum fT3 levels and muscle mass indices (ALM or wSMI) or functional performance measures. **Conclusion:** In predominantly younger elderly women, serum fT3 levels were not associated with skeletal muscle mass or functional capacity. wSMI appeared more sensitive than ALM for identifying early adiposity-related muscle impairment. Longitudinal studies are needed to clarify the role of thyroid hormones in age-related muscle decline. **Keywords:** free T3; sarcopenia; elderly.



AUTOIMUNIDADE

2771 BEYOND ORBITAL INFLAMMATION: OCULAR SURFACE DISEASE IN THYROID EYE DISEASE

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Introduction: Thyroid eye disease (TED) is frequently associated with ocular surface alterations resulting from inflammation, eyelid retraction, lagophthalmos, and tear film instability. Ocular surface disease (OSD) contributes significantly to morbidity in these patients, even during inactive phases of TED. However, the relationship between disease activity and objective OSD parameters remains poorly defined. **Objective:** To evaluate the prevalence and severity of ocular surface disease (OSD) in patients with TED during active and inactive phases and to determine correlations among different OSD diagnostic tests. **Materials and methods:** This multicenter, cross-sectional, observational study included patients with TED evaluated at two tertiary hospitals in Salvador, Brazil. All participants underwent standardized ophthalmologic assessment including Clinical Activity Score (CAS), Schirmer test, tear break-up time (BUT), fluorescein and lissamine green staining, and evaluation of meibomian gland dysfunction (MGD). Symptoms were assessed using the Ocular Surface Disease Index (OSDI). **Results:** Fifty-one patients (102 eyes) were evaluated (mean age 47.9 ± 13.2 years; female-to-male ratio 2.9:1). Most patients (82.4%) were in the inactive phase (CAS < 3). Normal Schirmer test results were observed in 88.2% of eyes, while 88.2% showed abnormal BUT values. OSDI scores were higher in active TED (18.6 ± 13.1) compared to inactive disease (14.9 ± 10.9). MGD was more frequent in active TED (33.3%) than in inactive cases (11.9%). **Conclusion:** OSD is highly prevalent in patients with TED, particularly during the active phase. Inconsistent correlations among diagnostic tests reinforce the multifactorial nature of OSD and support the need for combined diagnostic approaches. **Keywords:** thyroid eye disease; dry eye; ocular surface.

NÓDULOS E CÂNCER DE TIREOIDE

2778 COMPARATIVE VOLUME REDUCTION RATE BETWEEN BETHESDA II AND MOLECULARLY NEGATIVE INDETERMINATE THYROID NODULES IN RESPONSE TO ENERGY-BASED ABLATION

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Introduction: Energy-based ablation (EBA) is a consolidated and widely utilized treatment for thyroid nodules with very low risk of malignancy (RoM), particularly those categorized as Bethesda II on cytology. Molecular tests allow for the reclassification of indeterminate thyroid nodules (ITNs; Bethesda III/IV) as “molecularly benign” with a low risk of malignancy (<4%) comparable to Bethesda II, suggesting the possible use of EBA in these cases. Nevertheless, data regarding the efficacy and safety of EBA in these molecularly defined cases remain scarce. **Objective:** To compare the performance of EBA in Bethesda II nodules and in ITNs with benign molecular results (mir-THYpe full negative), and to analyze these outcomes in relation to follow-up volume reduction. **Methods:** Two complementary evaluations were conducted. In the first analysis, 23 Bethesda II nodules and 31 ITNs with benign molecular results (mir-THYpe full negative) treated with EBA were assessed at 6 months to compare volume reduction rate (VRR). In the second analysis, the cohort of molecularly negative ITNs was monitored for up to 24 months to describe VRR evolution over time. Procedure-related complications and need for additional intervention were recorded. **Results:** At 6 months, mean VRR was 57.63% in Bethesda II nodules and 64.67% in ITNs with mir-THYpe full negative results ($p = 0.27$), indicating comparable efficacy between groups. Among ITNs with extended follow-up, a sustained reduction pattern was observed, with mean VRRs of 69.0% at 12 months, 71.4% at 18 months, and 72.4% at 24 months. One patient required reintervention, and no major complications were identified. **Conclusion:** These preliminary findings indicate that EBA in ITNs reclassified as molecularly benign by mir-THYpe full negative results provides volume reduction rates comparable to those observed in Bethesda II nodules, with a continued increase in VRR over the subsequent 18 months of follow-up. These results demonstrate the feasibility and promising potential of using molecular tests to select cases ITNs eligible for EBA. **Keywords:** ablation; molecular testing; indeterminate thyroid nodules.



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2782 RISK FACTORS FOR ACTIVITY AND SEVERITY IN GRAVES' ORBITOPATHY: A BRAZILIAN RETROSPECTIVE COHORT

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Introduction: Thyroid eye disease, particularly Graves' orbitopathy (GO), is the most relevant extrathyroidal manifestation of Graves' disease (GD). Current or past inflammatory activity influences clinical presentation, which ranges from mild forms to moderate-to-severe cases and, less frequently, vision-threatening disease. In Brazil, clinical data on GO remain limited, and few studies describe factors associated with disease activity or severity. **Objective:** To characterize the initial presentation of GO in a tertiary center and to assess clinical factors associated with greater inflammatory activity or structural severity. **Methods:** Observational, retrospective and descriptive study. The medical records of forty patients followed at the Endocrinology Outpatient Clinic of the Clinical Hospital of the Federal University of Goiás were evaluated. Clinical and laboratory data were collected, including smoking status, dyslipidemia, TRAb levels, GD treatment modality, and time between ocular symptom onset and treatment initiation. Activity was assessed using the Clinical Activity Score (CAS), and severity was classified according to EUGOGO criteria. **Results:** Most patients were women (92.5%), with a mean age of 43.2 years and a mean TRAb of 11.2 ± 14.2 ULN, consistent with previously published cohorts. Mild GO was the most frequent presentation (65%). No statistically significant associations were found between smoking, dyslipidemia, TRAb levels, or prior radioactive iodine therapy and increased disease activity or severity, likely influenced by the small sample size. Patients with active GO showed a shorter interval between symptom onset and treatment. A significant association was observed between activity and severity: 95.2% of patients with CAS < 3 were classified as mild, whereas 68.4% of those with CAS ≥ 3 were classified as severe. **Conclusion:** The sample presented an average age between 40 and 50 years, a female predominance, and a prevalence of mild cases, similar to other populations studied. The time between symptom onset and treatment initiation was significantly shorter in patients with CAS ≥ 3 , consistent with the recommended therapeutic window. Inflammatory activity and disease severity were closely linked. The study provides valuable data on GO in a Brazilian setting and highlights the need for multicenter and prospective studies with larger samples to improve understanding of the disease and guide clinical care. **Keywords:** Graves' orbitopathy; graves' disease; risk factors.

AUTOIMUNIDADE

2783 CLINICAL AND EPIDEMIOLOGICAL PROFILE AND THERAPEUTIC RESPONSE TO DIFFERENT PULSE THERAPY REGIMENS IN THYROID EYE DISEASE

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Introduction: Thyroid eye disease (TED) is an autoimmune condition associated with Graves' disease and may result in significant functional impairment. Intravenous methylprednisolone pulse therapy is the first-line treatment for active, moderate-to-severe forms; however, clinical response is variable. **Objective:** To describe the clinical and epidemiological profile and to evaluate therapeutic response in patients with TED treated with different cumulative doses of intravenous methylprednisolone. **Methods:** This retrospective observational study was conducted at a tertiary referral outpatient clinic and included 40 patients with TED. Participants were stratified according to cumulative methylprednisolone dose (<4.5 g vs. ≥ 4.5 g). Clinical characteristics, thyroid status, Clinical Activity Score (CAS), severity criteria, need for adjunctive therapies, and outcomes after one year of follow-up were assessed. **Results:** Patients receiving ≥ 4.5 g were significantly older than those treated with <4.5 g (52.2 ± 7.6 vs. 39.8 ± 11.5 years; $p = 0.045$), suggesting an association between advanced age and greater clinical severity. Indication for pulse therapy was strongly associated with higher activity and severity at diagnosis ($p < 0.001$), with diplopia being the main initial severity criterion (68.8%). After one year, 85.7% of patients showed resolution of severity criteria, regardless of cumulative dose. However, 46.2% maintained CAS ≥ 3 , particularly among those treated with ≥ 4.5 g, likely reflecting greater baseline severity and a slower or incomplete clinical response. Thyroid function control was essential, with 69.2% achieving euthyroidism at one year, which was also associated with better severity control. Second-line therapies were required in 7.5% of cases, including pentoxifylline, colchicine, and mycophenolate mofetil, indicating refractoriness to conventional treatment and gaps in therapeutic standardization. **Conclusion:** Intravenous methylprednisolone pulse therapy resulted in high remission of severity criteria at one year (85.7%); however, nearly half of patients remained with CAS ≥ 3 , highlighting the need for improved response stratification and optimized management of refractory cases. Higher cumulative doses (≥ 4.5 g) were more frequent among older and moderate-to-severe patients. Achievement of euthyroidism was associated with better clinical outcomes, reinforcing the importance of thyroid function control in TED management. **Keywords:** Graves ophthalmopathy; methylprednisolone; therapeutic response.



CIRURGIA DA TIREOIDE

2784 TRANSORAL ROBOTIC SURGERY (TORS) FOR THE MANAGEMENT OF A 50 MM RETROPHARYNGEAL LYMPH NODE METASTASIS FROM PAPILLARY THYROID CARCINOMA

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Introduction: Retropharyngeal lymph node metastasis (RLNM) from papillary thyroid carcinoma (PTC) is an infrequent clinical entity, with a reported prevalence below 0.5%. The retropharyngeal space is anatomically challenging due to its deep position and proximity to the internal carotid artery and lower cranial nerves. Traditional management, often requiring aggressive transcervical approaches or mandibulotomy, is associated with significant postoperative morbidity and functional impairment. Transoral Robotic Surgery (TORS) has emerged as a minimally invasive alternative, utilizing 3D visualization and articulated instrumentation to facilitate oncological resection in constrained spaces, potentially shifting the surgical paradigm for such high-risk pathologies. **Case report:** A 26-year-old male with a history of PTC, post-thyroidectomy and neck dissection, presented with a massive 50 mm right-sided retropharyngeal mass identified during surveillance. The lesion caused significant medial compression of the oropharyngeal airway and abutted the prevertebral fascia. Given the tumor's volume and risk of neurovascular injury, TORS was performed using the Da Vinci Xi system. Under mouth retractor, the robotic platform provided superior depth perception, enabling the identification of the surgical plane between the tumor capsule and the superior pharyngeal constrictor muscle. Monopolar curved scissors were employed for meticulous dissection, ensuring safe separation from the carotid sheath and parapharyngeal planes. Despite the intimate vascular contact, stable robotic articulation facilitated complete en bloc resection of the 50 mm node without capsule rupture. Postoperative recovery was uneventful; the patient experienced no cranial nerve deficits, dysphagia, or airway compromise, permitting early hospital discharge. **Conclusion:** This case demonstrates that giant retropharyngeal metastases can be safely managed through a minimally invasive robotic approach. TORS overcomes the technical limitations of traditional open surgeries by providing the dexterity required for oncological resection within confined anatomical corridors. This technique achieves complete tumor clearance with significantly reduced morbidity, even for masses of exceptional volume. We propose the robotic route as a robust, first-line treatment for voluminous retropharyngeal recurrences in PTC, establishing a new standard for functional and oncological preservation in complex thyroid cancer management. **Keywords:** transoral robotic surgery (TORS); papillary thyroid carcinoma; retropharyngeal metastasis.

AUTOIMUNIDADE

2785 SEVERE PRIMARY HYPOTHYROIDISM ASSOCIATED WITH THYROID AUTOIMMUNITY-ASSOCIATED ENCEPHALOPATHY: A DIAGNOSTIC CHALLENGE IN A PATIENT WITH REFRACTORY SEIZURES

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Introduction: Primary hypothyroidism, classically associated with metabolic manifestations, may be part of the spectrum of Hashimoto's encephalopathy, a rare entity characterized by seizures, cognitive impairment, and a fluctuating clinical course, frequently associated with elevated antithyroid antibody titers and responsiveness to immunosuppressive therapy. **Case report:** A 41-year-old previously healthy man developed psychiatric symptoms, including disorientation, insomnia, heteroaggressive behavior, and his first seizure in March 2025. Thyroid function tests revealed TSH > 50 mIU/L and free T4 < 0.25 ng/dL, and levothyroxine therapy was initiated. In November 2025, he developed status epilepticus, aphasia, and apathy, requiring ICU admission. TSH remained elevated and free T4 low at that time. Antithyroid antibodies were markedly elevated: anti-TPO 760 IU/mL and antithyroglobulin 2266 IU/mL. Brain magnetic resonance imaging showed no structural lesions, mass effect, or signs of infectious encephalitis. Cerebrospinal fluid analysis was nonspecific, without pleocytosis, with normal glucose levels and mild protein elevation; cultures were negative. Pulse corticosteroid therapy was initiated due to suspected autoimmune encephalitis, followed by maintenance prednisone. In January 2026, recurrent seizures occurred, refractory to treatment, leading to a second course of pulse therapy and the introduction of rituximab. At evaluation by the Endocrinology team, the patient was undergoing motor rehabilitation and was receiving prednisone 60 mg/day and levothyroxine 50 mcg/day. After progressive dose adjustment, thyroid function improved (TSH 9.97 mIU/L; free T4 1.28 ng/dL). Thyroid ultrasound was consistent with chronic autoimmune thyroiditis. Levothyroxine was increased to 112 mcg/day, and outpatient follow-up was planned. **Conclusion:** This case highlights the association between primary hypothyroidism and autoimmune encephalopathy with refractory seizures, in the absence of structural abnormalities or infection. Markedly elevated anti-TPO and antithyroglobulin titers reinforce the immunological basis of the condition and support the hypothesis of encephalopathy associated with thyroid autoimmunity. Although corticosteroid therapy remains the standard treatment, immunosuppressive agents such as rituximab may be considered in refractory cases. Early recognition of this entity is essential to guide immunosuppressive therapy and optimize neurological prognosis. **Keywords:** hipotireoidismo; autoimunidade; encefalite de hashimoto.

DISFUNÇÕES TIREOIDIANAS

2786 THE THYROID-NUTRITION-INFLAMMATION-MUSCLE AXIS: INTEGRATED PREDICTORS OF SARCOPENIA IN HAEMODIALYSIS PATIENTS

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Introduction: Thyroid dysfunction is common in chronic kidney disease (CKD) and may exacerbate malnutrition, inflammation, and sarcopenia in patients undergoing haemodialysis (HD). However, the integrated role of thyroid hormones, nutritional status, and inflammatory biomarkers in muscle health among HD patients remains unclear. **Objective:** To investigate the interaction among thyroid function, nutritional status, inflammation, and sarcopenia in HD patients, and to develop and internally validate a predictive model to identify sarcopenia risk. **Methods:** In this cross-sectional study, 101 HD patients and 33 euthyroid controls were evaluated. Thyroid hormones, cytokines (IL-6, TNF- α), C-reactive protein (CRP), leptin, and albumin were measured. Nutritional status was assessed by the Geriatric Nutritional Risk Index (GNRI), body composition by multifrequency bioelectrical impedance; and sarcopenia by handgrip strength confirmed by skeletal muscle mass or skeletal muscle index. **Results:** Compared with controls [48 years (IQR 43–53)], HD patients [58 years (IQR 49–67)] showed higher TSH, CRP, IL-6, TNF- α , and leptin levels, and lower FT3, FT4, albumin, and GNRI values (all $p < 0.05$), while BMI did not differ. Probable and confirmed sarcopenia were more prevalent in HD patients (48.5% and 26.7%, respectively) than in controls (18.1% and 6.0%, respectively), $p = 0.004$. In the penalized regression model (LASSO), FT3, TSH, GNRI, and HD status emerged as independent predictors of sarcopenia (AUC = 0.79 after recalibration). Each 1 pg/mL increase in FT3 was associated with an 18% reduction in the odds of sarcopenia, whereas each 1 mIU/L increase in TSH was associated with a 6.6% increase in odds. **Conclusion:** Haemodialysis patients exhibited an interrelated pattern of thyroid dysfunction, inflammation, and nutritional impairment closely linked to sarcopenia. FT3, TSH, GNRI, and HD status emerged as integrated risk markers for sarcopenia, underscoring the need for multidimensional assessment and management. Longitudinal multicentre studies are warranted to clarify causal pathways and evaluate interventions targeting thyroid function and nutrition in this high-risk population. **Keywords:** thyroid; sarcopenia; haemodialysis patients.

NÓDULOS E CÂNCER DE TIREOIDE

2787 PAPILLARY THYROID MICROCARCINOMA IN A NORTHEASTERN BRAZILIAN COHORT: CLINICAL-PATHOLOGICAL CHARACTERISTICS AND POTENTIAL REAL-WORLD OVERTREATMENT

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Introduction: Papillary thyroid microcarcinoma (PTMC) is typically associated with indolent behavior and excellent prognosis. Although current guidelines support less invasive management, real-world practice often remains aggressive. In Northeastern Brazil, where data on PTMC are limited, this pattern raises concerns about potential overtreatment. **Objective:** To characterize the clinicopathological features, management patterns, and long-term outcomes of patients with PTMC. **Methods:** We conducted a retrospective observational study reviewing the medical records of patients with PTMC referred for postoperative follow-up at a public tertiary endocrinology center in Northeastern Brazil. Demographic data, histopathological features, and clinical outcomes were analyzed according to the 2025 American Thyroid Association (ATA) guidelines. **Results:** From 224 patients with differentiated thyroid carcinoma, 64 (28.6%) had PTMC and were included in the analysis. The cohort was predominantly female (95.3%) and self-declared mixed-race (93.8%), with a mean age of 44.8 ± 12.2 years. The mean tumor size was 6.1 ± 2.8 mm. Total thyroidectomy was performed in 93.8%, and 12.5% underwent neck dissection. Most tumors were unifocal (60.3%), while 19% showed bilateral multifocality. The classic subtype was the most frequent (54.1%), followed by the follicular subtype (31.1%). Aggressive features were infrequent, including vascular invasion (7.8%), extrathyroidal extension (10.9%), and lymph node metastases at diagnosis (15.6%). Positive surgical margins were identified in 17% of cases. According to the 2025 ATA risk stratification system, 60.9% were classified as low risk, 17.2% as intermediate-low risk, 15.6% as intermediate-high risk, and 6.3% as high risk. Despite the predominantly low-risk profile, 45.3% of patients received radioiodine therapy (RAI). After a mean follow-up of 8.1 ± 4.8 years, 75.4% had an excellent response. Structural recurrence occurred in 10.9% of patients, with no distant metastases or disease-specific mortality. **Conclusion:** These findings reaffirm the indolent nature of PTMC in this public health cohort in Northeastern Brazil. The favorable long-term clinical outcomes contrast with the high rates of total thyroidectomy and RAI in a predominantly low-risk group, suggesting a scenario of overtreatment. These findings reinforce the need to implement individualized strategies, such as lobectomy or active surveillance, to minimize unnecessary morbidity. **Keywords:** thyroid cancer, papillary; prognosis; overtreatment.

AUTOIMUNIDADE

2790 WHEN THYROID EYE DISEASE IS NOT THE ONLY CAUSE: OBSTRUCTIVE HYDROCEPHALUS MIMICKING SIGHT-THREATENING ORBITOPATHY

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Introduction: Thyroid eye disease (TED) is an autoimmune disorder most commonly associated with Graves' disease (GD) and is characterized by inflammation and remodeling of orbital tissues. This process is mediated by thyroid-stimulating hormone receptor antibodies (TRAb), which activate orbital fibroblasts and promote characteristic ophthalmologic manifestations. **Case report:** A 24-year-old female with a prior diagnosis of GD and no evidence of TED was treated with methimazole for 36 months, followed by treatment withdrawal. Nine months after discontinuation, she was referred to the endocrinology service due to disease relapse. At presentation, she exhibited clinical signs of hyperthyroidism, including tachycardia and tremor, along with orbital involvement characterized by right eyelid retraction and mild convergent esotropia. Biochemical evaluation demonstrated suppressed thyroid-stimulating hormone (TSH) and elevated free thyroxine (FT4). Orbital imaging revealed bilateral extraocular muscle edema, more pronounced on the right side, and supratentorial ventricular dilatation. Methimazole therapy was reinitiated to restore euthyroidism, and lubricating eye drops were prescribed, resulting in significant symptomatic improvement. After 24 months of sustained euthyroidism on continuous methimazole therapy, the patient presented to the emergency department with progressive headache, bilateral periorbital edema, blurred vision, and pain with eye movement. Clinical evaluation classified the condition as sight-threatening TED according to the European Group on Graves' Orbitopathy (EUGOGO) criteria. Ophthalmologic examination revealed bilateral papilledema. Magnetic resonance imaging demonstrated obstructive hydrocephalus with marked ventricular enlargement and optic nerve sheath dilatation. The patient underwent endoscopic third ventriculostomy via trepanation at Kocher's point, resulting in significant radiological improvement. Despite successful neurosurgical intervention, she continued to exhibit mild residual TED, with a Clinical Activity Score (CAS) of 2, stable proptosis, and unchanged eyelid aperture. **Conclusion:** This case highlights that aqueductal stenosis and obstructive hydrocephalus may mimic or exacerbate clinical features suggestive of severe TED. It underscores the critical importance of comprehensive radiological evaluation in patients with atypical or progressive orbital symptoms to exclude alternative diagnoses and guide appropriate management. **Keywords:** thyroid eye disease; differential diagnosis; thyroid eye disease management.

DISFUNÇÕES TIREOIDIANAS

2792 GRAVES' DISEASE IN CHILDREN AND ADOLESCENTS: CLINICAL PROFILE AND TREATMENT OUTCOMES IN A TERTIARY BRAZILIAN CENTER

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Introduction: Hyperthyroidism caused by Graves' disease (GD) is relatively uncommon in children (1 in 10,000). However, it has significant clinical impact, potentially leading to accelerated growth, impaired school performance, and behavioral changes. Treatment options include antithyroid drugs (ATDs), radioactive iodine (RAI) therapy or thyroidectomy. Data regarding the clinical presentation and management of pediatric GD in Brazil remain limited. **Objective:** To evaluate the clinical characteristics at diagnosis, management strategies and outcomes in pediatric patients with GD at a tertiary public hospital. **Methods:** This retrospective observational study was conducted through medical record review of patients diagnosed with GD before 18 years of age who attended visits between 2023 and 2025 at a tertiary public hospital in Porto Alegre, Brazil. GD was diagnosed based on clinical and laboratory criteria. Data were extracted from electronic medical records, continuous variables are expressed as mean $\pm$ sd or median (interquartile range) according to distribution. **Results:** Eighteen patients were included in the study (66.7% female). The mean age at diagnosis was 13.98 ± 2.94 years. The BMI-for-age Z-score at diagnosis was 0.52 ± 1.12 . Initial free T4 levels were 2.19 ± 1.71 ng/dL. The median initial TRAb level was 8.46 (IQR 6.22–14.03). Three of 15 patients (20%) had negative TRAb at presentation. Six patients developed thyroid eye disease during follow-up. The mean initial methimazole (MMZ) dose was $16.25.0 \pm 8.06$ mg/day (median 17.5 mg/day, IQR 12.5–20), and the median maximum dose was 20 mg/day, IQR 13.75–20). Six patients (33%) underwent RAI therapy. The median age at RAI administration was 15.16 years (IQR 12.95–16.54). One patient required a second RAI dose. The median administered dose was 12.5 mCi (range 7–20 mCi). The overall cure rate was 80%, and all successfully treated patients developed hypothyroidism. No patient underwent thyroidectomy. At the last follow-up, nine patients remained on MMZ therapy. No severe adverse events related to treatment were observed. **Conclusion:** Long term antithyroid drug therapy was the primary treatment strategy for pediatric DG, while radioactive iodine was required in approximately one-quarter of cases. No severe treatment-related adverse events were observed. These findings contribute to the limited national data on pediatric GD and may help inform management strategies in similar settings. **Keywords:** Grave's disease; hyperthyroidism; children.



AUTOIMUNIDADE

2794 PREDICTORS OF SUSTAINED REMISSION OF GRAVES DISEASE FOLLOWING ANTITHYROID DRUG THERAPY

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Introduction: Sustained remission of hyperthyroidism in Graves' disease after antithyroid drug (ATD) therapy is variable and influenced by several clinical and biochemical factors. Identifying predictors of sustained remission may assist clinicians in individualizing ATD duration and determining the optimal timing for drug withdrawal. **Objective:** Evaluate clinical outcomes in patients with Graves' disease treated exclusively with ATDs and identify clinical and laboratory factors associated with sustained remission. **Methods:** This retrospective study included patients evaluated in a single tertiary university hospital between January 2015 and January 2025. Sustained remission was defined as maintenance of euthyroidism or hypothyroidism for at least 12 months after ATD withdrawal. Clinical, laboratory, ultrasonographic, and therapeutic variables were analyzed. FT4 and TSH receptor antibody (TRAb) levels were standardized as number of times above the upper limit of normal according to assay (xULN). Univariate and multivariate logistic regression analyses were performed. Discriminative performance of continuous variables was assessed with receiver operating characteristic (ROC) curves, area under the curve (AUC), and optimal cutoff obtained using Youden index. **Results:** A total of 108 patients met eligibility criteria with 38 (35.2%) achieved sustained remission. In univariate analyses, older age at diagnosis, lower FT4 levels at diagnosis, smaller thyroid volume, lower maximal methimazole dose and lower TRAb levels at the time of ATD withdrawal were associated with sustained remission. TRAb at withdrawal demonstrated the highest discriminative performance (AUC = 0.81) with cutoff 2.55 xULN compared with thyroid volume (AUC = 0.72) with cutoff 24.1 mL. However, no variable retained statistical significance in multivariate logistic regression, probably due to collinearity among severity markers and limited statistical power. **Conclusion:** Sustained remission after ATD therapy in Graves' disease was associated with milder hyperthyroidism, smaller thyroid volume and reduced autoimmune activity, particularly evidenced by lower TRAb levels at withdrawal. These findings highlight the importance of individualized decisions regarding ATD discontinuation. **Keywords:** Graves disease; treatment; prognosis.

REGULAÇÃO DA FUNÇÃO TIREOIDIANA

2796 THYROID DYNAMICS DURING PROGESTIN-PRIMED FREEZE-ALL IVF: IMPLICATIONS FOR TSH MONITORING

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Introduction: Controlled ovarian stimulation (COS) for *in vitro* fertilization (IVF) induces supraphysiological estradiol levels that may transiently influence the hypothalamic-pituitary-thyroid axis by increasing thyroxine-binding globulin and altering free hormone fractions. Most available data derive from conventional protocols using hCG trigger and fresh embryo transfer. Evidence regarding progestin-primed ovarian stimulation (PPOS) combined with freeze-all strategies remains limited, and its impact on thyroid homeostasis in euthyroid women, as well as the influence of thyroid autoimmunity (TAI), is not well established. **Objective:** To evaluate thyroid function changes during PPOS freeze-all IVF cycles and to assess the influence of TAI on TSH dynamics. **Methods:** This prospective cohort included 275 euthyroid women undergoing IVF between May 2021 and May 2023 (mean age 37.7 ± 3.9 years). Women with thyroid dysfunction or baseline TSH > 2.5 mIU/L were excluded. COS was performed with recombinant FSH/LH and dydrogesterone for pituitary suppression; final oocyte maturation was triggered with a GnRH agonist, and all embryos were cryopreserved. Serum TSH, free T4 (FT4), total T4 (TT4), TPOAb, and TgAb were measured at baseline, after COS, during endometrial preparation, at embryo transfer, and at pregnancy confirmation. **Results:** TSH increased from 1.47 ± 0.47 mIU/L at baseline to 1.82 ± 0.79 mIU/L after COS ($p = 0.001$), declined during endometrial preparation (1.61 ± 0.72 mIU/L), and rose again at pregnancy confirmation (1.86 ± 0.74 mIU/L; $p < 0.001$ vs. baseline). TSH variation occurred independently of estradiol levels. No significant correlations were observed between TSH and FT4 or TT4 at any time point. TPOAb and TgAb positivity rates were 4.9% and 1.7%, respectively, without differences in TSH trajectories between antibody-positive and -negative women. **Conclusion:** PPOS freeze-all IVF cycles are associated with a mild and transient increase in TSH that remains within reference limits, supporting a physiological and reversible modulation of the pituitary-thyroid axis rather than clinically relevant thyroid dysfunction. TAI did not modify TSH behavior. These findings suggest that TSH assessment at baseline and pregnancy confirmation may be sufficient in euthyroid women undergoing PPOS protocols. **Keywords:** thyroid function tests; fertilization *in vitro*; pregnancy



AUTOIMUNIDADE

2797 TOCILIZUMAB IN THE TREATMENT OF MODERATE-TO-SEVERE GLUCOCORTICOID-RESISTANT GRAVES' ORBITOPATHY: A REPORT OF TWO CASES

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Introduction: In Graves' orbitopathy (GO), TSH receptor antibodies (TRAb) bind to TSH receptor and activate IGF-1R expressed on orbital fibroblasts, leading to cell proliferation and inflammation. Interleukin-6 (IL-6) acts as a pro-inflammatory cytokine, amplifying and perpetuating the inflammation. The recommended treatment for active moderate-to-severe GO is high-dose intravenous glucocorticoids (IVGC). In the absence of clinical improvement, alternative therapies should be considered. Tocilizumab (TCZ) is a monoclonal antibody targeting IL-6 receptor that may be used. **Case 1:** A 42-year-old male patient was diagnosed with hyperthyroidism, bilateral proptosis and clinical inflammatory activity (CAS3) in 2021. In 2022, he showed intermittent diplopia and CAS4 and prednisone 80 mg/day with gradual tapering with minimal improvement was prescribed. In 2023, diplopia and inflammatory signs worsened (CAS5) and intravenous methylprednisolone 500 mg/week for 6 weeks, followed by 250 mg/week for 6 weeks (IVGC) was given, with improvement in pain but persistent diplopia. Three months later, another course of prednisone 80 mg/day was given without improvement. In 2025, ophthalmologic examination showed visual acuity of 20/20 in both eyes (OU), exophthalmometry 25 mm in right eye (OD) and 24 mm in left eye (OS) and CAS 4 (eyelid edema and erythema, conjunctival hyperemia and caruncular inflammation). TCZ 8 mg/kg was given monthly for 4 months. At the end, he improved to CAS1 (mild eyelid edema), with a 3 mm reduction in exophthalmometry in OU and no diplopia. Thyroid function remained stable under methimazole. **Case 2:** A 61-year-old female patient with hypothyroidism due to Hashimoto's thyroiditis since her 40s was on levothyroxine. In 2024, she developed eyelid edema, hyperemia, pain (CAS4), bilateral proptosis and diplopia. She had high TRAb levels and computed tomography findings consistent with GO. She received IVGC without response. In 2025, exophthalmometry 22/21 mm (OD/OS), persistent diplopia and CAS4 (eyelid edema and erythema, conjunctival hyperemia and caruncular inflammation) were noted. She received TCZ 8 mg/kg monthly for 4 months and improved to CAS1 (mild eyelid edema) without diplopia. She remained euthyroid on levothyroxine. No hepatic, hematologic, renal abnormalities or infections were observed during or after TCZ. **Conclusion:** TCZ was effective in reducing inflammatory activity in patients with GC-resistant GO, without serious adverse effects. **Keywords:** thyroid eye disease; treatment; orbitopathy.

DISFUNÇÕES TIREOIDIANAS

2798 HYPERTHYROIDISM AND AMIODARONE USE — A CASE REPORT OF DIFFICULT TREATMENT

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Introduction: Amiodarone can lead to thyroid dysfunction due to its high iodine content and to the cytotoxic effect on thyroid cells. Amiodarone-induced thyrotoxicosis (AIT) type 1 is due to increased thyroid hormone (TH) synthesis, usually in patients with prior thyroid disease; treatment is with high-dose antithyroid drugs. Type 2 involves destructive thyroiditis in a previously normal gland and responds better to corticosteroids. A mixed form requires combined treatment. The authors report a case of difficult-to-control amiodarone-induced thyrotoxicosis. **Case presentation:** A 38-year-old woman with a history of rheumatic cardiomyopathy presented to the emergency department with atrial flutter. Her history included rheumatic valvular heart disease, with a bioprosthesis in the last two years. She was using warfarin sodium, bisoprolol hemifumarate, and benzathine benzylpenicillin. She didn't report previous hyperthyroidism. Two intravenous amiodarone boluses (600 mg) and one adenosine bolus (6 mg) were administered. Test results collected before amiodarone administration showed suppressed TSH and elevated FT4, confirming pre-dose hyperthyroidism. One month later, she was referred to the endocrinologist with uncontrolled hyperthyroidism, using 800 mg/day propylthiouracil (PTU), 20 mg/day prednisone, and 150 mg/day metoprolol. TSH was suppressed, FT4 = 4.39 ng/dL, TT3 = 149 ng/dL, and TRAb was negative. Thyroid ultrasound, performed after corticosteroid initiation, showed small colloid cysts and no alteration in vascularization. PTU dose reached 1,000 mg/day and was used for more than 5 months; prednisone was increased to 60 mg/day for 3 months, then decreased and withdrawn. Despite no improvement in T4, total T3 remained within the target range most of the time, and she showed no signs of hyperthyroidism, but TSH remained suppressed. After 5 months, there was no uptake of radioiodine on scintigraphy. After 9 months, she returned with a TSH of 10.5 μ IU/mL, normal FT4 (0.90 ng/mL), and TT3 (130 ng/mL). **Conclusion:** Managing hyperthyroidism in a patient on amiodarone is difficult. We highlight the importance of characterizing thyroid function before and during treatment with this drug, as recommended by the specialty societies. We also draw attention to the long duration and the challenges of treating hyperthyroidism. **Keywords:** hyperthyroidism; amiodarone-induced thyrotoxicosis; thyroid dysfunction.



DISFUNÇÕES TIREOIDIANAS

2799 SEVERE AND REFRACTORY THYROID EYE DISEASE: METHOTREXATE AS A STEROID-SPARING AND IMMUNOMODULATORY AGENT IN A CASE REPORT

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Introduction: Thyroid eye disease (TED) is the primary extrathyroidal manifestation of Graves' disease. Its pathophysiology involves inflammatory activation and glycosaminoglycan deposition, which may progress to fibrotic and adipogenic phases, leading to diplopia, disfigurement, and irreversible visual loss. Although intravenous (IV) glucocorticoids are the first-line treatment, studies indicate that 20%–40% of patients experience therapeutic failure. In this context, methotrexate (MTX) — an antimetabolite that modulates T-cell and cytokine responses — emerges as a viable steroid-sparing immunomodulatory alternative for controlling prolonged inflammatory activity. **Case report:** A 63-year-old male smoker with Graves' hyperthyroidism, pharmacologically controlled with methimazole, presented with active TED (Clinical Activity Score — CAS ≥ 5), characterized by marked exophthalmos, eyelid retraction, chemosis, and restrictive diplopia due to extraocular muscle involvement. Initially, the patient underwent IV corticosteroid therapy (cumulative dose of 4.5 g) and bilateral surgical orbital decompression, which yielded a transient response followed by inflammatory relapse (CAS 4). Due to this refractoriness, oral methotrexate (15 mg/week) was initiated, resulting in an early response (CAS decreased from 4 to 1 within 30 days). External beam radiotherapy was added during the treatment course, achieving complete clinical inactivity (CAS 0) after four months of MTX therapy. Sustained regression of orbital congestion, stabilization of motility, and improved quality-of-life scores (GO-QoL) were observed. MTX facilitated the tapering of oral prednisone while maintaining clinical inactivity, with no detectable hematological or hepatic toxicity. **Conclusion:** The management of severe TED necessitates early recognition of corticosteroid refractoriness to prompt the initiation of second-line agents. The integration of surgical decompression and radiotherapy, potentiated by MTX, established an essential synergistic strategy to reduce visual morbidity and promote sustained remission in a complex clinical scenario. MTX proved to be a safe and effective alternative, ensuring inflammatory control and significantly reducing the total glucocorticoid burden, thus consolidating its role as a robust immunomodulatory option for refractory TED. **Keywords:** thyroid eye disease; methotrexate; steroid-sparing.

NÓDULOS E CÂNCER DE TIREOIDE

2800 THE IMPACT OF EARLY GENETIC SCREENING IN A FOUR-GENERATION FAMILIAL MEDULLARY THYROID CARCINOMA: A CASE REPORT

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Introduction: Medullary thyroid carcinoma (MTC) accounts for 1%–2% of thyroid malignancies, with up to 25% occurring in hereditary forms due to germline RET mutations. Early genetic identification allows risk stratification and timely intervention capable of significantly modifying disease trajectory. We report a four-generation familial MTC with RET codon 618 mutation, illustrating the clinical consequences of delayed diagnosis and the measurable benefit of cascade screening. **Case report:** The index case was diagnosed in 2015 with markedly elevated calcitonin (481 pg/mL) and CEA (53 ng/mL), and confirmed RET codon 618 mutation. Cascade genetic screening identified mutation carriers across three additional generations. In the second generation, one daughter underwent total thyroidectomy (TT) after biochemical and structural confirmation of MTC (initial calcitonin 438 pg/mL), achieving complete biochemical remission without structural recurrence. A mutation-positive son declined surgery despite elevated calcitonin (304 pg/mL) and two suspicious TI-RADS 4 nodules. In the third generation, a granddaughter presented with RET mutation, calcitonin 1,443 pg/mL, and cytology consistent with MTC. TT confirmed multifocal carcinoma with extrathyroidal extension and nodal metastases (pT3N1). Eight years later, she developed biochemical and structural recurrence with cervical lymph node metastases and pulmonary nodules, requiring repeated surgical interventions. Conversely, a RET-positive great-granddaughter underwent prophylactic TT at minimal biochemical elevation (calcitonin 11.4 pg/mL) and no structural disease on ultrasound. Pathology revealed a 0.4 cm intrathyroidal MTC without nodal involvement, demonstrating stage migration enabled by early cascade screening. **Conclusion:** Across four generations, this family illustrates the heterogeneous clinical behavior of RET-associated MTC and the profound impact of early genetic screening. While delayed diagnosis resulted in advanced disease and persistent recurrence in older generations, proactive RET identification enabled early surgical intervention and superior disease control in younger carriers. Structured cascade screening in RET-mutated families is essential to reduce morbidity and improve long-term outcomes. **Keywords:** medullary thyroid carcinoma; thyroid malignancies; germline RET mutations.



NÓDULOS E CÂNCER DE TIREOIDE

2802 RECURRENT LOCOREGIONAL MEDULLARY THYROID CARCINOMA IN A RET-MUTATED PATIENT DESPITE GUIDELINE-BASED MANAGEMENT: A LONG-TERM FOLLOW-UP CASE

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Introduction: Hereditary medullary thyroid carcinoma (MTC), associated with germline RET mutations, is characterized by multifocal disease and a substantial risk of locoregional recurrence. Although total thyroidectomy with adequate lymph node dissection represents the standard of care, persistent biochemical disease and structural relapse remain significant clinical challenges. **Case report:** A 22-year-old woman was diagnosed with hereditary MTC during familial screening. Initial evaluation revealed markedly elevated calcitonin (481 pg/mL; reference < 10 pg/mL), carcinoembryonic antigen (CEA) of 53 ng/mL (reference < 5 ng/mL), and confirmed germline RET mutation. Cervical ultrasonography demonstrated suspicious lymph nodes. She underwent total thyroidectomy with central and lateral neck dissection according to current guidelines. Histopathology confirmed multifocal MTC with lymph node metastases. Despite appropriate initial management, postoperative calcitonin remained persistently elevated, ranging from 59.1 to 201.6 pg/mL, and CEA ranged from 5.3 to 9.9 ng/mL, consistent with biochemical persistence. Serial imaging demonstrated recurrent cervical nodal disease. Over long-term follow-up, the patient required four additional cervical reoperations due to structural recurrence. Thoracic computed tomography revealed small, nonspecific bilateral pulmonary nodules without definitive metastatic characterization. Whole-body PET/CT with a somatostatin analog demonstrated increased tracer uptake in left supraclavicular, cervical (levels VI and VII), and mediastinal (right paratracheal and para-aortic) lymph nodes measuring up to 1.2 cm, suspicious for secondary neoplastic involvement. Mild uptake was also observed in the right pulmonary hilum. Most recently, calcitonin was 168 pg/mL and CEA 5.3 ng/mL, and new suspicious cervical lymph nodes prompted a fifth surgical intervention. Throughout follow-up, screening for pheochromocytoma and hyperparathyroidism remained negative. **Conclusion:** This case highlights the aggressive locoregional behavior of RET-associated MTC and demonstrates that disease recurrence may occur despite adherence to established surgical guidelines. Persistent calcitonin elevation, somatostatin-receptor-positive nodal relapse, and repeated reoperations underscore the biological complexity of hereditary MTC and the limitations of surgery alone, reinforcing the need for individualized long-term surveillance and multidisciplinary management. **Keywords:** germline RET mutation; hereditary medullary thyroid carcinoma; thyroid malignancies.

EPIDEMIOLOGIA

2803 ASSESSMENT OF THYROID FUNCTION AND BIOCHEMICAL PROFILE IN CHILDREN WITH OBESITY

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Introduction: The literature describes a correlation between obesity and alterations in thyroid hormone levels. This association occurs as a physiological adaptation aimed at promoting weight loss in these individuals. **Objective:** The present study aimed to investigate the correlation between plasma concentrations of thyroid-stimulating hormone (TSH), free T4 (fT4), and biochemical parameters in eutrophic children and children with obesity. **Methods:** Children of both sexes, with a mean age of 6.8 years, were allocated into two groups according to their nutritional status assessed by Body Mass Index (BMI) Z-score: the eutrophic group (EG, n = 30; 15 boys and 15 girls; BMI Z-score = 0.7) and the obesity group (OG, n = 25; 14 boys and 11 girls; BMI Z-score = +2.3). Clinical evaluations were performed at baseline and after 12 weeks of lifestyle modification (LM). **Results:** At baseline, plasma levels were as follows: TSH (OG = 4.78 ± 0.98; EG = 1.10 ± 0.30), fT4 (OG = 1.3 ± 1.11; EG = 1.1 ± 2.21), glucose (OG = 83.05 ± 7.31; EG = 78.86 ± 6.93), total cholesterol (OG = 156.77 ± 25.62; EG = 109.12 ± 13.80), HDL (OG = 33.42 ± 11.02; EG = 32.74 ± 13.05), LDL (OG = 98.05 ± 12.20; EG = 70.13 ± 21.38), and triglycerides (OG = 110.30 ± 22.91; EG = 104.94 ± 32.94). After 12 weeks of LM, the observed values were: TSH (OG = 1.78 ± 0.48; EG = 0.80 ± 0.10), fT4 (OG = 1.1 ± 1.0; EG = 1.2 ± 1.1), glucose (OG = 73.05 ± 5.21; EG = 68.86 ± 1.93), total cholesterol (OG = 98.5 ± 15.2; EG = 78.1 ± 3.0), HDL (OG = 45.2 ± 8.2; EG = 49.4 ± 10.5), LDL (OG = 99.5 ± 10.0; EG = 80.3 ± 17.38), and triglycerides (OG = 75.30 ± 12.1; EG = 56.4 ± 12.4). Children in the obesity group presented significantly increased baseline levels of LDL (p < 0.001), triglycerides (p = 0.028), and TSH (p = 0.02), with normalization of these parameters after 12 weeks of LM. **Conclusion:** Children with obesity exhibited higher baseline TSH and adverse lipid profile parameters compared to eutrophic children. Following 12 weeks of lifestyle modification, both groups demonstrated an improvement in metabolic parameters and the restoration of a euthyroid status. **Keywords:** obesity; children; TSH.



EPIDEMIOLOGIA

2806 SPATIAL CORRELATION OF HOSPITALIZATIONS FOR HYPERTHYROIDISM (ICD-10 E05) AND CARDIAC ARRHYTHMIAS (ICD-10 I44-I49) IN BRAZIL, 2015-2025

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Introduction: Hyperthyroidism (ICD-10 E05) is a recognized risk factor for cardiac arrhythmias (ICD-10 I44-I49) and related hospitalizations. Nationwide analyses evaluating whether hospitalization patterns for these conditions evolve in parallel remain limited in Brazil. **Objective:** To assess spatial distribution, temporal trends, and population-level correlation between hospitalization rates for hyperthyroidism and cardiac arrhythmias across Brazilian states from 2015 to 2025. **Methods:** Ecological retrospective study using data from the Brazilian Unified Health System Hospital Information System (SIH/SUS). Hospitalizations among individuals aged 20-69 years were analyzed. Rates per 100,000 inhabitants were calculated using 2020 population estimates. Temporal trends were evaluated using linear regression. Spatial variability across states was examined, and associations were tested using Spearman's correlation ($p < 0.05$). **Results:** Hospitalization rates for hyperthyroidism increased over the study period. Cardiac arrhythmia hospitalizations also showed an upward trend. Marked interstate variability was observed for both conditions. States with higher hyperthyroidism hospitalization rates tended to present higher arrhythmia hospitalization rates. A statistically significant moderate positive correlation was identified (Spearman's $r = 0.6$; $p < 0.05$). **Conclusion:** Hospitalizations for hyperthyroidism and arrhythmias increased concurrently and remained moderately correlated across Brazilian states. These findings indicate a consistent association at the population level and highlight the importance of strengthening early diagnosis and adequate management of hyperthyroidism to potentially reduce cardiovascular complications and related hospitalizations. **Keywords:** hyperthyroidism; cardiac arrhythmias; hospitalization trends.

NÓDULOS E CÂNCER DE TIREOIDE

2808 NEUROFIBROMATOSIS TYPE 1 WITH RET-NEGATIVE MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A: A RARE ASSOCIATION

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Introduction: Multiple endocrine neoplasia type 2A (MEN2A) and neurofibromatosis type 1 (NF1) are autosomal dominant hereditary disorders. MEN2A results from germline mutations in the RET proto-oncogene while NF1 is caused by mutations in the NF1 tumor suppressor gene. Although both conditions predispose to neuroendocrine tumors (NETs) development, their coexistence is rare and scarcely reported. **Case report:** A 79-year-old woman with NF1 diagnosed at age 57, prior gastrointestinal stromal tumor and invasive ductal breast carcinoma. At age 71, she manifested nephrolithiasis and osteoporosis, with hypercalcemia (total calcium 10.6 mg/dL; ionized calcium 1.50 mmol/L), hypercalciuria (310.8 mg/24h), and elevated parathyroid hormone (355 pg/mL), consistent with primary hyperparathyroidism (PHPT). Thyroid ultrasonography revealed multiple nodules (two TIRADS 5 and one TIRADS 4) and a hypoechoic lesion compatible with parathyroid adenoma, confirmed by scintigraphy. Cytology of one thyroid nodule was benign, evaluation of the remaining nodules was not feasible. Given the diagnosis of PHPT associated with suspicious nodules, total thyroidectomy with right parathyroidectomy was performed. Histopathology revealed parathyroid hyperplasia and medullary thyroid carcinoma (MTC) measuring 15 × 13 mm, confined to the gland, with C-cell hyperplasia and multinodular colloid goiter. Immunohistochemistry was positive for calcitonin, CD56, CEA, and chromogranin, with Ki-67: 1%. Right lateral and central cervical lymph node dissection identified metastases in 6 of 29 nodes. MEN2A was suspected, and pheochromocytoma screening was negative. Molecular testing confirmed a pathogenic NF1 variant (Leu695Pro, c.2084T>C; exon 8, chromosome 15), while RET germline analysis was negative. Postoperatively, calcium normalized, but calcitonin remained detectable (15.3-80.4 pg/mL), with a doubling time of 27.3 months, indicating an incomplete biochemical response and low-aggressiveness disease. **Conclusion:** This case describes genetically confirmed NF1 associated with RET-negative MEN2A. Notably, RET-negative status is reported in only 2%-3% of MEN2A. This rare association raises hypotheses such as uncommon genetic variants or NF1-related neural crest dysfunction. Although, the relationship between NF1 mutations and MTC or PHPT remains uncertain, this report highlights the need of NETs surveillance in NF1 patients, as phenotypic overlap may arise through incompletely understood mechanisms. **Keywords:** neurofibromatosis type 1; multiple endocrine neoplasia type 2A; medullary thyroid carcinoma.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2811 EVALUATION OF THYROID FUNCTION AND MORPHOLOGY BEFORE AND SIX MONTHS AFTER BARIATRIC SURGERY

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Introduction: Severe obesity is associated with functional alterations of the hypothalamic-pituitary-thyroid axis, often characterized by mildly elevated thyrotropin (TSH) levels. However, the relationship between anthropometric parameters, thyroid function and morphology, as well as the impact of bariatric surgery (BS) on these findings, has not been fully elucidated. **Objective:** To evaluate thyroid function and morphology in patients with class III obesity before and six months after BS, and to investigate their associations with anthropometric parameters. **Methods:** A longitudinal study including 59 patients with class III obesity undergoing BS. Body weight, body mass index (BMI), serum TSH, and thyroid volume assessed by ultrasonography were evaluated preoperatively and six months after surgery. Comparisons between time points were performed using the Mann-Whitney test, and correlations were assessed using Spearman's coefficient. A p value < 0.05 was considered statistically significant. **Results:** The mean age was 42.56 ± 9.94 years, with a predominance of female participants (89,8%). A significant reduction in BMI was observed after six months ($45.4 [42.94-48.5]$ vs. $33.67 [31.24-35.99]$ kg/m²; p < 0.001). No significant differences were found in TSH levels ($2.09 [1.44-2.92]$ vs. $1.92 [1.13-2.50]$ mIU/L; p = 0.23) or thyroid volume ($9.93 [6.74-12.36]$ vs. $8.76 [5.88-11.62]$ mL; p = 0.12) between the study periods. In the preoperative assessment, TSH correlated with body weight (r = 0.28; p = 0.02) but not with BMI (r = 0.20; p = 0.12). Baseline thyroid volume correlated with body weight (r = 0.35; p = 0.006), with no association with BMI. After six months, no significant correlations were observed between TSH or thyroid volume and anthropometric parameters. **Conclusion:** In patients with class III obesity, TSH levels and thyroid volume were associated with absolute body weight but not with BMI, suggesting that total body mass exerts a greater influence on the modulation of the thyroid axis than height-adjusted indices. Despite significant weight loss following bariatric surgery, no relevant short-term changes were observed in thyroid function or morphology, reinforcing the adaptive nature of these alterations. Studies with longer follow-up and assessment of additional hormonal markers may further clarify these mechanisms. **Keywords:** thyroid volume; thyroid function; bariatric surgery.

NÓDULOS E CÂNCER DE TIREOIDE

2815 SPHENOID SINUS METASTASIS AS THE INITIAL PRESENTATION OF FOLLICULAR THYROID CARCINOMA WITH REPEATEDLY BENIGN FNAB: A CASE REPORT

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Introduction: Follicular thyroid carcinoma (FTC) has a greater propensity for hematogenous dissemination, with preferential metastases to bone and lung. Metastases to the sphenoid sinus and skull base are rare and may present with headache, ophthalmoplegia, and visual loss due to compression of neurovascular structures. Cytological diagnosis is limited, as fine-needle aspiration biopsy (FNAB) does not assess capsular or vascular invasion; therefore, FTC is usually classified as Bethesda III or IV. However, benign results (Bethesda II) may occur and delay diagnosis, being reported in up to 10.9% of cases in Asian series. **Case report:** A 60-year-old woman presented in May 2022 with ocular deviation, left ophthalmoplegia (sixth cranial nerve palsy), visual loss in the left eye, and headache. Cranial magnetic resonance imaging revealed an expansive lesion in the sphenoid sinus measuring 3.4 cm. Biopsy of the lesion demonstrated ectopic thyroid tissue without atypia. Thyroid ultrasound showed a 2.1 cm nodule, TI-RADS 4, with FNAB Bethesda II. In 2024, the patient developed visual loss in the right eye and persistent headache and underwent an attempted decompressive surgery, which was aborted due to significant intraoperative bleeding. A new biopsy revealed proliferation of well-differentiated follicular cells. Serum thyroglobulin level was markedly elevated at 2,329 ng/mL. Repeat thyroid ultrasound demonstrated a 2.3 cm TI-RADS 5 nodule, with FNAB again Bethesda II. Given the strong clinical suspicion of bone metastasis from differentiated thyroid carcinoma despite two benign FNAB results, total thyroidectomy was performed in April 2025. Histopathological examination revealed minimally invasive follicular thyroid carcinoma. Staging demonstrated metastasis to the sphenoid sinus with intracranial invasion and compression of orbital structures, bone metastases involving T1, T2, and L4 with a pathological fracture of L4, as well as pulmonary metastases. The patient was treated with radiotherapy to the cranial lesion and radioiodine therapy. **Conclusion:** This is a rare case of follicular thyroid carcinoma presenting initially as a bone metastasis to the sphenoid sinus, an uncommon site associated with severe neurological manifestations. This report highlights both the rarity of this metastatic location and the limitations of cytology in the diagnosis of follicular thyroid carcinoma. **Keywords:** follicular thyroid carcinoma; fine-needle aspiration biopsy; metastasis.



CIRURGIA DA TIREOIDE

2818 THE USE OF LARYNGEAL NERVE MONITORING IN PATIENTS UNDERGOING THYROIDECTOMY: DOES IT REDUCE THE INCIDENCE OF DYSPHAGIA OR VOICE ALTERATIONS?

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Introduction: Thyroidectomy is one of the most frequently performed procedures in head and neck surgery, associated with relevant functional complications, especially voice and swallowing alterations related to recurrent laryngeal nerve injury. Intraoperative neuromonitoring (IONM) has been proposed as an auxiliary strategy for neural identification and preservation, although its routine clinical benefit remains controversial. **Objective:** To prospectively evaluate the impact of intraoperative neuromonitoring of the vagus and laryngeal nerves in patients undergoing thyroidectomy, analyzing changes in surgical strategy, self-reported functional outcomes (voice and swallowing), return to work, and treatment costs. **Methods:** Prospective cohort study conducted at A.C.Camargo Cancer Center including 200 patients undergoing partial or total thyroidectomy, with or without neck dissection, between February and October 2025. Assessment of vocal function using the Voice Handicap Index (VHI-10) and swallowing using the MD Anderson Dysphagia Inventory (MDADI), in addition to analysis of return to work and institutional costs. **Results:** Neuromonitoring was used in the majority of procedures and promoted changes in surgical conduct in 14.8% of cases, although alteration of the initially proposed strategy occurred in only 2.2%. No statistically significant differences were observed in voice and swallowing functional outcomes at 30-day follow-up. The use of neuromonitoring was associated with increased treatment costs. **Conclusion:** Intraoperative neuromonitoring may influence specific intraoperative decisions; however, it did not demonstrate significant benefit in the functional outcomes evaluated in the short term. Its routine use should be considered in light of the economic impact, without evidence of superiority in voice, swallowing, or return-to-work outcomes at 30 days. **Keywords:** thyroidectomy; monitoring; voice.

AUTOIMUNIDADE

2819 MHC CLASS I AND II POLYMORPHISMS AND TREATMENT OUTCOMES IN GRAVES' DISEASE: HLA-DQA1 ALLELES AS PREDICTORS OF REMISSION AFTER ANTITHYROID DRUG THERAPY

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Introduction: Predictors of Graves' disease (GD) development and response to antithyroid drugs (ATD) include Major Histocompatibility Complex (MHC) class I and II alleles. **Objective:** To investigate whether MHC class I and II alleles are associated with remission or relapse after ATD therapy in GD patients referred to a university hospital with a highly admixed population. **Methods:** Ninety-nine patients treated with ATD, for at least 18 months, were enrolled. Of these, 77 achieved remission (REM) and 22 were referred to definitive treatment (DT). REM was defined as euthyroidism after ATD withdrawal with negative TSH-receptor antibodies (TRAb). Patients who maintained remission during a two-year follow-up were classified as therapeutic success (TS). Genomic DNA was extracted from leukocytes of 61 patients (40 TS) for preliminary analysis. Next-generation sequencing was used for HLA typing (122 alleles) at the following loci: HLA-A, HLA-B, HLA-C, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1 and HLA-DRB1. **Results:** The most frequent alleles were HLA-DPA1R0103 (68.8%), HLA-CR0401 (26.3%), HLA-AR0201 (24.6%) and HLA-DQA1R0501 (24.6%). REM was associated with HLA-DQA1 ($\chi^2 = 20.27$; $df = 7$; $p = 0.005$). Alleles *01:02 and *03:01P were exclusively found in REM patients (43.2% and 31.4%; $p = 0.01$ and 0.03), whereas *05:01 was more frequent in non-REM patients (70% vs. 37%; $p = 0.05$). Although some MHC class II loci were associated with REM, no association was observed with relapse after remission or with TS over two years. No significant association was found between TS and MHC class I loci. **Conclusion:** HLA-DPA1R0103 was the most frequent allele, which was previously linked to type 1 diabetes (especially in Asian populations), immune checkpoint thyroiditis and cardiovascular events in GD. HLA-DQA1R0501, classically associated with GD susceptibility and poorer treatment response, was also frequent and related to absence of REM. HLA-DQA1*01:02 and *03:01P emerged as potential markers of remission. These findings require comparison with controls and confirmation in larger cohorts with longer follow-up. **Keywords:** Graves' disease; HLA; remission and relapse.



NÓDULOS E CÂNCER DE TIREOIDE

2821 MCCUNE-ALBRIGHT SYNDROME IN AN ADULT WOMAN WITH POLYOSTOTIC FIBROUS DYSPLASIA AND PAPILLARY THYROID CARCINOMA: A RARE CASE REPORT

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Introduction: McCune-Albright syndrome (MAS) is a non-hereditary genetic disorder caused by a postzygotic activating mutation in the *GNAS* gene, resulting in somatic mosaicism. The classic triad consists of polyostotic fibrous dysplasia, café-au-lait macules, and precocious puberty. Additional endocrine manifestations may occur, including hyperthyroidism, hyperprolactinemia, and hypercortisolism. The occurrence of papillary thyroid carcinoma (PTC) in MAS is rare, although autonomous thyroid dysfunction has been described in the literature. **Case report:** A 37-year-old female nursing technician, born in Juazeiro do Norte and residing in Salvador, presented in 2020 with diplopia and a sensation of heaviness in the occipital region. She underwent neurological evaluation, and magnetic resonance imaging (MRI) revealed focal bone thickening of the cranial vault and occipital condyle, without a definitive diagnosis at that time. She remained without medical follow-up for three years. In 2022, a thyroid nodule was detected, and fine-needle aspiration cytology confirmed papillary thyroid carcinoma (T1aN0M0). She underwent total thyroidectomy in 2023. Bone scintigraphy demonstrated multiple areas of increased radiotracer uptake involving the skull, humerus, ulna, right hand, spine, pelvis, and right femur, suggestive of polyostotic fibrous dysplasia. These findings were confirmed by MRI and positron emission tomography/computed tomography (PET/CT), which also demonstrated lytic lesions with increased metabolic activity. The patient subsequently developed pathological fractures of the T9 vertebra and the proximal right femur, both managed surgically, with biopsy specimens consistent with fibrous tissue. Her medical history revealed menarche at 9 years of age, associated with precocious pubertal development, particularly advanced breast development. Physical examination revealed irregularly bordered café-au-lait macules on the back (3 cm in the right upper quadrant and 8 cm in the lumbar region). She is currently receiving levothyroxine 125 µg/day and reports chronic cervical pain radiating to both upper limbs. **Conclusion:** This case illustrates a classic presentation of McCune-Albright syndrome, rarely associated with papillary thyroid carcinoma. Recognition of its clinical and skeletal manifestations facilitates diagnosis, which remains primarily based on clinical and radiological findings. This report contributes to the discussion regarding the potential association between McCune-Albright syndrome and neoplasia and highlights the importance of continuous multidisciplinary follow-up to monitor endocrine and orthopedic complications. **Keywords:** McCune-Albright syndrome; polyostotic fibrous dysplasia; papillary thyroid carcinoma.

NÓDULOS E CÂNCER DE TIREOIDE

2822 DISTINCT PROGNOSTIC PATTERNS IN ATA 2025 INTERMEDIATE RISK PAPILLARY THYROID CARCINOMA: A REAL-WORLD COHORT

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Introduction: The 2025 American Thyroid Association (ATA) guidelines refined the Intermediate Risk category into Intermediate-Low and Intermediate-High. However, the applicability of classic prognostic factors within these subcategories remains understudied in specific demographics. **Objective:** To identify clinicopathological factors associated with structural recurrence within the ATA 2025 Intermediate Risk group and assess the influence of established risk factors. **Methods:** Retrospective study of 113 patients with papillary thyroid carcinoma (PTC) classified as Intermediate Risk (Intermediate-Low or Intermediate-High) at a public endocrinology center in Northeastern Brazil. The cohort was divided into those with structural lymph node and/or distant recurrence and disease-free. Univariate and multivariate analyses were performed to identify independent predictors. **Results:** The cohort was predominantly female (90.2%) and mixed-race (89.3%), with a mean follow-up of 8.38 ± 4.9 years. Structural recurrence occurred in 23.0% ($n = 26$). Comparing recurrence vs. disease-free groups, no differences were found regarding age, tumor size, vascular/lymphatic invasion, or extrathyroidal extension. Although lymph node metastases at diagnosis were more frequent in the recurrence group (76.9% vs. 39.1%; $p = 0.0015$), N1b status was not associated with higher recurrence compared to N1a ($p = 0.845$). Conversely, bilateral multifocality was higher in the recurrence group (65.2% vs. 30.1%; $p = 0.017$). On multivariate analysis, only bilateral multifocality emerged as an independent predictor of recurrence (OR: 4.03, 95%: 1.1–14.8; $p = 0.035$). Latest dynamic stratification showed excellent response in 38.5% of the recurrence group vs. 73.6% of the disease-free group, while structural incomplete response was present in 53.8% and 5.7%, respectively. Regarding therapy, all recurrence patients and 83.9% of disease-free patients received radioiodine (RAI). **Conclusion:** In this cohort, classic features like N1b status did not predict recurrence within the ATA 2025 Intermediate Risk category. Instead, bilateral multifocality was the only independent predictor of recurrence, although its wide confidence interval reflects sample size limitations. Furthermore, the high rate of RAI usage in disease-free patients suggests potential overtreatment. These results underscore the need to refine international guidelines with demographically validated markers to optimize therapeutic decisions. **Keywords:** thyroid neoplasms; prognosis; risk assessment.



DISFUNÇÕES TIREOIDIANAS

2824 TYPE 2 DEIODINASE ORFA-GLY3ASP POLYMORPHISM (RS12885300) AND MODERATE TO SEVERE COVID-19: A RETROSPECTIVE COHORT

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Introduction: The thyroid gland expresses ACE2 and TMPRSS2, key receptors for SARS-CoV-2 entry. While the DIO2 rs12885300 polymorphism is linked to variations in thyroid hormone levels, its influence on COVID-19 severity is unknown. **Objective:** To investigate the association of the DIO2 ORFa-Gly3Asp polymorphism (rs12885300) with severity and mortality in hospitalized COVID-19 patients. **Methods:** We conducted a retrospective cohort study (June–August 2020) including moderate-to-severe COVID-19 patients hospitalized at a tertiary referral center in Paraíba, Brazil. The polymorphism was genotyped via TaqMan Real-Time PCR. Primary outcome was in-hospital mortality; secondary outcomes included thyroid function tests (TSH, fT3, fT4, rT3, thyroglobulin), and clinical severity scores (NEWS2, qSOFA, CT-score) assessed within 48h of admission. Hardy-Weinberg equilibrium was verified, and intergroup comparisons used Kruskal-Wallis and Mann-Whitney tests. Univariate logistic regression identified mortality predictors. Statistical significance was set at $p < 0.05$; analyses were performed using GraphPad Prism 7.0. **Results:** Among 220 included patients, genotype distribution was in equilibrium: 54.5% C/C, 36.8% C/T, and 8.6% T/T. Median age was 62 years, and 60.4% were male. No differences across genotypes were observed in age ($p = 0.196$), sex ($p = 0.16$), comorbidities, thyroid function tests, length of hospital stay (median 6 days; $p = 0.224$), or clinical severity scores. Overall mortality was 17.3% ($n = 38$), and 24.5% required ICU admission, with no significant intergroup differences. Univariate analysis identified cardiovascular shock (OR 48.7; $p < 0.0001$) and ICU admission (OR 30.6; $p < 0.0001$) as the strongest mortality predictors. Although the DIO2 polymorphism was not associated with mortality ($p = 0.730$), thyroid parameters revealed as prognostic markers: lower fT3 (OR 0.496; $p = 0.003$), and lower fT3/fT4 ratio (OR 0.636; $p = 0.040$) were significantly associated with death, while elevated rT3 showed a protective association (OR 0.012; $p = 0.015$). **Conclusion:** Although the DIO2 rs12885300 polymorphism was not directly associated with clinical outcomes, thyroid hormones were associated with prognostic markers for mortality in hospitalized COVID-19 patients. **Keywords:** COVID-19; thyroid function; DIO2.

EPIDEMIOLOGIA

2827 SELENIUM STATUS AND THYROID FUNCTION IN BRAZILIAN ADULTS: NO INDEPENDENT ASSOCIATION IN ELSA-BRASIL

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Introduction: Selenium plays an essential role in thyroid hormone metabolism and antioxidant defense and is frequently used as a complementary therapy in thyroid disorders. However, evidence supporting a beneficial effect of higher selenium status on thyroid function in the general population remains limited and inconsistent. **Objective:** To evaluate whether serum selenium status is independently associated with thyroid dysfunction and thyroid hormone levels in a large Brazilian adult cohort. **Methods:** We conducted a cross-sectional analysis of 1,644 participants from the ELSA-Brasil cohort with available serum selenium measurements. Selenium levels were categorized as low (<70 ; $n = 749$), adequate ($70-120$; $n = 768$), and high (≥ 120 ; $n = 127$). Thyroid dysfunction was defined according to TSH-based criteria. Linear regression models assessed associations between selenium categories and TSH levels, while logistic regression models evaluated associations with hypothyroidism. Multivariable models were adjusted for age, sex, body mass index, smoking status, race/ethnicity, education level, and alcohol consumption. **Results:** In unadjusted analyses, higher selenium categories were associated with modestly higher TSH concentrations and increased odds of hypothyroidism (OR 1.92; 95% CI 1.08–3.44 for high vs. low selenium). However, these associations were attenuated after multivariable adjustment and were no longer statistically significant (adjusted OR 1.63; 95% CI 0.88–3.00). Similarly, selenium status was not independently associated with TSH levels in adjusted linear models. No significant associations were observed between selenium status and free T4, free T3, or anti-thyroid peroxidase antibodies. **Conclusion:** In this large population-based study, serum selenium status was not independently associated with thyroid dysfunction or thyroid hormone levels after adjustment for relevant confounders. These findings do not support a protective effect of higher selenium status on thyroid health and reinforce the need for individualized supplementation decisions guided by documented deficiency or clear clinical indication. **Keywords:** selenium; thyroid function; epidemiology.



NÓDULOS E CÂNCER DE TIREOIDE

2830 SCREENING FOR RET SOMATIC VARIANTS IN A COHORT OF PATIENTS WITH MEDULLARY THYROID CANCER IN A TERTIARY CENTER

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Introduction: Medullary thyroid carcinoma (MTC) arises from the parafollicular C cells of the thyroid gland and it may occur sporadically or as part of the inherited cancer syndrome multiple endocrine neoplasia type 2 (MEN2), which is caused by germline pathogenic variants in the *RET* gene. In most sporadic cases, pathogenic variants in *RET* can be identified. Approximately 70% of these tumors harbor a single somatic variant, while about 20% present additional coexisting variants, likely contributing to intratumoral heterogeneity. **Objective:** To investigate somatic *RET* variants in patients with hereditary or sporadic MTC. **Methods:** DNA was extracted from 132 formalin-fixed paraffin-embedded (FFPE) tumor samples from patients with MTC and polymerase chain reaction amplification of *RET* exons 11, 14, and 16 was performed, followed by Sanger sequencing. **Results:** To date, 61 samples have been successfully analyzed. In exon 16, 16 samples presented the pathogenic variant p.M918T. In exon 11, two samples harbored pathogenic variants in codon 634; seven samples presented the polymorphism p.G691S, and one sample exhibited the variant of uncertain significance (VUS) p.P628S. No pathogenic variants were identified in exon 14 (52/61); however, the synonymous polymorphism p.S836S was detected in three cases. Other variants detected in this cohort included p.A545A (exon 8), p.L712R, p.L769L (exon 13), and p.A883P (exon 15). The p.G691S variant identified in 7/61 tumors in our cohort has been reported by Elisei et al. to occur more frequently in MTC patients than in the general population. **Conclusion:** These findings reinforce the central role of *RET* variants in sporadic MTC and highlight the molecular heterogeneity of these tumors. Molecular characterization of this cohort may contribute to understanding tumor characteristics with possible prognostic and therapeutic implications. **Keywords:** medullary thyroid cancer; *RET*; sanger sequencing.

NÓDULOS E CÂNCER DE TIREOIDE

2831 DETECTION OF RET VARIANTS IN LIQUID BIOPSY OF MEDULLARY THYROID CARCINOMA: A COMPARISON BETWEEN DIGITAL PCR AND NEXT-GENERATION SEQUENCING

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Introduction: Multiple endocrine neoplasia type 2 (MEN2) is caused by pathogenic *RET* germline variants. Our laboratory focuses on the detection of circulating tumor DNA (ctDNA) as a non-invasive strategy to identify metastatic disease in patients with medullary thyroid carcinoma (MTC). Preliminary studies have shown that somatic *RET* variants (V804L/M, Y806C/N and, G810C/S), acquired during MTKI therapy, may alter RET structure, thereby contributing to treatment resistance and disease progression. **Objective:** To develop and validate a liquid biopsy (LB) assay for the detection of *RET* variants acquired during MTC progression. **Methods:** Peripheral blood samples were collected from patients with advanced MTC using Cell-Free DNA tubes. ctDNA was extracted from plasma and variants in codons 630/634, 804/806/810 were analyzed by digital PCR (dPCR) with customized TaqMan probes. Detection of the M918T variant was performed using a commercially validated dPCR probe. The dPCR results were compared with next-generation sequencing (NGS) data obtained from the same samples. **Results:** Two probe strategies were designed to detect the target variants. The first one, “double wild-type (WT) resistance probe”, employs a FAM-labeled probe that binds to the WT-sequence adjacent to the mutation site; the presence of a variant disrupts this binding. A VIC-labeled probe binds to a nearby region, allowing signal detection only when the mutation is present. This approach was applied to codons 804/806/810. The second strategy, the “degenerated probe” approach, used for codons 630/634, involves FAM and VIC-probes targeting the same region, with the VIC-probe recognizing the WT sequence and the FAM-probe recognizing the mutated sequence. Fifteen patients were analyzed. Using the M918T strategy, dPCR detected the variant in 3/15 patients, consistent with the NGS results, which identified *RET* variants in the same cases. However, the customized TaqMan probes based on double-WT and degenerated strategies did not yield robust results. They failed to detect variants in samples known to harbor mutations, and a control sample negative for *RET* variants showed probe detection for codons 630/634 in LB analysis. In contrast, NGS not only confirmed the dPCR findings but also identified additional variants in several LB samples. **Conclusion:** NGS demonstrated greater sensitivity and provided more comprehensive information than dPCR for the detection of *RET* variants in LB samples from patients with MTC. **Keywords:** next-generation sequencing; liquid biopsy; medullary thyroid carcinoma.

METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

2832 PREVALENCE OF HEPATIC STEATOSIS IN PATIENTS WITH RESISTANCE TO THYROID HORMONE BETA (RTH β) EVALUATED BY MRI-PDFF

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Introduction: Resistance to Thyroid Hormone type Beta (RTH β) is a rare disorder caused by mutations in the thyroid receptor β gene, leading to impaired action of triiodothyronine (T₃) in tissues with high expression of this receptor, such as the liver. While thyroid hormones play a key role in hepatic lipid metabolism, the prevalence of steatosis in RTH β remains unclear in the literature. Previous studies used less sensitive imaging methods compared to Proton Density Fat Fraction (PDFF) magnetic resonance imaging (MRI).

Objective: To evaluate the prevalence of hepatic steatosis using MRI-PDFF, the non-invasive gold standard for liver fat quantification, in patients with a clinical and molecular diagnosis of RTH β . **Methods:** This cross-sectional study evaluated 7 patients (age ≥ 16 years) with RTH β followed at HCFMRP-USP. Hepatic fat content was quantified using MRI-PDFF (1.5T). Anthropometric data and laboratory tests (lipid profile, glycemic markers, liver and thyroid function) were collected. **Results:** The prevalence of hepatic steatosis was 28% (2/7), with both cases classified as moderate steatosis (PDFF between 11.3% and 13.2%). Both affected individuals presented coexisting metabolic risk factors, such as overweight and increased abdominal circumference. The mean global hepatic fat fraction was $5.4 \pm 4.9\%$. **Conclusion:** The prevalence of hepatic steatosis in RTH β was similar to the global population prevalence. These findings suggest that RTH β alone may not be sufficient for the development of hepatic steatosis, manifesting predominantly in the presence of associated metabolic risk factors. Studies with a larger number of participants, and compared to control individuals matched for other important factors involved in the pathophysiology of the disease — BMI, abdominal circumference, insulin resistance parameters, total cholesterol and triglyceride levels, as well as alcohol consumption — would be needed to reach more assertive conclusions. **Keywords:** resistance to thyroid hormone type beta; steatosis; MRI-PDFF.

NÓDULOS E CÂNCER DE TIREOIDE

2833 COMPARISON BETWEEN INVASIVE ENCAPSULATED FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA (IEFVPTC) AND THE INFILTRATIVE FOLLICULAR AND CLASSIC SUBTYPES OF PAPILLARY THYROID CARCINOMA REGARDING RESPONSE TO THERAPY: A RETROSPECTIVE COHORT STUDY

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Introduction: Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the thyroid gland. Historically, the Classic subtype has been the most prevalent, followed by the Follicular Variant of PTC (FVPTC). In 2022, the World Health Organization reorganized FVPTCs, classifying them according to histological and molecular criteria. Among these categories are the Invasive Encapsulated Follicular Variant of PTC (IEFVPTC) and the Infiltrative Follicular PTC subtype, whose biological behavior and prognosis remain incompletely characterized, particularly concerning response to therapy. **Objective:** To compare patients with IEFVPTC, Infiltrative Follicular PTC, and Classic PTC regarding the presence of an excellent response to therapy one year after initial treatment and at the last follow-up evaluation. **Methods:** This retrospective cohort study comparatively analyzed patients with the three aforementioned tumor types who underwent total thyroidectomy and were treated or not with radioactive iodine. The outcomes were the presence of an excellent response to therapy one year after initial treatment and at the last follow-up visit. Statistical analysis of numerical variables was performed using the Gamma and Wald tests, and categorical variables were analyzed using the chi-square and proportion tests. **Results:** A total of 164 patients were included in the analysis. The mean age was 50.7 ± 14.2 years, and the majority of patients were women (134; 84.8%). The mean follow-up time for the cases was 70.7 ± 45.2 months. An excellent response at one year was observed in 10/13 (76.9%) cases with IEFVPTC, 39/49 (79.6%) with Infiltrative Follicular PTC, and 66/102 (64.7%) with Classic PTC ($p = 0.149$). At the last follow-up visit, the group with Infiltrative Follicular PTC showed a higher percentage of excellent response compared with the other two groups [IEFVPTC: 9/13 (69.2%), Infiltrative Follicular PTC: 44/49 (89.8%), and Classic PTC: 72/102 (70.6%); $p = 0.029$]. **Conclusion:** Although the groups did not differ in the rate of excellent response to therapy one year after initial treatment, patients with Infiltrative Follicular PTC exhibited a higher rate of excellent response at the last follow-up visit compared with those with IEFVPTC and Classic PTC. **Keywords:** carcinoma, papillary, follicular; prognosis; thyroid neoplasms.

NÓDULOS E CÂNCER DE TIREOIDE

2835 REAL-WORLD OUTCOMES WITH MULTIKINASE INHIBITORS IN DIFFERENTIATED THYROID CANCER: AN INSTITUTIONAL ANALYSIS

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Introduction: Radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) is associated with poor prognosis. Multikinase inhibitors (MKIs) improve progression-free survival in phase III trials; however, real-world outcomes remain heterogeneous. **Objective:** To evaluate the effectiveness and safety of MKIs in patients with RAI-R DTC treated at tertiary referral center. **Methods:** We conducted a retrospective cohort study including patients with progressive RAI-R DTC treated with MKIs between 2015 and 2024. Patients were eligible for systemic therapy if they had evidence of structural disease progression, symptomatic disease, or clinically significant tumor burden considered not amenable to local therapies. RAI-refractory disease was defined according to standard criteria. Tumor response was assessed according to RECIST 1.1 criteria based on imaging studies performed during follow-up. Data regarding demographics, tumor characteristics, treatment exposure, adverse events, dose modifications, and survival status were extracted from medical records. All patients accessed MKI therapy through judicialization. **Results:** A total of 28 patients were included, the majority of whom were female (n = 17; 60.7%) and had papillary thyroid carcinoma (n = 15; 53.6%). The mean age at diagnosis was 57.2 ± 11.3 years. First-line MKI therapy was sorafenib in 25 patients (89.3%) and lenvatinib in 3 patients (10.7%). The median time between treatment indication and initiation was 3 months. All patients experienced at least one adverse event, and dose reductions were required in 19 (68%) patients, with a mean time to first dose reduction of 2 months. The best objective response to first-line therapy was partial response in 2 patients (8%), stable disease in 10 (40%), and progressive disease in 13 (52%). Nine patients (32%) received second-line therapy, most commonly lenvatinib (8 patients). Among those treated with sorafenib as first-line therapy, 18 (72%) discontinued treatment (10 due to adverse events and 8 due to disease progression). Survival status was available for 25 patients; of these, 16 (64%) had died and 9 (36%) were alive at the last follow-up. **Conclusion:** In this real-world cohort of patients with RAI-R DTC, treatment with MKIs was associated with frequent adverse events and a high rate of dose reductions and treatment discontinuation. Objective response rates were modest, highlighting the challenges of managing advanced DTC in routine clinical practice. **Keywords:** radioiodine-refractory differentiated thyroid cancer; multikinase inhibitors; real world.

NÓDULOS E CÂNCER DE TIREOIDE

2837 PATHOLOGICAL LYMPH NODE STATUS AS THE DOMINANT INDEPENDENT PREDICTOR OF RECURRENCE IN DIFFERENTIATED THYROID CARCINOMA: A 3,983-PATIENT SINGLE-CENTER ANALYSIS

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Introduction: Differentiated thyroid carcinoma (DTC) has an excellent prognosis, yet accurately identifying patients at higher risk of recurrence remains essential for tailoring follow-up and adjuvant therapy. Current risk stratification systems incorporate multiple pathological features, but the relative contribution of each variable in predicting structural recurrence is not well established in large contemporary cohorts. **Objective:** To evaluate independent predictors of structural recurrence in a large single-center cohort of patients undergoing total thyroidectomy for DTC, with emphasis on the role of pathological lymph node status. **Methods:** Retrospective analysis of 3,983 consecutive total thyroidectomies performed for DTC at a tertiary oncology center (2014–2024). Data were extracted from an integrated surgical logbook, pathology reports, and the institutional Hospital Cancer Registry. ATA 2015 risk stratification was applied using pathological staging (pT/pN). Recurrence was defined as structural disease documented in the cancer registry. Univariate and multivariate logistic regression analyses were performed to identify independent predictors. **Results:** Among 3,654 patients with follow-up data (median 9.5 months), 81 (2.2%) developed structural recurrence, predominantly regional (72/81, 88.9%). Recurrence rates by pN status were: N0, 1.1% (12/1,081); N1a, 5.9% (31/529); and N1b, 6.2% (14/227; p < 0.001). By ATA risk category, rates were: low 1.0%, intermediate 4.4%, and high 5.7% (p < 0.001). On multivariate analysis (n = 1,931; 57 events), pathological lymph node metastasis was the strongest independent predictor: pN1a (OR 4.74; 95%CI 2.41–9.30; p < 0.001) and pN1b (OR 3.94; 95%CI 1.66–9.38; p = 0.002). Male sex was also significant (OR 1.76; 95%CI 1.01–3.05; p = 0.045). Notably, advanced pT stage, extrathyroidal extension, and multifocality did not reach statistical significance. Disease-specific mortality was 0.15% (6/3,983). **Conclusion:** Pathological lymph node metastasis is the dominant independent predictor of structural recurrence in DTC, outweighing primary tumor characteristics. These findings reinforce the central role of nodal status in postoperative risk assessment and may inform decisions regarding prophylactic central neck dissection and the appropriate follow-up intensity. **Keywords:** lymph node metastasis; differentiated thyroid cancer; risk factor.



AUTOIMUNIDADE

2839 GRAVES' DISEASE IN CHILDREN AND ADOLESCENTS: CLINICAL CHARACTERISTICS, MANAGEMENT STRATEGIES, AND THYROID EYE DISEASE PROFILE

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Introduction: Graves' disease (GD) is the leading cause of hyperthyroidism worldwide. Although its clinical presentation is well characterized in adults, data on pediatric GD remain limited, particularly regarding thyroid eye disease (TED). **Objective:** To evaluate the clinical presentation and treatment strategies in children diagnosed with GD. **Methods:** This retrospective study included patients diagnosed with GD before the age of 18 years. Patients were evaluated for epidemiological characteristics, thyroid function biomarkers, clinical features of TED, therapeutic interventions, and GD treatment modalities. **Results:** A total of 88 patients were included, of whom 78% were female. The mean age at diagnosis was 12 ± 4.2 years. Thyroid function assessment showed a mean TSH of 1.89 ± 3.42 μ IU/mL and mean free T4 of 4.26 ± 2.61 ng/dL. TSH receptor antibodies (TRAb) were positive in 84.62% of patients, with a mean level of 29.41 ± 27.46 IU/L (reference < 3.10 IU/L). At initial evaluation, the mean thyroid volume measured by ultrasound was 24.84 ± 14.86 mL. TED evaluation demonstrated a mean proptosis of 20.95 ± 3.37 mm, mean palpebral fissure height of 12.4 ± 1.75 mm, and mean Clinical Activity Score (CAS) of 0.7 ± 1.0 . According to EUGOGO classification, TED severity was mild in 50% of patients and moderate-to-severe in 25%, while no patients had sight-threatening disease. Notably, 25% of patients had no clinical signs of TED. The primary treatment for mild TED consisted of lubricating eye drops. Only one patient required intravenous glucocorticoid therapy, receiving a cumulative dose of 4.5 g of methylprednisolone over 12 weeks. The preferred initial treatment modality for GD was anti-thyroid drugs (ATD), used in 79.31% of patients, followed by radioiodine therapy (RAI) in 6.98% and thyroidectomy 13.79%. The mean initial methimazole dose was 21.75 ± 14.3 mg. After 12 months, 85.5% of patients remained on ATD therapy, 12.5% had received RAI, and 2% had achieved remission. At 24 months, 84% remained on ATD, 13% had received RAI, and 3% achieved remission. At 36 months, 75% remained on ATD, 15% had received RAI, and 10% achieved remission. At 48 months, 55% remained on ATD, 11% had received RAI, 22% achieved remission, and 11% thyroidectomy. **Conclusion:** This study demonstrates a high prevalence of TED in pediatric patients with GD compared with adult; however, most cases presented with mild disease and a low frequency of severe or sight-threatening manifestations. **Keywords:** Graves' disease; children; thyroid eye disease.

DISFUNÇÕES TIREOIDIANAS

2844 TSH-PRODUCING PITUITARY ADENOMA (TSHOMA) IN A PATIENT UNDERGOING TOTAL THYROIDECTOMY FOR PAPILLARY THYROID CARCINOMA

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Case presentation: G.L.R., 35 years old, male, underwent total thyroidectomy with neck dissection in 2022 for classic and follicular papillary thyroid carcinoma with lymph node metastasis. The AJCC (American Joint Committee on Cancer) TNM staging system was T2N1BMx. He underwent radioiodine therapy, showing an excellent response with a TSH goal of 0.5 to 2.0 mIU/L. Even with high doses of up to 450 mcg (4.3 mcg/kg) of levothyroxine, the patient did not present suppression of TSH levels and free T4 levels were high (see table). Before surgery, the patient's thyroid function showed free T4 levels at the upper limit of normal: TSH 1.6 (0.4 to 4.5 mIU/L) and FT4 1.79 (RV 0.85 to 1.86). To rule out alterations in TBG, FT4 was measured by mass spectrometry, maintaining a high value of 3.3 (RV up to 2.2). The genetic test for thyroid hormone resistance was negative. The thyroid function of the patient's siblings showed no alterations. The dosage of the alpha subunit of the patient's pituitary hormones was 1.25 IU/L (RV < 0.7 IU/L), and the alpha subunit/TSH x 10 ratio was 9. The patient underwent magnetic resonance imaging of the pituitary gland, which revealed an image suggestive of a pituitary adenoma measuring 10 mm. Given this, a TSH-producing pituitary adenoma (TSHoma) was suspected and the patient was referred for evaluation by neurosurgery. **Discussion:** TSHoma is the least common type of pituitary tumor (0.5 to 3%). It usually presents with obvious symptoms of hyperthyroidism with normal or high TSH levels and high levels of total and free T4 and T3. Approximately 50%–85% of patients with TSHoma have high concentrations of the alpha subunit of pituitary hormones. The presence of a macroadenoma on MRI is strong evidence of a TSH-secreting tumor, particularly in the presence of an elevated alpha subunit. The main differential diagnoses of TSHoma are resistance to thyroid hormones and TBG alterations, which were ruled out in this patient. Finally, surgical removal of the tumor is the best treatment for TSHoma. **Final Comments:** TSHoma is a rare pathology of hyperthyroidism and was suspected in this patient due to non-suppression of TSH with high doses of levothyroxine. Because of its rarity, the diagnosis must involve the exclusion of other conditions such as resistance to thyroid hormone and TBG alterations. **Keywords:** thyrotropin-secreting adenoma; central hyperthyroidism; papillary thyroid carcinoma.

CIRURGIA DA TIREOIDE

2850 TEMPORAL TRENDS IN THE SURGICAL MANAGEMENT OF PAPILLARY THYROID CANCER: A DECADE OF TRANSITION TOWARD PARTIAL THYROIDECTOMY

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Introduction: Thyroid cancer is the most common endocrine malignancy, with a steadily increasing incidence in recent decades, largely driven by the detection of small papillary carcinomas. The optimal surgical management of differentiated thyroid cancer (DTC) remains debated, particularly regarding the extent of thyroid resection. Historically, total thyroidectomy was considered the standard approach because it facilitates radioactive iodine therapy and postoperative surveillance with serum thyroglobulin. However, growing evidence over the past two decades has questioned the need for extensive surgery in all patients, especially those with low-risk tumors. This has led to a paradigm shift toward surgical de-escalation aimed at maintaining oncologic control while reducing morbidity and improving quality of life. **Materials and methods:** We analyzed patients treated at a single tertiary institution between January 2014 and December 2024. Inclusion criteria were suspicion of papillary thyroid carcinoma on preoperative fine-needle aspiration and no previous treatment. **Results:** A total of 4,379 consecutive patients were included, comprising 1,097 males (25.0%) and 3,282 females (74.9%). Age at diagnosis ranged from 10 to 94 years (mean 42.8 years), and the mean tumor size was 11 mm. Partial thyroidectomy was performed in 800 patients (18.3%), whereas 3,579 patients (81.7%) underwent total thyroidectomy. There was no significant difference in mean tumor size between surgical groups. Over time, the proportion of partial thyroidectomies increased significantly from 3.3% in 2014 to 57.6% in 2024 ($p < 0.001$). This increase was associated with a significant reduction in complications, particularly vocal fold paralysis and postoperative hypocalcemia, without affecting event-free or overall survival. **Conclusion:** The progressive adoption of partial thyroidectomy was associated with fewer complications while maintaining equivalent oncologic outcomes, supporting surgical de-escalation in appropriately selected patients with differentiated thyroid cancer. **Keywords:** thyroidectomy; thyroid; cancer.

CIRURGIA DA TIREOIDE

2851 DECOMPENSATED GRAVES' DISEASE IN PREGNANCY: WHEN SECOND-TRIMESTER THYROIDECTOMY BECOMES INEVITABLE

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Introduction: Decompensated hyperthyroidism during pregnancy is a high-risk maternal-fetal condition, associated with heart failure, preeclampsia, thyroid storm, and increased perinatal morbidity and mortality. Management requires accurate laboratory diagnosis, prompt initiation of antithyroid drugs with dose adjustment according to gestational age, adjunctive beta-blocker therapy for adrenergic symptom control, and strict monitoring of thyroid function. Thyroidectomy is reserved for selected situations, including failure of clinical and biochemical control, severe drug intolerance, or absolute contraindications to antithyroid therapy, with the second trimester representing the period of lowest surgical risk. **Case report:** A 29-year-old woman with Graves' disease presented with severe hyperthyroidism, with free T4 of 7.76 ng/dL (reference range [RR]: 0.54–1.70), total T3 > 650.97 ng/dL (RR: 78–189), TSH < 0.005 μ IU/mL (RR: 0.38–5.33), and TRAb 20.3 IU/L (RR $\leq$ 1.75). These findings were associated with significant systemic symptoms and cardiovascular involvement, including persistent tachycardia, dyspnea on mild exertion, lower-limb edema, and left ventricular systolic dysfunction (initial ejection fraction of 28%). Treatment was initiated with methimazole 40 mg/day combined with beta-blocker therapy, with unsatisfactory clinical and biochemical response. During hospital admission the patient developed liver enzyme elevation, with ALT up to 73 U/L (RR < 33), GGT 154 U/L (RR < 38), and alkaline phosphatase 554 U/L (RR: 65–300). After partial clinical stabilization and cardiologic evaluation, an ongoing pregnancy was identified. Given the absolute contraindication to radioiodine therapy, inadequate biochemical control, and persistent maternal risk, preoperative preparation with methimazole, a beta-blocker (metoprolol), and potassium iodide was undertaken, followed by total thyroidectomy performed during the second trimester of pregnancy. Postoperatively, hypoparathyroidism was observed and replacement therapy with levothyroxine, calcium carbonate, and calcitriol was initiated. The patient remained under high-risk obstetric follow-up, with favorable maternal and fetal outcomes. **Conclusion:** This case highlights the importance of individualized management of decompensated hyperthyroidism during pregnancy. Although clinical treatment is the first line of defense, thyroidectomy in the second trimester is an option in exceptional situations. **Keywords:** Graves' disease; pregnancy; thyroidectomy.



NÓDULOS E CÂNCER DE TIREOIDE

2852 FROM TOXICITY TO CONTROL: INDIVIDUALIZED LENVATINIB DOSE ADJUSTMENT IN ADVANCED THYROID CANCER

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Introduction: Radioiodine-refractory follicular thyroid carcinoma represents a complex clinical scenario in which tyrosine kinase inhibitors, such as Lenvatinib, play a central role in controlling metastatic disease. Despite its antitumor efficacy, Lenvatinib is associated with a relevant toxicity profile related to inhibition of the VEGFR and FGFR pathways, resulting in cardiovascular, renal, metabolic, and mucocutaneous adverse events. Therefore, systematic monitoring and individualized toxicity management are essential to ensure safe treatment continuation and optimize clinical outcomes. **Case description:** A 67-year-old female patient with radioiodine-refractory follicular thyroid carcinoma and pulmonary and bone metastases, with comorbid systemic arterial hypertension, type 2 diabetes mellitus, dyslipidemia, and osteoporosis. Treatment with Lenvatinib was initiated at the full dose of 24 mg/day in July 2023. After approximately two months, the patient developed significant toxicities, including severe mucositis, severe hyponatremia, and hypocalcemia, leading to drug discontinuation. Following clinical resolution of adverse events and correction of hydroelectrolytic disturbances, a multidisciplinary reassessment was performed, and Lenvatinib was reintroduced at a reduced dose (10 mg + 4 mg) in November 2025. After reintroduction, a management protocol was implemented based on: (1) serial laboratory monitoring of electrolytes (sodium, calcium, and magnesium), renal and hepatic function, and proteinuria; (2) frequent clinical follow-up for early identification of mucocutaneous and metabolic toxicities; and (3) continuous adjustment of supportive therapy. Recurrent but less severe episodes of hyponatremia, hypomagnesemia, serum calcium fluctuations, and proteinuria were managed with targeted supplementation, medication adjustments, and specialized follow-up, without progression to dose-limiting toxicities. The reduced-dose regimen resulted in sustained improvement in tolerability. **Conclusion:** This report highlights that appropriate management of Lenvatinib-associated toxicities is crucial to ensure treatment continuity in patients with advanced follicular thyroid carcinoma. Reintroduction at a reduced dose, combined with intensified clinical and laboratory surveillance and a multidisciplinary approach, proved to be an effective strategy for controlling adverse events while preserving treatment safety. **Keywords:** follicular thyroid carcinoma; lenvatinib; drug toxicity.

NÓDULOS E CÂNCER DE TIREOIDE

2853 CUTANEOUS METASTASIS FROM ADVANCED PAPILLARY THYROID CARCINOMA: A CASE REPORT

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Introduction: Cutaneous metastases from papillary thyroid carcinoma (PTC) represent an exceptionally rare manifestation of disseminated disease, associated with poor prognosis and a median survival of approximately 19 months after diagnosis. Although distant metastases occur in 10%–15% of differentiated thyroid carcinomas, the skin is an uncommon site, with lungs and bones being the most frequent locations. PTC accounts for approximately 41% of cutaneous thyroid metastases, with typical presentation as nodules on the scalp, face, and neck, retaining the histopathological and immunohistochemical characteristics of the primary tumor. **Case report:** A 64-year-old male patient, diagnosed with stage IVB PTC (T3bN0M1) in 2017, underwent total thyroidectomy, bilateral neck dissection, and required a cumulative dose of 900 mCi of iodine-131 over 7 years. He has been using Lenvatinib for about 1 year, currently at 10 mg/day, a dose reduced due to intolerance to higher doses (fatigue, loss of appetite, and diarrhea). During follow-up, a cutaneous nodule was identified in the sternal region in the last year, an atypical site compared to the classic distribution described in the literature. Anatomopathological and immunohistochemical analysis (February 21, 2026) revealed a morphological pattern compatible with metastasis of primary thyroid carcinoma: partially positive CK7, positive TTF-1, and positive PAX8 in neoplastic cells, with negativity for CK20, calcitonin, CD56, and Napsin A. This profile confirms the thyroid origin and excludes relevant differential diagnoses, including medullary carcinoma, neuroendocrine neoplasm, and lung adenocarcinoma. This scenario was corroborated by serum thyroglobulin of 14,073 ng/mL in the context of TSH suppression, reflecting active structural disease and high tumor burden. **Conclusion:** This report illustrates a rare cutaneous manifestation of advanced, radioiodine-refractory PTC in an atypical location, with diagnostic confirmation supported by a classic immunohistochemical profile (TTF-1+, PAX8+, CK7+, CK20-, calcitonin-). Early identification is clinically relevant, as it may signal disease progression and guide adjustments in multimodal therapeutic strategy. This case reinforces the importance of biopsy and immunohistochemical investigation in the presence of atypical cutaneous lesions in patients with differentiated thyroid carcinoma. **Keywords:** papillary thyroid carcinoma; cutaneous metastasis; radioiodine-refractory thyroid cancer.



NÓDULOS E CÂNCER DE TIREOIDE

2858 BRAIN METASTASES FROM DIFFERENTIATED THYROID CARCINOMA: DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN A TERTIARY-CENTER COHORT

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Introduction: Brain metastases (BM) from differentiated thyroid carcinomas (DTC) are rare, and evidence guiding their management remains limited. **Objective:** To evaluate clinical characteristics, treatment strategies, and outcomes of patients with DTC who developed BM. **Methods:** We retrospectively analyzed 11 patients with radiologically confirmed BM among 1532 DTC patients followed at an university hospital in southern Brazil between 1986 and 2026. Collected data included demographics, histology, treatments, clinical and radiological features, and outcomes. Overall survival (OS) from BM diagnosis to death or last follow-up was estimated using Kaplan-Meier analysis. **Results:** BM occurred in 11 patients (0.72%), five males and six females, with a mean age of 56.3 years at DTC diagnosis and 60.3 years at BM diagnosis. BM lesions were predominantly solitary (91%) and associated with peritumoral edema in 82% of patients. All patients had other extracranial metastatic sites, including the lungs (n = 8, 73%), bones (n = 8, 73%), liver (n = 2, 18%) and adrenal gland (n = 1, 9%). BM were diagnosed after the identification of other distant metastases in 55% of patients, before in 18%, and synchronously in 27%. The initial treatments included neurosurgery (three patients), stereotactic radiosurgery (five patients) and radioactive iodine (two patients). One patient received only palliative care due to poor clinical condition. Disease progression was observed in four patients within six months of the initial therapy, while two patients achieved a complete response following neurosurgical intervention. Median OS was 28 months, with seven deaths (64%) recorded during follow-up. Patients with performance status (PS) < 2 had significantly improved survival compared to those with PS ≥ 2 (53.5 vs. 9 months; p = 0.017). **Conclusion:** In patients with DTC, BM are associated with unfavorable outcomes, and PS at diagnosis appears to be an important prognostic factor for survival. Further studies are needed to define optimal management strategies, particularly for patients with good performance status who may benefit from aggressive treatment approaches. **Keywords:** brain metastasis; thyroid cancer; outcomes.

DISFUNÇÕES TIREOIDIANAS

2860 SUBACUTE THYROIDITIS MIMICKING A TI-RADS 5 THYROID NODULE IN AN HIV-POSITIVE PATIENT

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Introduction: Subacute thyroiditis (SAT), also known as De Quervain thyroiditis, is a relatively uncommon thyroid disorder. Viral infections are considered a possible trigger, often showing seasonal distribution. SAT is characterized by painful inflammation of the thyroid gland that may initially present with thyrotoxicosis and later progress to transient or permanent hypothyroidism. On ultrasound (US), it may appear as focal or diffuse hypoechoic areas with ill-defined margins, which can mimic thyroid nodules. **Case report:** R.C.C., a 42-year-old male with HIV infection and undetectable viral load, as well as dyslipidemia, presented with anterior cervical discomfort lasting approximately 45 days after a self-limited upper respiratory tract infection. He was referred with a thyroid US showing a TI-RADS 5 nodule (solid, hypoechoic, well-defined, with echogenic foci, measuring 34 × 11 mm and occupying the entire left lobe) and fine-needle aspiration biopsy (FNAB) with inconclusive cytology (Bethesda I). At the initial evaluation, he denied other symptoms; physical examination was unremarkable except for a palpable 3 cm thyroid nodule in the left lobe. Thyroid function tests, antithyroid antibodies, and repeat ultrasound were requested. One month later, he returned asymptomatic with laboratory results showing suppressed TSH (0.29 mIU/L) and normal free T4 (1.17 ng/dL), positive anti-thyroglobulin antibodies (205 IU/mL), and negative anti-TPO antibodies. Repeat ultrasound demonstrated reduction in left lobe volume and nodular images in the right lobe measuring 15 mm and 12 mm, classified as TI-RADS 3 and TI-RADS 2. Two months later, the patient developed constipation, cold intolerance, and somnolence. Laboratory tests showed elevated TSH (10.50 mIU/L) and low free T4 (0.6 ng/dL), positive anti-TPO antibodies (136 IU/mL), and increased anti-thyroglobulin levels (527 IU/mL). A new ultrasound showed no evidence of nodular lesions. Hypothyroidism was confirmed on repeat testing, and levothyroxine 50 mcg was initiated, leading to symptom improvement and normalization of thyroid function within six weeks. **Conclusion:** SAT may clinically and ultrasonographically mimic thyroid nodules, and FNAB findings may be inconclusive, increasing the risk of misdiagnosis. Therefore, SAT should be considered in the differential diagnosis of nodular thyroid lesions, particularly in atypical cases or when cytological findings are indeterminate, to avoid unnecessary interventions. **Keywords:** subacute thyroiditis; thyroid nodules; ultrasonography.



NÓDULOS E CÂNCER DE TIREOIDE

2865 OCCULT PAPILLARY THYROID MICROCARCINOMA INCIDENTALLY DETECTED ON PET SCAN DURING LYMPHOMA FOLLOW-UP

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Introduction: Occult papillary thyroid carcinoma is a well-recognized entity, generally considered low risk. The primary tumor in the thyroid is microscopic or undetectable on imaging; however, it may clinically manifest through cervical lymph node metastases, detected during physical examination or imaging studies. **Case report:** F.P.R., female, 76 years old, with hearing impairment and a history of stage II A diffuse large B-cell lymphoma, treated with reduced-dose R-CHOP and in remission since 2021. In 2022, a whole-body PET scan was performed to assess response to oncologic treatment and revealed a hypermetabolic cervical lymph node. Lymph node resection was performed, and histopathological examination showed metastatic papillary carcinoma to a lymph node measuring $2.1 \times 2.7 \times 1.3$ cm. The patient subsequently underwent total thyroidectomy with lymph node dissection. Histopathology revealed a papillary thyroid microcarcinoma (occult papillary carcinoma), follicular variant, located in the left thyroid lobe, measuring 0.2 cm in greatest dimension, adjacent to and interspersed with a subcapsular sclerotic area measuring 0.4 cm. The remaining lymph nodes were free of neoplasia. Final pathological staging was pT1a; pN1b; Mx. The patient was classified as intermediate-high risk, with a target TSH level of 0.5–1.0 mIU/L, and did not undergo radioactive iodine therapy. She remains under endocrinology follow-up with dynamic risk stratification, showing an excellent response at the last evaluation: thyroglobulin 0.98 ng/mL, anti-thyroglobulin antibodies 22 IU/mL, and cervical ultrasound without abnormalities. **Conclusion:** Papillary thyroid microcarcinoma (PTMC) may occasionally present aggressive features, including lymph node metastasis and extrathyroidal extension. In this case, early diagnosis of occult papillary carcinoma resulted from an incidental finding on PET scan, highlighting the importance of appropriate investigation of incidental uptake, even when imaging is performed for unrelated clinical indications. **Keywords:** occult papillary thyroid carcinoma; cervical lymph node metastasis; PET scan.

TRANSLACIONAL

NÓDULOS E CÂNCER DE TIREOIDE

2774 MIR-146B-5P OVEREXPRESSION IN PEDIATRIC DIFFERENTIATED THYROID CARCINOMA: DOES IT MIRROR THE AGGRESSIVE PROFILE OBSERVED IN ADULTS?

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Introduction: The incidence of differentiated thyroid carcinoma (DTC) in children and adolescents has increased over recent decades. In adults, microRNA (miRNA) profiling contributes to risk stratification, and miR-146b-5p is consistently associated with aggressive tumor behavior, including lymph node metastasis, recurrence, and BRAFV600E mutation. However, its prognostic role in pediatric DTC remains poorly defined. **Objective:** To evaluate miR-146b-5p expression in pediatric DTC and investigate its association with clinicopathological features, exploring parallels with adult prognostic data. **Methods:** In this retrospective study, miR-146b-5p expression was quantified by RT-qPCR in formalin-fixed paraffin-embedded samples from 23 patients ≤ 18 years diagnosed with DTC, along with matched adjacent normal thyroid tissue. Expression levels were correlated with clinicopathological variables, risk stratification, and long-term follow-up outcomes. **Results:** miR-146b-5p was overexpressed in 73.9% (17/23) of cases, displaying greater heterogeneity compared to adult cohorts. Increased expression was significantly associated with multifocality ($p = 0.044$), lymphatic invasion ($p = 0.007$), lymph node metastasis ($p = 0.002$), and number of metastatic lymph nodes ($p = 0.016$). No significant associations were observed with vascular invasion, extrathyroidal extension, tumor size, age at diagnosis, risk category, treatment response, or distant metastasis. **Conclusion:** Similar to adult DTC, miR-146b-5p overexpression in pediatric patients correlates with features of lymphatic dissemination and tumor aggressiveness. These findings suggest a potentially shared molecular prognostic signature across age groups and support further investigation of miR-146b-5p as a potential biomarker for risk stratification in pediatric thyroid cancer. **Keywords:** differentiated thyroid carcinoma; miR-146b-5p; pediatric thyroid cancer.

NÓDULOS E CÂNCER DE TIREOIDE

2854 COMPONENTS AND ANALYTICAL METHODS OF TUMOR MICROENVIRONMENT IN THYROID CANCER: A SCOPING REVIEW

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Introduction: The tumor microenvironment (TME) plays a central role in tumor progression, immune evasion, and response to therapy across many malignancies. In thyroid cancer — papillary, follicular, medullary, and anaplastic — immune and stromal interactions may influence tumor behavior and prognosis. However, literature on TME in thyroid cancer remains fragmented, with heterogeneous analytical approaches and inconsistent reporting of clinical outcomes. **Objective:** To systematically map the literature on the tumor microenvironment in thyroid cancer, identifying studied components, analytical methods, and reported clinical associations. **Methods:** A scoping review registered at Open Science Framework was conducted according to Joanna Briggs Institute methodology and reported following PRISMA-ScR guidelines. Searches were performed in MEDLINE, Embase, LILACS, Web of Science, and Scopus without restrictions on language or publication date. Eligible studies included original research using human samples from patients with histologically confirmed thyroid cancer. Two reviewers independently performed study selection and data extraction. Extracted variables included study characteristics, tumor subtype, TME components, analytical techniques, and clinical outcomes. Data were synthesized descriptively to map research trends and gaps. **Results:** A total of 420 studies were included. Publication activity increased markedly after 2021. Most studies originated from Asia, particularly China. Differentiated thyroid carcinomas — especially papillary thyroid carcinoma — accounted for most tumors, whereas medullary and anaplastic carcinomas were underrepresented. Immunohistochemistry was the most common analytical technique, followed by transcriptomic and bioinformatic approaches. Immune cell infiltration, including tumor-infiltrating lymphocytes and tumor-associated macrophages, was the most investigated TME component. Reporting of clinical variables such as staging, mortality, and prognostic outcomes was inconsistent. **Conclusion:** Research on the tumor microenvironment in thyroid cancer has expanded in recent years; however, important gaps remain. Studies focus mainly on differentiated tumors and conventional techniques. Rare but aggressive subtypes, such as medullary and anaplastic carcinomas, remain insufficiently explored. Greater methodological standardization and integration of molecular, spatial, and clinical data are needed to improve understanding of the TME and its clinical relevance. **Keywords:** thyroid cancer; microenvironment; analytical methods.



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