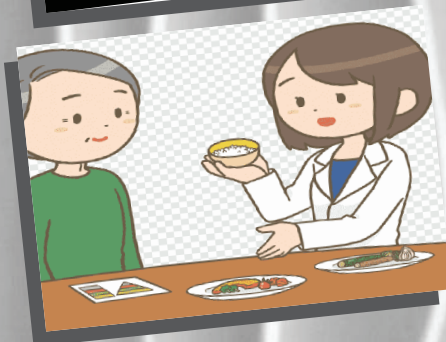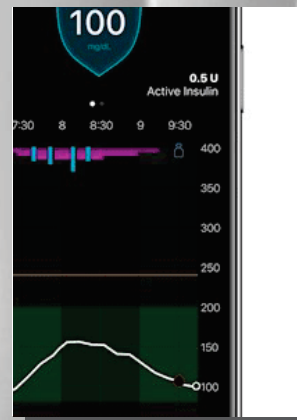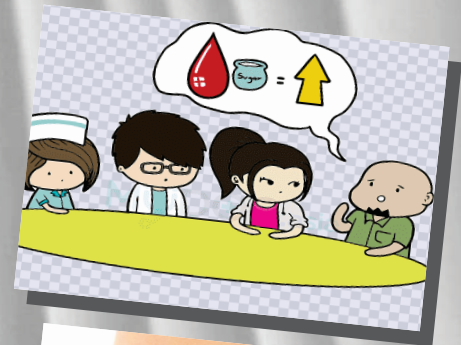# ENDOCRINOLOGIA & DIABETES CLÍNICA E EXPERIMENTAL

FACULDADE EVANGÉLICA MACKENZIE DO PARANÁ (FEMPAR)
HOSPITAL UNIVERSITÁRIO EVANGÉLICO MACKENZIE DE CURITIBA

Diabetes
Education versus Technology

Diabetes: Technology is ineffective without disease knowledge and education

The increase in the incidence of diabetes worldwide in this second millennium is worrying. Every year the number of people with type 1 diabetes and especially type 2 diabetics at younger ages grows. During the pandemic, there was an increase in the incidence of autoimmune diseases, including type 1 diabetes and Hashimoto's thyroiditis.

The main point of attention for this disease is the prevention of its complications that reduce quality and quantity of diabetic life. The prevention of such complications and even diabetes involves well-designed mass campaigns over a long period of time. We know that education programs administered without goals and for a short term do not achieve effective results in the control and education of a chronic pathology such as diabetes.

The results of studies on education and knowledge in diabetes, carried out at the end of the last century, gave endocrinologists the certainty that it is necessary to form a multidisciplinary team for the treatment of diabetes. It is important to remember that the strict control of diabetes, a chronic disease, demands expenses, but in the long term, with the control of complications, these costs are offsetted in relation to the decrease in the number of hospitalizations and absence from work.

The development of a well-structured program for educating the patient as well as his or her relatives, emphasizing that the main treatment is lifestyle change and blood glucose monitoring with intensive insulinization of three to four bites/day is crucial. A simple program presenting a balanced diet with more freedom as proved by the DAFNE study (Dose Adjustment For Normal Eating) gives more quality of life to insulin dependents. Having said that, we have to understand that freedom has its price and for better results knowledge is demandable through continuing education.

The DOCE project study (**Diabetes Objetivando Controle e Educação**) began 15 years ago by the Endocrinology and Diabetes Service of the *Hospital Universitário Evangélico Mackenzie*, in Curitiba, aiming at concomitant clinical and educational care. In order to have **Freedom**, it is necessary **Education** about a chronic disease, and it means to have an understandable chronic condition for the patient´s entire life! In other words, it means, in current times, that a child who developed DM1 at age 6 will deal with the disease during the most lively periods of his or her life such as childhood and adolescence.

At DOCE, we witness what the disease can do to a child: abandonment, guilt, maternal oppression, bullying at school, fear, horror of the bites, even using insulin on top of clothes and self-application without the presence of adults. It is much worse with these patients in adolescence: early sexual initiation, drugs, drinking, lying behavior in relation to the disease and family breakdown, that more frequently occur in the lower social strata. Exaggerated maternal protection is frequent in more affluent classes, which will make this child become an insecure adult.

The search for technology and miracle cure is inherent to all social strata. The start of using Libre sensor, insulin infusion pump, carbohydrate counting by specialized apps is expected as total freedom, until they realize that miracles do not exist and that responsibility in diabetes control will have to continue as part of their every day life. Believe us, in these 15 years, it was necessary in every clinical appointment to reiterate all the need for glycemic control, time in the goal, glycemic variability percentage, the balance of insulinization adjustments and the count of carbohydrates and how hypoglicemia should be avoided, recognized and promptly treated; understanding that an hypoglicemic event is not linked to have total freedom to eats sweets, chocolates and ice cream. It is usual to observe patients getting tired and many of them leaving the treatment, complaining about the demands related to it. Patients spend time without medical care, abandoning the technologies offered, returning to square one! How many times have we witnessed such attitudes and waited them to return to DOCE project study?

Despite all the mishaps, we achieved good results. The group of 15 years of assistance has no retinopathy or neuropathy. Some have albuminuria under treatment, but with stable creatinine clearance. This group has exams of unaffected large arteries and dyslipidemia under treatment even at a younger age (12 years). We continue to offer education, knowledge about the disease and, after this achievement, we offer technology; because **Technology** without **Education** is totally ineffective!

Maria Augusta Karas Zella

Mirnaluci Paulino Ribeiro Gama

Coordinators of the *DOCE project study*

References

DAFNE STUDY GROUP. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomized control trial. **BMJ**; 2002, v. 325, n. 7367, p. 746.

Ana Paula F. Pacheco,Simone van de Sande-Lee,Rita de Cássia B. Sandoval, Sônia Batista and Jefferson L. B. Marques Effects of a structured education program on glycemic control in type 1 diabetes **Arch. Endocrinol. Metab**; 2017, 61 (6).

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MINI REVIEW
THYROID CANCER MICROENVIRONMENT AND IMMUNE RESPONSE

MICROAMBIENTE DO CÂNCER DE TIRÓIDE E RESPOSTA IMUNE

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Abstract

The immune response to cancer has long been known, and one of the main characteristics of the neoplastic cell is to prevent its destruction by the immune system. For a neoplastic cell to proliferate, it requires an adequate environment, which is already present in the tumor itself, and propitious conditions for the transformation of a physiological process, a normal cell, into a pathological condition. The relationship between a neoplastic cell and the microenvironment in which it develops and proliferates disorderly is one of the emerging topics in medicine, due to the various possibilities for clinical and therapeutic approaches in thyroid cancer. The characteristics of cancer encompass ten biological abilities acquired in the course of the evolution of the various tumor stages: 1. inducing angiogenesis, 2. resisting cell death, 3. avoiding immune destruction, 4. evading growth suppression, 5. deregulating cellular energetics, 6. sustaining proliferative signaling, 7. enabling replicative immortality, 8. genome instability and mutation, 9. activating invasion and metastasis, and 10. Tumor promoting inflammation. Tumors contain a collection of normal cells that assist in achieving essential properties by producing the tumor microenvironment. Thus, a better understanding of the immunological and molecular aspects of the tumor microenvironment will provide the development of more efficient immunotherapeutic strategies for the treatment of thyroid cancer. In this study we reviewed the relation between thyroiditis, thyroid cancer and immune response. **Endocrinol diabetes clin exp 2022 / 2266 - 2269.**

Resumo

A resposta imunológica ao câncer já é estudada há algum tempo, e a célula neoplásica tem como característica principal evitar sua destruição através sistema imunológico. A proliferação de uma célula neoplásica requer um ambiente adequado, presente na própria célula, e condições propícias para a transformação de um processo fisiológico em uma condição patológica. A relação entre uma célula neoplásica e o microambiente na qual ela se desenvolve e prolifera desordenadamente é tópico emergente na biologia, em função das possibilidades de abordagens clínicas e terapêuticas para o câncer. As características da célula neoplásica abrangem dez habilidades biológicas adquiridas durante a evolução dos vários estágios do tumor: 1. induzir a angiogênese, 2. resistência à morte celular, 3. evitar a destruição imunológica, 4. evitar a supressão do crescimento, 5. desregulação da energia celular, 6. sustentação à sinalização proliferativa, 7. possibilitar a imortalidade replicada, 8. instabilidade e mutação do genoma, 9. ativar a invasão e metástase, e 10. inflamação promotora de tumores. Os tumores contêm uma coleção de células normais que ajudam a alcançar propriedades essenciais, produzindo o microambiente tumoral. Assim, uma melhor compreensão dos aspectos imunológicos e moleculares do microambiente tumoral proporcionará o desenvolvimento de estratégias imunoterapêuticas mais eficientes para o tratamento do câncer de tireoide. Neste estudo, é revisada a relação entre tireoidite autoimune, o microambiente da célula neoplásica da tireoide e sua resposta imunológica. **Endocrinol diabetes clin exp 2022 / 2266 - 2269.**

INTRODUCTION

The relationship between a neoplastic cell and the microenvironment in which it develops and proliferates disorganized is one of the developing subjects in the current medical field, according to the various perspectives for clinical and therapeutic approaches in thyroid cancer. The characteristics of cancer encompass ten biological abilities acquired in the course of the evolution of the various tumor stages: inducing angiogenesis, resisting cell death, avoiding immune destruction, evading growth inhibiting, unbalancing the cellular energy, contributing with the multiplicative signaling, possibility of perennial replication, genome variability and mutation, activating invasion and metastasis, and tumor-promoting inflammation (1).

In the tumor microenvironment, immune cells and tumor cells perform a fundamental function, expanding the performance of the immune system in cancer (2). The primary neoplastic cell is recognized and attacked immediately by the immune system, and consequently this neoplastic cell will produce specific capacities for its preservation and thus continue in its proliferation and metastasis.

The prevention of immune destruction and the promotion of inflammation are recognized essential properties of the neoplastic cell, and this has provided a series of possibilities related to the tumor cells themselves, such as the development of new drugs capable of acting in the tumor microenvironment. These drugs can provide immunomodulation of tumor development, inhibiting antibodies and metalloproteinases or inhibiting tumor angiogenesis, as well as the development of drugs that act by repolarizing or re-educating macrophages in addition to inhibiting tumor necrosis factor (3). Thus, the knowledge gained with the interrelationship between thyroid cancer and the immune response has been extremely important, but the development of immune therapies has been difficult due to the knowledge of how each type of tumor reacts.

Thyroid microcarcinomas have a high prevalence, and it has been suggested that the immune system arrests the growth of these microtumors and likewise act in suppressing metastasis through immune surveillance, a mechanism involving immune

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cells such as lymphocytes and macrophages (4). In this study we reviewed the relation between thyroid cancer microenvironment and immune response.

THYROID CANCER

Thyroid cancer is the most frequent endocrine neoplasm, with an increasing incidence, which presents a multifactorial etiology. In addition to radiation as an eminent risk factor, genetic factors implicated in the development of this pathology have been studied (5).

The majority of thyroid cancers originates from follicular epithelial cells and is categorized into two basic histological types: differentiated thyroid cancer which includes papillary and follicular carcinoma and poorly differentiated and undifferentiated (anaplastic) thyroid cancer (6). Medullary thyroid cancer is originated from parafollicular cells and it is considered a neuroendocrine tumor.

The molecular mechanism implicated in thyroid carcinogenesis includes alteration in the phosphatidylinositol-3 kinase (*PI3K*)/*AKT* and mitogen-activated protein kinase (*MAPK*) signaling pathway. Papillary thyroid carcinoma is initiated by *MAPK* activation, resulting from specific mutations of the BRAF and RAS genes or genetic aggregation of *TRK* and *RET/PTC* oncogene. On the other hand, the stimulation of *PI3K/AKT* is essential for the triggering of thyroid follicular carcinoma, and may be mobilized through mutations in *RAS*, *PIK3CA* and *AKT1* as well as deactivation of *PTEN*, negatively regulating this signaling pathway. Other signaling pathways involving thyroid carcinoma dedifferentiation into poorly differentiating carcinoma and anaplastic thyroid carcinoma may occur due to complementary mutations spanning *p53, Wnt/β*-catenin and more recently *TERT*, especially in undifferentiated thyroid carcinomas (7). **(Figure 1)**.
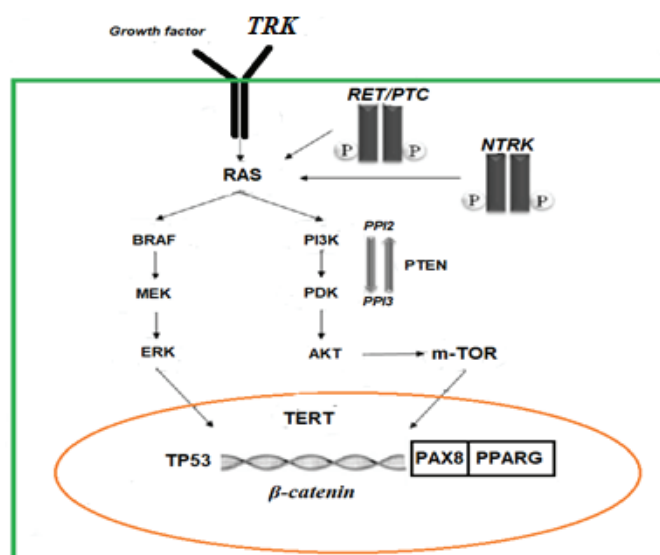
Fig. 1. The molecular pathogenesis of thyroid cancer
Source: Adapted from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7082927/

Risk factors for thyroid cancer include ionizing radiation (especially in children and adolescents), familial genetic causes (familial carcinoma) and syndromes related to thyroid carcinoma. A thyroid nodule has some clinical characteristics that raise the possibility of malignancy such as: rapidly growing nodule, non--movable nodule, lymphadenopathy, and hoarseness (8).

Ultrasonography is the main imaging exam for the diagnosis of thyroid nodule, and diagnostic ultrasound standards are currently based on the ultrasound scoring systems of the American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS), and of American Thyroid Association (ATA) that predicts cancer risk in thyroid nodules (9,10). Some guidelines such as that of the German society of nuclear medicine, recommend Tc-99 scintigraphic study for thyroid nodules larger than 1 cm before the indication of a fine needle aspiration (FNA) cytology (11); while the ATA recommends scintigraphy only when the thyroid stimulating hormone (TSH) level is suppressed. However, these guidelines cannot be used worldwide without properly being suited to differences in populations (10). Having said that, it is almost consensual that ultrasound-guided FNA is the recommendation for suspicious nodules according to TIRADS or ATA (9,10).

Differentiated thyroid cancer requires a multidisciplinary team for its treatment that involves the surgeon, the endocrinologist and the nuclear physician, and its treatment and follow-up is usually individualized.

THYROIDITIS AND THYROID CANCER

Studies have shown that the inflammatory process plays an important role in the origin and progression of cancer, affecting exactly the neoplastic cells, promoting epithelial proliferation, mutually acting with chemokines, and intensifying the metastatic process.

Thyroid carcinoma usually presents in its adjacent parenchyma an infiltrate of lymphocytes, mast cells and macrophages, secreting reactive oxygen species which seems to play a pro--tumorigenic activity. In addition, proto-oncogenes expressed in thyroid cancer also trigger a pro-inflammatory process in thyroid cells (12).

Studies have shown that the parenchyma adjacent to thyroid cancer has concomitant chronic inflammatory elements that characterize chronic lymphocytic thyroiditis, especially in less aggressive tumors (13,14). Systematic review with meta-analysis showed that almost a quarter of papillary thyroid carcinomas were associated with autoimmune thyroiditis (15). The presence of interleukin (IL), especially IL-10, is shown to be a link between autoimmune thyroiditis and a less aggressive tumor response (16,17).

In the relationship between thyroiditis and thyroid cancer, the activation of the mitogen-activated protein kinase cascade leads to the activation of the BRAF, RAS and RET/PTC oncogenes which have a pro-inflammatory action involving, especially, cytokines, chemokines and their receptors, leading to mainte-

nance of thyroid cancer malignant phenotypic characteristics and the induction of remodeling of tumor stroma by recruitment of inflammatory cells, endothelial cells and immune cells (18). Summing up, cytokines control the generalized inflammatory reaction, playing a significant role in autoimmune thyroiditis, and modulate the genesis and multiplication of both normal and thyroid cancer cells, in the later generating an anti-tumor response (**Figure 2**).
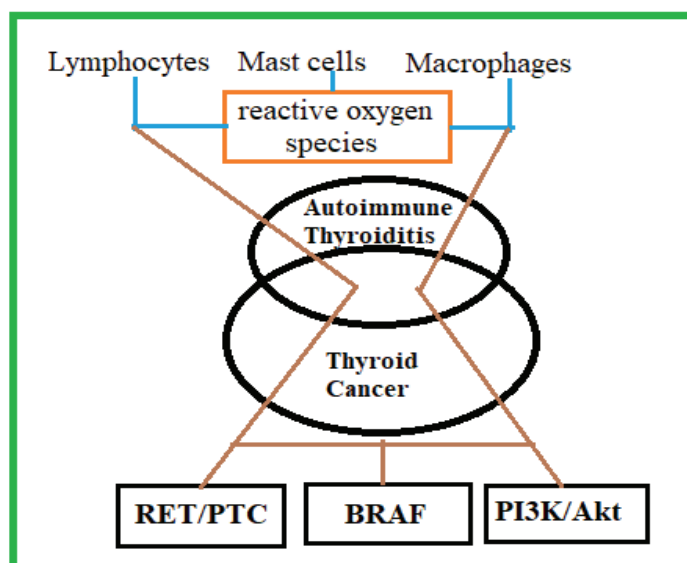
Fig. 2. Thyroiditis and thyroid cancer – Pro-tumorigenic activity
Source: Adapted from https://pubmed.ncbi.nlm.nih.gov/25306886/

Thus, the development of thyroid cancer has interference from two inflammatory elements, one which depends on the cells present in the cancer cell stroma and the other which depends on the signaling of oncogenes.

THYROID CANCER MICROENVIRONMENT

Thyroid cancer is influenced by many factors and its prognosis is closely tied to the tumor microenvironment which is dependent of ten major characteristics (19). (**Figure 3**)
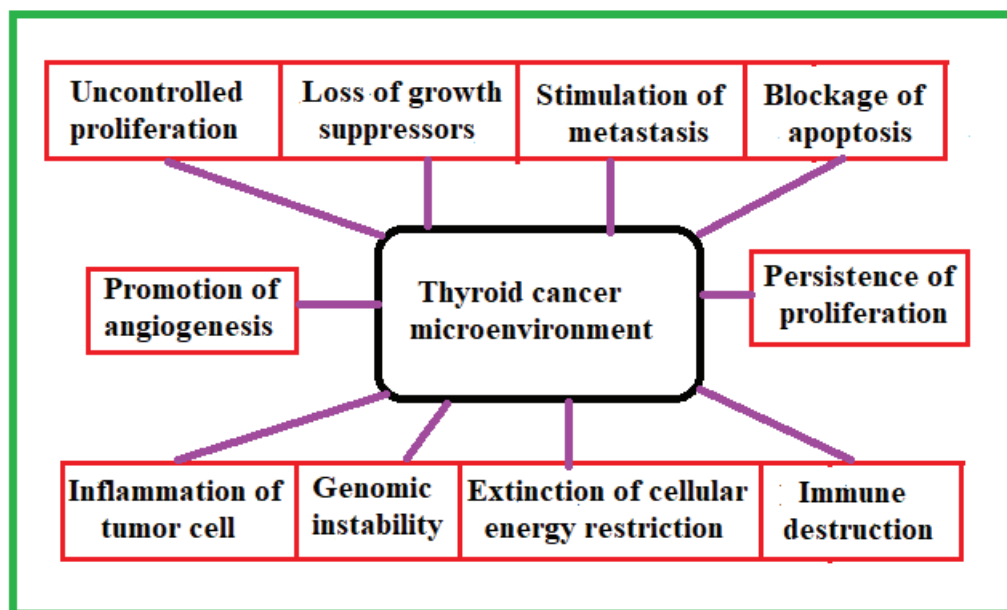
Fig. 3. Thyroid Cancer Microenvironment
Source: Adapted from https://pubmed.ncbi.nlm.nih.gov/28382138/

Several elements are involved in the immune response in the presence of the cancer cell, and these elements have shown a variable behavior, because the same macrophage can have a double differentiation, in macrophage type M1 with anti-tumor activity or in macrophage type M2 that has activity in tumor growth, and this differentiation can occur at different moments in the same tumor (20).

In autoimmune thyroiditis, cytotoxic lymphocytes and T helper lymphocytes predominate, while in differentiated thyroid carcinoma, more precisely in papillary thyroid carcinoma, lymphocytes that do not express CD4 and CD8 predominate, that is, lymphocytes that inhibit the immune response. The presence of these "double negative" lymphocytes in the presence of a papillary thyroid carcinoma transforms what should be an inflammatory response directed to eliminate the tumor in a chronic inflammatory response not effective, which would lead to an insidious, making the tumor evolution less aggressive (21).

The immune response is related to the molecular profile of the developing cancer itself. FoxP3 is a transcriptional suppressor that physiologically prevents autoimmunity and is associated

with features of cancer aggressiveness. Foxp3 is a regular T-lymphocyte that is expressed in the core of papillary thyroid carcinoma, mainly in young subjects, and shows a favorable immune response in the evolution of the tumor (22).

The B7H1 is associated with immune system blockade in most solid tumors, and when expressed in the tumor cell, this protein "tricks" the immune system. Thus, there is a relationship between aggressiveness from the pathological point of view and the expression of B7H1, especially in the elderly, explaining the greater aggressiveness of thyroid cancer in older individuals (23).

Other markers seem to be associated with the development of the tumor microenvironment. Among these markers, a study demonstrated that indolamine acts in the microenvironment of thyroid cancer by exerting immunosuppression through an immune escape system in which lymphocyte inhibition and FoxP3 induction occurs (24).

In lymph node metastasis from thyroid carcinomas there is a decrease in B7H1, COX2, and IL-10, and on the other hand, there is an increase in immunologically activated lymphocytes with low production of anti-inflammatory cytokines and evasion molecules that will determine a more effective immune response in blocking the tumor cell within the lymph node (25).

Thus, the development of a thyroid cancer has inherent characteristics of the cell itself, predisposition within an inflammatory tumor microenvironment and unresponsiveness to the immune system arising from the immune response against cancer. Therefore, studies of the immune profile in thyroid cancer have been performed in order to evaluate mechanisms of immune escape and to define the fundamental characteristics of the tumor microenvironment.

CONCLUDING REMARKS

In general, there is a favorable microenvironment in differentiated thyroid cancer, especially in papillary thyroid carcinoma, in concomitance with chronic autoimmune thyroiditis also associated with favorable characteristics and a suppression of metastasis due to the activation of lymphocytes and an effective immune response.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. **Cell**. 2011;144(5):646-74.
2. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. **N Engl J Med**. 1986; 315(26):1650-9.
3. Nuevo-Tapioles C, Santacatterina F, Stamatakis K, Núñez de Arenas C, Gómez de Cedrón M, Formentini L, et al. Coordinate beta-adrenergic inhibition of mitochondrial activity and angiogenesis arrest tumor growth. **Nat Commun**. 2020;11(1):3606.
4. Scouten WT, Francis GL.Thyroid cancer and the immune system: a model for effective immune surveillance. **Expert Rev Endocrinol Metab**. 2006;1(3):353-366.
5. Silva SN. Special Issue: Genetic Perspectives in Thyroid Cancer. **Genes** (Basel). 2021;12(2):126.
6. Chmielik E, Rusinek D, Oczko-Wojciechowska M, Jarzab M, Krajewska J, Czarniecka A, et al. Heterogeneity of Thyroid Cancer. **Pathobiology**. 2018;85(1-2):117-129.
7. Prete A, Borges de Souza P, Censi S, Muzza M, Nucci N, Sponziello M. Update on Fundamental Mechanisms of Thyroid Cancer. **Front Endocrinol (Lausanne).** 2020;11:102.
8. Schmidbauer B, Menhart K, Hellwig D, Grosse J. Differentiated Thyroid Cancer-Treatment: State of the Art. **Int J Mol Sci**. 2017;18(6):1292.
9. Grant EG, Tessler FN, Hoang JK, Langer JE, Beland MD, Berland LL, et al. Thyroid Ultrasound Reporting Lexicon: White Paper of the ACR Thyroid Imaging, Reporting and Data System (TIRADS) Committee. **J Am Coll Radiol.** 2015;12(12 Pt A):1272-9.
10. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. **Thyroid**. 2016;26(1):1-133.
11. Feldkamp J, Führer D, Luster M, Musholt TJ, Spitzweg C, Schott M. Fine Needle Aspiration in the Investigation of Thyroid Nodules. **Dtsch. Arztebl. Int**. 2016;113:353–359.
12. Guarino V, Castellone MD, Avilla E, Melillo RM. Thyroid cancer and inflammation. **Mol Cell Endocrinol**. 2010;321(1):94-102.
13. Souza SL, Montalli Da Assumpção LV, Ward LS. Impact of previous thyroid autoimmune diseases on prognosis of patients with well-differentiated thyroid cancer. **Thyroid.** 2003;13(5):491-5.
14. Seok JY, An J, Cho HY, Kim Y, Ha SY. Nuclear features of papillary thyroid carcinoma: Comparison of Core needle biopsy and thyroidectomy specimens. **Ann Diagn Pathol**. 2018;32:35-40.
15. Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. **Eur J Endocrinol**. 2013;168(3):343-9.
16. Cunha LL, Tincani AJ, Assumpção LV, Soares FA, Vassallo J, Ward LS. Interleukin-10 but not interleukin-18 may be associated with the immune response against well-differentiated thyroid cancer. **Clinics (Sao Paulo)**. 2011;66(7):1203-8.
17. Cunha LL, Ferreira Rde C, de Matos PS, da Assumpção LV, Ward LS. Both gender and concurrent chronic lymphocytic thyroiditis may influence the nuclear texture of papillary thyroid carcinomas cells. **Endocr Res**. 2014;39(3):126-9.
18. Melillo RM, Castellone MD, Guarino V, De Falco V, Cirafici AM, Salvatore G, et al. The RET/PTC-RAS-BRAF linear signaling cascade mediates the motile and mitogenic phenotype of thyroid cancer cells. **J Clin Invest**. 2005;115(4):1068-81.
19. Wang M, Zhao J, Zhang L, Wei F, Lian Y, Wu Y, et al. Role of tumor microenvironment in tumorigenesis. J Cancer. 2017;8(5):761-773.
20. Imam S, Paparodis R, Sharma D, Jaume JC. Lymphocytic profiling in thyroid cancer provides clues for failure of tumor immunity. **Endocr Relat Cancer**. 2014;21(3):505-16.
21. D'Acquisto F, Crompton T. CD3+CD4-CD8- (double negative) T cells: saviours or villains of the immune response? **Biochem Pharmacol**. 2011;82(4):333-40.
22. Cunha LL, Morari EC, Nonogaki S, Soares FA, Vassallo J, Ward LS. Foxp3 expression is associated with aggressiveness in differentiated thyroid carcinomas. **Clinics (São Paulo)**. 2012;67(5):483-8.
23. Cunha LL, Marcello MA, Morari EC, Nonogaki S, Conte FF, Gerhard R, et al. Differentiated thyroid carcinomas may elude the immune system by B7H1 upregulation. **Endocr Relat Cancer**. 2013;20(1):103-10.
24. Moretti S, Menicali E, Voce P, Morelli S, Cantarelli S, Sponziello M, et al. Indoleamine 2,3-dioxygenase 1 (IDO1) is up-regulated in thyroid carcinoma and drives the development of an immunosuppressant tumor microenvironment. **J Clin Endocrinol Metab**. 2014;99(5):E832-40.
25. Cunha LL, Marcello MA, Nonogaki S, Morari EC, Soares FA, Vassallo J, et al. CD8+ tumour-infiltrating lymphocytes and COX2 expression may predict relapse in differentiated thyroid cancer. **Clin Endocrinol (Oxf)**. 2015;83(2):246-53.

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ORIGINAL ARTICLE
PATHOLOGICAL FACTORS ASSOCIATED WITH LYMPH NODE METASTASIS IN PAPILLARY THYROID CARCINOMA

FATORES PATOLÓGICOS ASSOCIADOS COM METÁSTASE LINFONODAL EM CARCINOMA PAPILÍFERO DE TIREOIDE

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Abstract

Objective: Improved tools for identification of factors associated with worse prognosis in papillary thyroid carcinoma are still needed. The aim of this study was to identify the pathological characteristics associated with the presence of metastatic lymph nodes at diagnosis, up to 1 year after surgery (*i.e.*, persistent disease) or after this period (i.e., recurrent disease) in patients with papillary thyroid carcinoma. **Methods:** Retrospective analysis of 145 patients who underwent thyroidectomy due to papillary thyroid carcinoma between 2002–2018. Pathology reports were analyzed for the number of tumoral foci and presence of tumor capsule, capsular invasion, angiolymphatic invasion, and microscopic or macroscopic extra-thyroidal extension. Medical data were retrieved from the clinical records. **Results:** During a mean follow of 36.5 months (0–241 months), 38 patients (26.2%) had lymph node metastasis, including 7 (4.8%) patients with associated distant metastasis (lungs). Patients with tumors ≤ 1 cm (n=57) were less likely to develop lymph node metastasis compared with those with tumors > 1 cm (OR 4.86, 95% CI 1.88 – 12.57, p=0.001). In multivariate analysis, angiolymphatic invasion emerged as significantly associated with lymph node metastasis (OR 3.07, 95% CI 1.25–7.56, p=0.014). **Conclusion:** The occurrence of angiolymphatic invasion on thyroidectomy specimen should raise awareness for the possibility of lymph node metastasis in patients with papillary thyroid carcinoma. **Endocrinol diabetes clin exp 2022 / 2270 - 2275.**

Resumo

Objetivo: Preditores mais precisos para identificação de fatores associados com pior prognóstico em carcinoma papilífero de tireoide são ainda necessários. O objetivo deste estudo foi identificar fatores patológicos associados com a presença de metástase linfonodal, ao diagnóstico, até 1 ano após a cirurgia (doença persistente) ou após este período (doença recorrente) em pacientes com carcinoma papilífero de tireoide. **Métodos:** Análise retrospectiva de 145 pacientes submetidos à tireoidectomia por carcinoma papilífero de tireoide entre 2002-2018. Relatórios de patologia foram revisados quanto à presença de multifocalidade, presença da cápsula tumoral, invasão da mesma, invasão angiolinfática, extensão microscópica e macroscópica da neoplasia. Informações clínicas foram extraídas dos prontuários médicos. **Resultados:** Com um período médio de seguimento de 36,5 meses (0–241 meses), 38 pacientes (26,2%) tiveram metástase linfonodal, incluindo 7 (4,8%) pacientes com metástases pulmonares associadas. Pacientes com tumores ≤ 1 cm (n=57) eram menos propensos a apresentar metástase linfonodal comparados àqueles com tumores > 1 cm (OR 4,86, 95% IC 1,88 – 12,57, p=0,001). Na análise multivariada, a invasão angiolinfática mostrou-se associada de forma significante com metástase linfonodal (OR 3,07, 95% IC 1,25–7,56, p=0,014). **Conclusão:** A ocorrência de invasão angiolinfática no produto de tireoidectomia, deve alertar para a possibilidade de doença linfonodal metastática em pacientes com carcinoma papilífero de tireoide. **Endocrinol diabetes clin exp 2022 / 2270 - 2275.**

INTRODUCTION

Papillary thyroid carcinoma (PTC) has survival rates above 90% in 10 years (1-4). Increased use of thyroid ultrasonography has improved the identification of these malignant tumors (5,6), but has not helped decrease mortality (5, 7-9).

Treatment of patients diagnosed with thyroid malignancies is a controversial topic. Most specialists treat patients with PTC based on guidelines, but tumor characteristics may vary in different countries (7,10). It is unclear whether these variations are due to regional differences in tumor characteristics or access to early diagnosis. The World Health Organization (WHO), in its more recent publication, recognizes that certain histological subtypes of differentiated thyroid carcinoma are more aggressive than others (4) and are associated with residual and recurrent disease after initial proposed treatment (11).

Bearing in mind that histological variations, local cancer incidence and patterns of clinical presentation are essential for initial management and follow-up of patients with PTC, the staging system (TNM) proposed by the American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC) (12) is recommended for all patients with differentiated thyroid carcinoma and is endorsed by the American Thyroid

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Association (ATA) (9). Stratification of patients based on this staging system allows for data organization and mortality prediction, but whether this is sufficient to predict long-term outcomes remains unclear. Most thyroid tumors fall into T1–T2 classification categories (tumors limited to the thyroid), but even patients classified into these categories may progress with residual / persistent, recurrent or distant metastatic disease. This reflects a remaining need for additional tools to identify characteristics associated with worse prognosis in patients with differentiated thyroid carcinoma. Specifically addressing persistent disease, that is usually diagnosed up to 1 year after proposed treatment completion, the comprehension of such risk factors in advance can avoid two surgical steps procedures (like lobectomy followed by total thyroidectomy), indicate profilatic or therapeutic lymphadenectomy upfront or even refer the patient to radioactive iodine therapy (RAI) right after the most complete surgery.

Based on these considerations, the aim of this study was to identify the pathological characteristics associated with the presence of metastatic lymph nodes during and up to 1 year after surgery (*i.e.*, persistent disease) and during long-term follow-up (i.e., recurrent disease) in patients with PTC.

MATERIALS AND METHODS

The study protocol was approved by the Ethics in Research Committee of the institutions involved.

The analysis included 145 consecutive patients identified from pathology reports of thyroidectomies performed for PTC across four public academic and private (academic or not) institutions between 2002 and 2018.

The authors reviewed clinical charts of patients to collect variables such as demographic data, family history of thyroid carcinoma, previous neck irradiation, thyroidectomy date and extension, postoperative complications, need for surgical reintervention, if radioiodine was administered, occurrence and location of persistent disease or recurrence or distant metastasis and duration of clinical follow-up. Thyroglobulin measurements were not available for all patients and were not considered in the analysis.

Patients with lymph node or distant metastasis detected ≤ 1 year after thyroidectomy were considered to have persistent disease and after this period were considered to have recurrent disease. For patients with more than one thyroidectomy, at the end, the procedure was considered as total thyroidectomy. Lymph node metastasis were determined by the presence of metastatic lymph nodes on pathology reports and by the development of local metastasis after the initial treatment (13, 14).

The number of tumoral foci and presence of tumor capsule, capsular invasion, angiolymphatic invasion, tumor variant, and microscopic or macroscopic extra-thyroidal extension described on the pathology report were recorded. Microcarcinomas were all PTC ≤1.0 cm in the largest diameter. Histological variants were determined according to the 2017 WHO classification (15). The presence of ≥2 tumor foci in one or both thyroid lobes characterized multifocality (16).

The majority of patients did not undergo neck dissection. Patients categorized as Nx were considered to be N0 for calculation of odds risk in univariate and multivariate analyses, providing that these patients had no persistent lymph node disease until last information.

The patients were categorized into prognostic stage groups according to the 2017 TNM classification for differentiated thyroid cancer (8th edition of the AJCC manual) (12) right after surgery in patients submitted to thyroidectomy alone and after whole-body scanning following radioiodine ablation.

Statistical Analysis

Categorical variables are summarized as absolute and percentage values, and continuous variables as mean ± standard deviation or minimum and maximum values. The chi-square test or Fisher's exact test verified the association between two categorical variables. The Mann-Whitney test compared groups with continuous variables. The data were fitted in a logistic regression model to assess significant variables related to metastatic lymph nodes, and the results are presented as odds ratios (ORs) and 95% confidence interval (CI). The analyses were performed using Statistica, v7 (StatSoft Inc., Tulsa, OK, USA); p values ≤ 5% were considered significant.

RESULTS

The mean age was 45.5±13.5 years, and most patients were women (82.7%). Among all, 57 patients (39.3%) had microcarcinomas. Most patients were younger than 55 years and had stage I disease. During a mean follow of 36.5 months (0–241 months), 109 (75.2%) patients received at least one radioiodine dose. Overall, 87 (60.0%) tumors were unifocal, and the mean tumor size was 1.78±1.37 cm. Eight patients (5.5%) had uncommon PTC variants (**Table 1**).

Table 1. Demographic, clinical, and pathological characteristics of 145 patients with papillary thyroid carcinoma (PTC)

Characteristics	Number of patients	Frequency
Age at diagnosis		
≥ 55 years	36	24.8%
< 55 years	109	75.2%
AJCC prognostic stage group*		
I and II – age > 55 years	35	97.2%
IV – age >55 years	1	2.8%
I – age < 55 years	103	94.5%
II – age < 55 years	6	5.5%
Sex		
Women	120	82.7%
Men	25	17.3%
History of head and neck irradiation	5	3.3%

Family history of thyroid carcinoma	14	9.1%
Histological subtype of papillary carcinoma		
Classic	50	34.5%
Follicular	30	20.7%
Other variants**	8	5.5%
Microcarcinoma	57	39.3%
Tumor size		
>1cm	88	60.7%
≤ 1cm	57	39.3%
Tumor focality		
Unifocal	87	60.0%
Multifocal	58	40.0%
Microscopic extra-thyroidal extension	23	15.8%
Gross extra-thyroidal extension	6	4.1%
Capsular invasion	12	8.3%
Angiolymphatic invasion	41	28.2%
Lymph node metastasis		
Nx	80	55.2%
N0	31	21.4%
N1	34	23.4%
Metastasis during follow-up (persistent or recurrent disease)		
Distant	7	4.8%
Lymph node	4	2.7%
Received at least one radioiodine dose	109	75.1%
Extension of thyroidectomy		
Total thyroidectomy	128	88.3%
Partial thyroidectomy	17	11.7%
Postoperative complications		
Transient hypoparathyroidism	2	1.3%
Definitive hypoparathyroidism	2	1.3%
Transient recurrent laryngeal nerve injury	2	1.3%
Definitive recurrent laryngeal nerve injury	3	2.06%

*2017 American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Eighth Edition. **Included tall cell (n=3), oncocytic (n=3), Warthin-like (n=1), and macrofollicular (n=1) variants.

Overall, 38 patients (26.2%) had lymph node disease at final staging and during follow-up and 7 (4.8%) also had distant (lung) metastasis. Lymph node involvement was assessed in 65 patients (44.8%) who underwent neck dissection, and metastatic lymph nodes were documented in 34 (52.3%) of them, including in five (7.6%) with microcarcinomas. Lymph nodes were not assessed in 80 (55.2%) thyroidectomies; of these, 78 had no lymph node metastasis within 1 year and were categorized as TNM N0 in univariate and multivariate analyses.

Absence of lymph node metastasis was more frequent in patients with tumors ≤1 cm compared with those with tumors between 1.1–2.0 cm (p=0.0005). Having said that, lymph node metastasis were more associated with tumor size >1.0 cm (**Table 2**).

Table 2. Presence or absence of metastatic lymph nodes according to tumor size

Tumor size at initial staging	Presence or absence of metastatic lymph nodes at initial staging or during follow-up		P
	Absence (n = 107)*	Presence (n = 38)**	
≤ 1 cm	47.7% (n = 51)	15.8% (n = 6)	**0.0005**
1.1–2.0 cm	29.9% (n = 32)	50.0% (n = 19)	**0.026**
2.1–4.0 cm	18.7% (n = 20)	26.3% (n = 10)	0.32
≥ 4.1 cm	3.7% (n = 4)	7.9% (n = 3)	0.27

Note: A total of 80 patients were classified as Nx. Of these, 78 had no lymph node metastasis detected within 1 year after surgery and were considered to be N0 for analysis purposes.
*For exploratory analysis purposes, this sample was calculated summing up N0+N1, taking out 4 previously N0 patients that developed metastatic disease during follow-up until the last information.
**For exploratory analysis purposes, this sample included all patients who presented with recurrent disease (n = 4) that were initially N0 summing up with those originally staged as N1.

Among factors predicting lymph node metastasis at diagnosis and during follow-up, tumors ≤1 cm were less likely to have metastatic lymph nodes compared with tumors >1 cm (OR 4.86, 95% CI 1.88–12.57, p=0.001). The odds of a patient presenting metastatic lymph nodes also increased with microscopic extension, macroscopic extension, tumor variant and angiolymphatic invasion (**Table 3**). On multivariate analysis including all variables that were significant in the univariate analysis (tumor size, tumor variant, microscopic extension, macroscopic extension, and angiolymphatic invasion), only angiolymphatic invasion emerged as a significant factor of lymph node metastases (OR 3.07, 95% CI 1.25–7.56, p=0.014).

Three patients with stage I papillary carcinoma (AJCC 2017) were lost to follow up. No deaths occurred associated with PTC.

Table 3. Univariate analysis of factors predicting lymph node metastasis at diagnosis, within 1 year after the initial treatment and after this period

Predictive factors (reference)	Category	Lymph node metastasis OR (95% CI), p value
Sex (*vs* women)	Men	1.41 (0.55–3.60), 0.63
Age (*vs* < 55 years)	≥ 55 years	0.61 (0.24–1.53), 0.40
Tumor size (*vs* T1a)	Other T	4.86 (1.88–12.57), **0.001**
Histological subtype (*vs* papillary microcarcinoma)	Other variants	4.86 (1.88–12.57), **0.001**
Tumor focality (*vs* unifocal)	Multifocal	1.51 (0.71–3.18), 0.38
Microscopic extension (*vs* absent)	Present	4.03 (1.60–10.17), **0.004**
Macroscopic extension (*vs* absent)	Present	16.06 (1.81–142.41), **0.005**
Angiolymphatic invasion (*vs* absent)	Present	14.30 (1.62–126.60), **0.009**

DISCUSSION

Papillary carcinomas comprise about 85% of all thyroid tumors (17) and frequently metastasize to cervical lymph nodes (18). According to 2017 TNM classification, the occurrence of lymph node metastasis is a more important prognostic factor for recurrence than tumor size. Since about 60–75% of all recurrences in patients with PTC occur in cervical lymph nodes (19,20), the detection of metastatic lymph nodes in the initial surgery is fundamental. Nearly, 18–90% of the patients with PTC develop cervical lymph node metastasis, which are associated with locoregional recurrence and distant metastasis (21). The 2009 ATA guidelines recommended prophylactic dissection of the central compartment (level VI) ipsilateral to the tumor in patients with PTC and advised against prophylactic dissection of the lateral neck compartment (22). The revised 2015 ATA guidelines ratified the need for dissection of level VI in patients with involvement of the central compartment, and ipsilateral or bilateral prophylactic level VI dissection in patients with T3, T4, or N1b. The 2015 guidelines also advised against prophylactic central neck dissection for small (T1–T2), noninvasive, N0 tumors (9).

This study included patients operated on between 2002–2018, thus managed according to both 2009 and 2015 guidelines. Lymph node metastasis were not assessed in a great number of patients (55.2%) undergoing thyroidectomy and among those patients submitted to neck dissection, more than a half had node metastasis. About 3.1–20% of all PTC microcarcinomas may present with metastatic lymph nodes (23-25). Indeed, we observed metastatic lymph nodes in 10.5% of the patients with

microcarcinomas. A retrospective series of 356 patients with PTC who underwent thyroidectomy with preoperative lymph node evaluation and central and lateral neck dissection reported that lateral metastatic lymph nodes were present in 75% and were associated with age ≤45 years, tumor size >1.5 cm, extra-thyroidal extension, location of the primary tumor in the upper lobe, and metastatic central lymph node (18). We found that tumors ≥1 cm were approximately almost 4 times more likely to present metastatic lymph nodes (p=0.001), but on multivariate analysis, only angiolymphatic invasion was associated with increased odds of metastatic lymph nodes.

In accordance with this study, Nam et al, demonstrated that in patients with PTC submitted to thyroidectomy plus central neck dissection, the multivariable analysis showed that among other pathological factors, tumor size, was an independent factor predictive of post-treatment recurrence (26). Partially in accordance with the current study, Yuan et al demonstrated that in clinically N0 patients with PTC microcarcinomas, ultrasonographic tumor size but not lymphovascular invasion was associated with central node metastasis in univariate analyses (27). Conversely, Buyruk et al, showed that, in patients with PTC, in the logistic regression analyses, lymph node metastasis was significantly related to patient age <45 years, tumor capsular invasion, presence of extra-thyroidal extension, multifocality and presence of lymphovascular invasion (28).

Limitations of this study include short-term follow-up, the absence of thyroglobulin results and lack of categorization of the patients according to the ATA 2015 recommendations into low, intermediate, and high risk since information about the size of metastatic lymph nodes and the number of invaded angiolymphatic vessels was limited.

Besides this limitations, and although literature controversies, the authors, based on the results presented, recommend that depending on tumor size, a prophylactic central neck dissection should be considered to avoid persistent nodal disease, usually seen in whole body scanning after RAI treatment or nodal recurrence mostly seen in a long term follow-up with raising thyroglobulin levels or imaging disease structural demonstration. This initial management can avoid two step procedure and prompt tumor control besides it is still controversial if it really impacts overall survival. Regarding lymphovascular invasion, as it can only be seen after thyroidectomy, it can not avoid a lobectomy procedure, but can indicate completion thyroidectomy and can raise a red flag for prophylactic neck dissection and RAI treatment, regardless of tumor size or macroscopic tumor extra-thyroid extension. More studies, including prospective trials and systematic review with meta-analysis, are needed to better clarify this hypothesis.

CONCLUSION

The 2017 AJCC/TNM classification was not helpful in characterizing tumor persistence according to the age of patients. Despite this limitation, the odds of metastatic lymph nodes increased substantially in tumors with size >1 cm and in the presence of angiolymphatic invasion, tumor variant and microscopic or macroscopic extra-thyroidal extension. These risk factors could serve as red flags to indicate the possibility of nodal disease persistence in patients with PTC right after proposed treatment completion.

References

1. Baloch Z, LiVolsi VA, Tondon R. Aggressive variants of follicular cell derived thyroid carcinoma; the so called 'real thyroid carcinomas'. **J Clin Pathol**. 2013;66(9):733-43.
2. Lam AK, Lo CY, Lam KS. Papillary carcinoma of thyroid: A 30-yr clinicopathological review of the histological variants. **Endocr Pathol**. 2005;16(4):323-30.
3. Lastra RR, LiVolsi VA, Baloch ZW. Aggressive variants of follicular cell-derived thyroid carcinomas: a cytopathologist's perspective. **Cancer Cytopathol**. 2014;122(7):484-503.
4. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, et al. Overview of the 2022 WHO Classification of Thyroid Neoplasms. **Endocr Pathol**. 2022; 33:27–63.
5. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. **Nat Rev Endocrinol**. 2016;12(11):646-53.
6. Sosa JA, Duh QY, Doherty G. Striving for Clarity About the Best Approach to Thyroid Cancer Screening and Treatment: Is the Pendulum Swinging Too Far? **JAMA Surg**. 2017;152(8):721-2.
7. La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, et al. Thyroid cancer mortality and incidence: a global overview. **Int J Cancer**. 2015;136(9):2187-95.
8. Li Z. CD133: a stem cell biomarker and beyond. **Exp Hematol Oncol**. 2013;2(1):17.
9. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. **Thyroid**. 2016;26(1):1-133.
10. Gillanders SL, O'Neill JP. Prognostic markers in well differentiated papillary and follicular thyroid cancer (WDTC). **Eur J Surg Oncol**. 2018;44(3):286-96.
11. Kazaure HS, Roman SA, Sosa JA. Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. **Ann Surg Oncol**. 2012;19(6):1874-80.
12. Amin MB, Edge SB, American Joint Committee on Cancer. AJCC cancer staging manual. Eighth edition. ed. Switzerland: **Springer**; 2017.
13. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. **Thyroid**. 2010;20(12):1341-9.
14. Bardet S, Ciappuccini R, Quak E, Rame JP, Blanchard D, de Raucourt D, et al. Prognostic value of microscopic lymph node involvement in patients with papillary thyroid cancer. **J Clin Endocrinol Metab**. 2015;100(1):132-40.
15. Lloyd RV, Osamura RY, Klöppel G, Rosai J, Cancer IAfRo. WHO Classification of Tumours of Endocrine Organs. **International Agency for Research on Cancer**; 2017.
16. Pisanu A, Saba A, Podda M, Reccia I, Uccheddu A. Nodal metastasis and recurrence in papillary thyroid microcarcinoma. **Endocrine**. 2015;48(2):575-81.
17. Tuttle RM. Differentiated thyroid cancer: Overview of management. Waltham, MA: **UpToDate**.
18. Nie X, Tan Z, Ge M, Jiang L, Wang J, Zheng C. Risk factors analyses for lateral lymph node metastases in papillary thyroid carcinomas: a retrospective study of 356 patients. **Arch Endocrinol Metab**. 2016;60(5):492-9.
19. Kwak JY, Kim EK, Kim MJ, Son EJ, Chung WY, Park CS, et al. Papillary microcarcinoma of the thyroid: predicting factors of lateral neck node metastasis. **Ann Surg Oncol**. 2009;16(5):1348-55.
20. Watkinson JC, Franklyn JA, Olliff JF. Detection and surgical treatment of cervical lymph nodes in differentiated thyroid cancer. **Thyroid**. 2006;16(2):187-94.
21. Rotstein L. The role of lymphadenectomy in the management of papillary carcinoma of the thyroid. **J Surg Oncol**. 2009;99(4):186-8.
22. American Thyroid Association Guidelines Taskforce on Thyroid N, Differentiated Thyroid C, Cooper DS, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. **Thyroid**. 2009;19(11):1167-214.
23. Bramley MD, Harrison BJ. Papillary microcarcinoma of the thyroid gland. **Br J Surg**. 1996;83(12):1674-83.
24. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. **Cancer**. 1985;56(3):531-8.
25. Pelizzo MR, Boschin IM, Toniato A, Pagetta C, Piotto A, Bernante P, et al. Natural history, diagnosis, treatment and outcome of papillary thyroid microcarcinoma (PTMC): a mono-institutional 12-year experience. **Nucl Med Commun**. 2004;25(6):547-52.
26. Nam SH, Roh J-L, Gong G, Cho K-J, Choi S-H, Nam SY, et al. Nodal Factors Predictive of Recurrence After Thyroidectomy and Neck Dissection for Papillary Thyroid Carcinoma. **Thyroid**. 2018;28(1):88-95.
27. Yuan J, Li J, Chen X, Lin X, Du J, Zhao G, et al. Identification of risk

factors of central lymph node metastasis and evaluation of the effect of prophylactic central neck dissection on migration of staging and risk stratification in patients with clinically node-negative papillary thyroid microcarcinoma. **Bull Cancer**. 2017;104(6):516-523.

28. Buyruk BA, Kebapci N, Yorulmaz G, Buyruk A, Kebapci M. An Evaluation of Clinicopathological Factors Effective in the Development of Central and Lateral Lymph Node Metastasis in Papillary Thyroid Cancer. **J Natl Med Assoc**. 2018;110(4):384-390.

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ORIGINAL ARTICLE
EVALUATION OF THE PREVALENCE OF BODY DISSATISFACTION AND CHANGES IN EATING BEHAVIOR IN TYPE 2 DIABETIC PATIENTS

AVALIAÇÃO DA PREVALÊNCIA DE INSATISFAÇÃO CORPORAL E ALTERAÇÕES DO COMPORTAMENTO ALIMENTAR EM PACIENTES DIABÉTICOS TIPO 2

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Abstract

Introduction: Eating disorders have been associated with patients with Diabetes Mellitus, however, few studies have focused on type 2 diabetes in the adult population. **Objective:** To investigate the prevalence of body dissatisfaction and the presence of changes in eating behavior in outpatient service. **Methods:** This is a cross-sectional epidemiological study. Type 2 diabetic patients will be evaluated in terms of body image and eating behavior through self-administered questionnaires, validated in their Brazilian version. **Results:** The sample of 67 patients consisted of middle-aged adults, most of them women. The mean weight was 81.6 kg, the mean height was 1.62 m, and having a mean BMI indicated obesity. Regarding the scores, most participants had risk behaviors to develop an eating disorder, being more prevalent in females. Patients also showed dissatisfaction with their self-image. There was a correlation between eating disorders and self-image satisfaction, and between eating disorder severity with age, BMI, and body satisfaction. **Conclusion:** Patients with type 2 diabetes have a higher risk of developing eating disorders and have a worse body self-perception, and should be screened as a possible risk group for the development of eating disorders. **Endocrinol diabetes clin exp 2022 / 2276 - 2282.**

Resumo

Introdução: Transtornos alimentares têm sido associados a pacientes com Diabetes Mellitus, no entanto, poucos estudos concentraram-se no diabetes tipo 2 na população adulta. **Objetivo:** Investigar a prevalência de insatisfação corporal e presença de alterações do comportamento alimentar em um serviço ambulatorial. **Métodos:** Trata-se de um estudo epidemiológico transversal. Pacientes diabéticos do tipo 2 serão avaliados quanto à imagem corporal e o comportamento alimentar através de questionários autoaplicáveis, validados em sua versão brasileira. **Resultados:** A amostra de 67 pacientes era composta por adultos de meia idade sendo a maioria mulheres. A média de peso foi de 81,6 kg, a média de altura foi de 1,62 m, tendo um IMC médio indicando obesidade. Quantos aos escores, a maioria dos participantes tinha comportamentos de risco para desenvolver um transtorno alimentar, sendo mais prevalente no gênero feminino. Os pacientes apresentaram também uma insatisfação com relação á autoimagem. Houve correlação entre transtorno alimentar e satisfação de autoimagem, bem como entre gravidade de transtorno alimentar com idade, IMC e satisfação corporal. **Conclusão:** Pacientes com diabetes tipo 2 têm maior risco de desenvolver distúrbios alimentares e possuem uma pior autopercepção corporal, devendo ser rastreados como possível grupo de risco para o desenvolvimento de transtornos alimentares. **Endocrinol diabetes clin exp 2022 / 2276 - 2282.**

INTRODUCTION

Eating disorder (ED) is a serious psychiatric illness that has a complex tangle of biopsychosocial components as factors. Among them are anorexia nervosa, bulimia nervosa, binge eating disorder, and restrictive or uncontrolled food intake disorder. These disorders have in common substances that regulate the body's homeostasis often altered during the sick state. Among these substances are hormones or neuroactive peptides, such as sex hormones and intestinal hormones, which may disturb the normal food reward circuits, causing stimulation or attenuation of the brain dopamine response, generating changes in this system (1).

Diabetes Mellitus (DM) characterized by a metabolic state of sustained hyperglycemia. Insulin is known for its metabolic effects on receptors in the liver, muscle, and adipose tissue. The identification of these same receptors widely distributed in the brain, together with the additional finding that insulin transport to this organ is reduced in patients with diabetes and patients with cognitive dysfunction, has led to the recognition of the brain as a new target organ. Despite this, the effects of some diseases that may be associated with this mechanism are still not well-understood (2).

There is an association between ED and metabolic alterations, as well as between diabetes and neurological alterations, which has led to investigations into the relationship between ED and DM. However, part of the literature remains inconclusive – some studies do not demonstrate a higher prevalence of eating disorders in diabetic patients when compared to the general population, while others reveal a significantly increased risk (3).

A recent study by Jones et al. involving approximately 1500 young people showed a risk 2.4 times greater for the development of ED in diabetic adolescents when compared to the control group (4). Herbert et al., in turn, showed a significant prevalence of ED in a sample of 663 type 1 and type 2 diabetic patients. The fact is that it is not easy to diagnose ED in diabetic patients, considering that the treatment itself diabetes requires greater attention to weight and dietary regimen, which determines the presence of behaviors similar to patients with ED (5).

It is believed, however, that this same fact increases the risk of diabetics both type 1 and type 2, developing some form of ED, such as bulimia nervosa, anorexia nervosa, or binge eating

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disorder. Therefore, both conditions can overlap and constitute a mutual risk factor (6).

ED could lead to eating behaviors risk for the development of diabetes, whereas diabetes could predispose to the development of eating disorders. It is true, however, regardless of the cause-effect relationship, inadequate eating habits can directly interfere with glycemic control, increasing the risk of acute and chronic complications of DM and, consequently, affecting significantly the prognosis and quality of life of these patients. In this fact lies the importance of identifying body dissatisfaction and eating disorders in diabetic patients, given the first being an important risk factor for the second, thus enabling early treatment.

Taking this into account, the present study aims to investigate the prevalence of body dissatisfaction and changes in eating behavior in adult type 2 diabetic patients treated at the Outpatient Clinic of the Endocrinology and Metabolism Service at the Hospital Universitário Evangélico Mackenzie.

MATERIAL AND METHODS

This is an observational cross-sectional cohort study. It was carried out at the Outpatient Clinic of Endocrinology and Metabology Service of the Hospital Universitário Evangélico Mackenzie in Curitiba - PR and was approved by the Research Ethics Committee of the Faculdade Evangélica Mackenzie do Paraná with the opinion number 3,466,618.

Patients with a previous diagnosis of type 2 DM and who did not have a previous diagnosis of psychiatric disorder were included. Those who were not literate, under 18 years of age, or who did not consent to participate in the study by signing an informed consent form (ICF) were excluded. Data were collected by the researchers through self-administered questionnaires. In addition to the data obtained from the validated questionnaires, information about age, gender, weight, and height.

To assess eating behavior, we used the reduced version of the Eating Attitudes Test (EAT-26), proposed by Garner and Garfinkel (7) and translated and validated by Nunes et al. (8). This instrument has 26 questions, each with six response options, for which scores range from 0 to 3. The questions assess 3 factors: The Diet Scale: assesses pathological refusal to eat high-calorie foods and intense preoccupation with fitness; Food Worry and Bulimia Scale: episodes of binge eating followed by vomiting or other behaviors to avoid weight gain; Oral control scale: self-control about food. The result of the test is obtained by the sum of all points and is considered an indicator of risk for an eating disorder if obtained a score equal to or greater than 20 (8).

To screen for Binge Eating Disorders, the Binge Eating Scale (ECAP) was used, developed by Gormally et al. (9), and validated and translated into Portuguese in 2002. This scale is composed of 16 items, and each of them must be marked with an answer option, ranging from absence ("0") to maximum severity ("3"). The final score is composed of the sum of the points of all items. Individuals with a score less than or equal to 17 are considered without binge eating;

scores between 18 and 26 are considered to have moderate compulsion; and those with a score greater than or equal to 27, with severe compulsion. For simplicity, the authors suggest that a score of 17 is used as a cut-off point to obtain sufficient sensitivity and that the diagnosis is always confirmed by a clinical interview (10).

To assess dissatisfaction with body image, we used the scale of 9 silhouettes Figure Rating Scale (FRS) proposed by Stunkart et al. The instrument consists of 9 silhouettes, varying between extremes of thinness and fat, with stable height, presented according to sex. The subject chooses the figures based on two questions: "Which drawing do you most resemble?" and "Which of the drawings would you most like to look like?". After the selection, the discrepancy between the image chosen as current and the image chosen as the ideal is calculated, by subtracting the values of the figures. Thus, as the result moves away from zero, the greater the individual's degree of body dissatisfaction (11,12).

Qualitative variables were described by absolute and relative frequencies and compared between groups using Pearson's Chi-Square test. Quantitative variables were described by means and standard deviations and compared by Student's t-test. Correlations between quantitative variables were evaluated using Spearman's correlation coefficient. All analyzes were carried out using the R software for statistical computing, always considering a significance level of 5%.

RESULTS

The study sample consisted of 67 patients who met the inclusion criteria.

It was also seen that most patients, 59.7% of the sample, were female (frequency 40/67).

Regarding weight, 43.3% of patients were obese (frequency 29/67). Of these, 19 patients were female and 10 were male.

Among the patients in the sample, the mean age was 58 years (± 10.8), the mean weight was 81.6 kg (±18.8), the mean height was 1.62 m (± 0.10) and the mean BMI was 30.9 kg/m2 (± 6.1).

Comparing the patients by the score on the EAT questionnaire, 67.2% (frequency 45/67) had a score greater than or equal to 20, among them 30 women and 15 men. That is, most participants had risk behaviors and attitudes for ED, with an average score of 25.4 (± 11.8), being more prevalent in females.

In the FRS, which assesses body satisfaction through the perception of real and ideal body image, the mean score was 2 (± 1.7).

When comparing patients at risk for ED (EAT >=20) and without this risk (EAT<20) in terms of gender, anthropometric data, and scores on the ECAP and FRS questionnaires, the difference only between the FRS scores was significant. The mean score of the group at risk of having ED was 1.4 units higher than that of patients without risk. There were no other differences between the groups, as shown in **Table 01**.

Table 01 - Comparison of the sample in terms of gender, anthropometric data, and scores on questionnaires about the risk of eating disorders by EAT questionnaire

Variable		EAT < 20	EAT >=20	p-value
Sex	Female	10 (25.0%)	30 (75.0%)	0.162
	Male	12 (44.4%)	15 (55.6%)	
Obesity	Yes	7 (24.1%)	22 (75.9%)	0.288
	No	15 (39.5%)	23 (60.5%)	
Positive ECAP	Yes	3 (21.4%)	11 (78.6%)	0.483
	No	19 (35.8%)	34 (64.2%)	
Age (years)		58.9 (12.3)	57.5 (10.1)	0.657
BMI		29.2 (4.7)	31.7 (6.6)	0.091
ECAP score		9.3 (7.4)	11.9 (8.8)	0.197
FRS score		1 (1.2)	2.4 (1.7)	**<0.001**

As for the score on the ECAP questionnaire, which assesses the severity of binge eating, the mean was 11.1 (± 8.4). It was seen that 79.1% of patients (frequency 53/67, 28 women and 25 men) did not have binge eating as they had a score lower than or equal to 17. Of patients with a score > 17 (that is, who had binge eating moderate to severe), 12 were female and 2 were male with a mean age of 53 years and 34.5% were obese.

When comparing patients without binge eating (ECAP <=17) and with binge eating (ECAP >17), the difference between obese and non-obese, age difference, BMI difference, and FRS questionnaire score was significant (**Table 02**).

Table 02 - Comparison of the sample regarding gender, anthropometric data, and, scores on questionnaires about the risk of eating disorders by ECAP questionnaire

Variable		ECAP <= 17	ECAP > 17	p-value
Sex	Female	28 (70.0%)	12 (30.0%)	0.054
	Male	25 (92.6%)	2 (7.4%)	
Obesity	Yes	19 (65.5%)	10 (34.5%)	**0.037**
	No	34 (89.5%)	4 (10.5%)	
EAT risk	Yes	34 (75.6%)	11 (24.4%)	0.483
	No	19 (86.4%)	3 (13.6%)	
Age (years)		59.2 (11.4)	53.3 (6.0)	**0.012**
BMI		30.1 (6.2)	33.8 (5.2)	**0.032**
EAT score		24.4 (11.1)	29.1 (13.8)	0.263
FRS score		1.6 (1.5)	3.5 (1.7)	**0.001**

About the Spearman correlation coefficients for the pairs of quantitative variables, the correlations between the EAT and FRS, ECAP and BMI, ECAP and FRS, and, FRS, and, BMI scores were significant and positive, indicating that above-average scores in one of these variables were associated with above-average scores on the second variable.

The correlation between ECAP score and patient age was significant and negative, indicating that higher scores on the questionnaire were associated with younger ages.

DISCUSSION

The sample of 67 patients had an age profile close to the sixth decade of life, with the majority of the sample being female.

Regarding the EAT score, most of the evaluated patients had a high risk of developing an ED (EAT >=20) and also presented dissatisfaction with their body self-image (FRS score 2.4). We concluded in this study that patients at risk of ED were dissatisfied with their bodies.

Regarding the ED severity score (ECAP), the patients who had a more severe ED (ECAP >17) were mostly women. They were also obese and dissatisfied with their body image (FRS 3.5).

There was a correlation between ED and self-image satisfaction, as well as between ED severity with age, BMI, and, body satisfaction.

The vast majority of studies that assess diabetes and ED report a profile of children and adolescents and patients with type 1 DM, as this is the group most affected by eating disorders. There is even a situation peculiar to this group described as diabulimia, which is the restriction of insulin use to lose weight (13,14).

Although older patients with type 2 DM are not the most prevalent profile for the involvement of eating disorders according to the literature, they represent most of the national diabetic population - type 2 DM (considered an epidemic) in Brazil corresponding to approximately 90% of all cases of diabetes, studies of ED in patients with type 2 DM are lacking.

In the present study, two-thirds of the patients in the sample were female. Worldwide and nationally, there are more men with diabetes than women, however, women control the disease more and have a more therapeutic follow-up in consultations (15,16).

The sample majority was female, recent studies have brought perimenopause as a period of vulnerability for the development of eating disorders which confirms the need to investigate eating disorders in this age group (17,18).

In medicine, few disorders have a gender distribution as asymmetrical as eating disorders, as only 10% of cases occur in males, which can be attributed to biological and cultural factors, as well as difficulties in diagnosing ED in men (19).

As for the anthropometric data, it was expected to find a high mean BMI, since obesity is linked to type 2 DM as part of a metabolic syndrome. Obesity ends up being a risk factor for eating disorders since individuals affected by this disease have a higher prevalence of symptoms of anxiety, depression, impulsive traits, and, eating behavior disorders such as lack of eating control and emotional eating (20).

The high risk of ED in the diabetic population and dissatisfaction with the self-image is in agreement with the study carried out by Dias Santana et al. and ED, in this case, a food compulsion and an overestimation of body weight and shape (21).

Still, about the risk of ED and dissatisfaction with self-image, there is a basis for this association in the work of Verbist and Condon, where 66% of the sample of patients with type 1 DM stated that the diabetes treatment, due to food surveillance in dietary therapy, affected their self-perception of body image (22).

In the correlations found, it is possible to see that both in type 1 and type 2 DM, there are similarities in the relationship between ED and body dissatisfaction with age and BMI. These factors end up interfering in both cases, jointly aggravating the condition (22,23).

As a limitation, the study used the BMI to determine the anthropometric index, which generates imprecision about the body composition of the participants, since this parameter does not distinguish between fat and lean mass. For greater precision, the use of a bioimpedance test would generate more accurate data in this regard.

CONCLUSION

Patients with type 2 DM are at greater risk of developing eating disorders and have a worse body self-perception and should be screened as a possible risk group for the development of eating disorders.

Efforts are needed to better understand the prevention and treatment of the ED observed in patients with type 2 DM and health professionals should be attentive to identify these serious conditions that are still poorly recognized in clinical practice.

TESTE DE ATITUDES ALIMENTARES (EAT-26)- Versão em Português

Nome:_____

Idade: _____   Peso: _____   Altura _____

Por favor, responda as seguintes questões:	Sempre	Muitas vezes	Às vezes	Poucas vezes	Quase nunca	Nunca
1 - Fico apavorada com a idéia de estar engordando.	O	O	O	O	O	O
2 - Evito comer quando estou com fome.	O	O	O	O	O	O
3 - Sinto-me preocupada com os alimentos.	O	O	O	O	O	O
4 - Continuar a comer em exagero faz com que eu sinta que não sou capaz de parar.	O	O	O	O	O	O
5 - Corto os meus alimentos em pequenos pedaços.	O	O	O	O	O	O
6 - Presto atenção à quantidade de calorias dos alimentos que eu como.	O	O	O	O	O	O
7 - Evito, particularmente, os alimentos ricos em carboidratos (ex. pão, arroz, batatas, etc.)	O	O	O	O	O	O
8 - Sinto que os outros gostariam que eu comesse mais.	O	O	O	O	O	O
9 - Vomito depois de comer.	O	O	O	O	O	O
10 - Sinto-me extremamente culpada depois de comer.	O	O	O	O	O	O
11 - Preocupo-me com o desejo de ser mais magra.	O	O	O	O	O	O
12- Penso em queimar calorias a mais quando me exercito.	O	O	O	O	O	O
13 – As pessoas me acham muito magra.	O	O	O	O	O	O
14 - Preocupo-me com a idéia de haver gordura em meu corpo.	O	O	O	O	O	O
15 - Demoro mais tempo para fazer minhas refeições do que as outras pessoas.	O	O	O	O	O	O
16 – Evito comer alimentos que contenham açúcar.	O	O	O	O	O	O
17 - Costumo comer alimentos dietéticos.	O	O	O	O	O	O
18 – Sinto que os alimentos controlam minha vida.	O	O	O	O	O	O
19 - Demostro auto-controle diante dos alimentos.	O	O	O	O	O	O
20 – Sinto que os outros me pressionam para comer.	O	O	O	O	O	O
21 - Passo muito tempo pensando em comer.	O	O	O	O	O	O
22 – Sinto desconforto após comer doces.	O	O	O	O	O	O
23 - Faço regimes para emagrecer.	O	O	O	O	O	O
24 – Gosto de sentir meu estômago vazio.	O	O	O	O	O	O
25 - Gosto de experimentar novos alimentos ricos em calorias	O	O	O	O	O	O
26 – Sinto vontade de vomitar após as refeições.	O	O	O	O	O	O

Refs (7,8)

FIGURE RATING SCALE

1 2 3 4 5 6 7 8 9
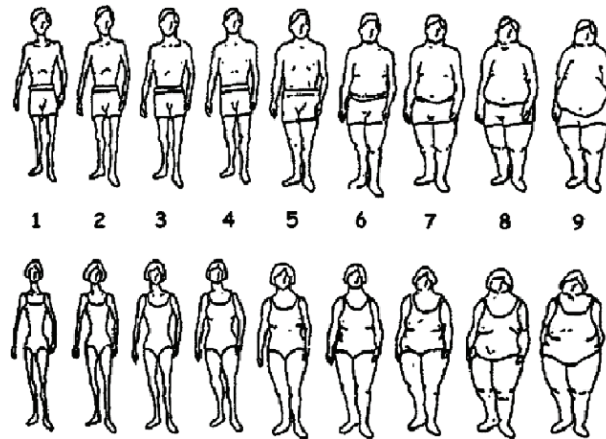
Refs (11, 12)

BES *(BINGE EATING SCALE)*

Nome:_____ Data: ___/___/___

Lista de verificação dos hábitos alimentares

Instruções:

Você encontrará abaixo grupos de afirmações numeradas. Leia todas as afirmações em cada grupo e marque, nesta folha, aquela que melhor descreve o modo como você se sente em relação aos problemas que tem para controlar seu comportamento alimentar.

#1
( ) 1. Eu não me sinto constrangido(a) com o meu peso ou o tamanho do meu corpo quando estou com outras pessoas.
( ) 2. Eu me sinto preocupado(a) em como pareço para os outros, mas isto, normalmente, não me faz sentir desapontado(a) comigo mesmo(a).
( ) 3. Eu fico mesmo constrangido(a) com a minha aparência e o meu peso, o que me faz sentir desapontado(a) comigo mesmo(a).
( ) 4. Eu me sinto muito constrangido(a) com o meu peso e, freqüentemente, sinto muita vergonha e desprezo por mim mesmo(a). Tento evitar contatos sociais por causa desse constrangimento.

#2
( ) 1. Eu não tenho nenhuma dificuldade para comer devagar, de maneira apropriada.
( ) 2. Embora pareça que eu devore os alimentos, não acabo me sentindo empanturrado(a) por comer demais.
( ) 3. Às vezes tendo a comer rapidamente, sentindo-me então desconfortavelmente cheio(a) depois.
( ) 4. Eu tenho o hábito de engolir minha comida sem realmente mastigá-la. Quando isto acontece, em geral me sinto desconfortavelmente empanturrado(a) por ter comido demais.

#3
( ) 1. Eu me sinto capaz de controlar meus impulsos para comer, quando eu quero.
( ) 2. Eu sinto que tenho falhado em controlar meu comportamento alimentar mais do que a média das pessoas.
( ) 3. Eu me sinto totalmente incapaz de controlar meus impulsos para comer.
( ) 4. Por me sentir tão incapaz de controlar meu comportamento alimentar, entro em desespero tentando manter o controle.

#4
( ) 1. Eu não tenho o hábito de comer quando estou chateado(a).
( ) 2. Às vezes eu como quando estou chateado(a) mas, freqüentemente, sou capaz de me ocupar e afastar minha mente da comida.
( ) 3. Eu tenho o hábito regular de comer quando estou chateado(a) mas, de vez em quando, posso usar alguma outra atividade para afastar minha mente da comida.
( ) 4. Eu tenho o forte hábito de comer quando estou chateado(a). Nada parece me ajudar a parar com esse hábito.

#5
( ) 1. Normalmente quando como alguma coisa é porque estou fisicamente com fome.
( ) 2. De vez em quando como alguma coisa por impulso, mesmo quando não estou realmente com fome.
( ) 3. Eu tenho o hábito regular de comer alimentos que realmente não aprecio para satisfazer uma sensação de fome, mesmo que fisicamente eu não necessite de comida.
( ) 4. Mesmo que não esteja fisicamente com fome, tenho uma sensação de fome em minha boca que somente parece ser satisfeita quando eu como um alimento, tipo um sanduíche, que enche a minha boca. Às vezes, quando eu como o alimento para satisfazer minha "fome na boca", em seguida eu o cuspo, assim não ganharei peso.

#6
( ) 1. Eu não sinto qualquer culpa ou ódio de mim mesmo(a) depois de comer demais.
( ) 2. De vez em quando sinto culpa ou ódio de mim mesmo(a) depois de comer demais.
( ) 3. Quase o tempo todo sinto muita culpa ou ódio de mim mesmo(a) depois de comer demais.

#7
( ) 1. Eu não perco o controle total da minha alimentação quando estou em dieta, mesmo após períodos em que como demais.
( ) 2. Às vezes, quando estou em dieta e como um alimento proibido, sinto como se tivesse estragado tudo e como ainda mais.
( ) 3. Freqüentemente, quando como demais durante uma dieta, tenho o hábito de dizer para mim mesmo(a): "agora que estraguei tudo, porque não irei até o fim". Quando isto acontece, eu como ainda mais.
( ) 4. Eu tenho o hábito regular de começar dietas rigorosas por mim mesmo(a), mas quebro as dietas entrando numa compulsão alimentar. Minha vida parece ser "uma festa" ou "um morrer de fome".

#8
( ) 1. Eu raramente como tanta comida a ponto de me sentir desconfortavelmente empanturrado(a) depois.
( ) 2. Normalmente, cerca de uma vez por mês, como uma tal quantidade de comida que acabo me sentindo muito empanturrado(a).
( ) 3. Eu tenho períodos regulares durante o mês, quando como grandes quantidades de comida, seja na hora das refeições, seja nos lanches.
( ) 4. Eu como tanta comida que, regularmente, me sinto bastante desconfortável depois de comer e, algumas vezes, um pouco enjoado(a).

#9
( ) 1. Em geral, minha ingesta calórica não sobe a níveis muito altos, nem desce a níveis muito baixos.
( ) 2. Às vezes, depois de comer demais, tento reduzir minha ingesta calórica para quase nada, para compensar o excesso de calorias que ingeri.
( ) 3. Eu tenho o hábito regular de comer demais durante a noite. Parece que a minha rotina não é estar com fome de manhã, mas comer demais à noite.
( ) 4. Na minha vida adulta tenho tido períodos, que duram semanas, nos quais praticamente me mato de fome. Isto se segue a períodos em que como demais. Parece que vivo uma vida de "festa" ou de "morrer de fome".

#10
( ) 1. Normalmente eu sou capaz de parar de comer quando quero. Eu sei quando "já chega".
( ) 2. De vez em quando, eu tenho uma compulsão para comer que parece que não posso controlar.
( ) 3. Freqüentemente tenho fortes impulsos para comer que parece que não sou capaz de controlar, mas, em outras ocasiões, posso controlar meus impulsos para comer.
( ) 4. Eu me sinto incapaz de controlar impulsos para comer. Eu tenho medo de não ser capaz de parar de comer por vontade própria.

#11
( ) 1. Eu não tenho problema algum para parar de comer quando me sinto cheio(a).
( ) 2. Eu, normalmente, posso parar de comer quando me sinto cheio(a) mas, de vez em quando, comer demais me deixa desconfortavelmente empanturrado(a).
( ) 3. Eu tenho um problema para parar de comer uma vez que eu tenha começado e, normalmente, sinto-me desconfortavelmente empanturrado(a) depois que faço uma refeição.
( ) 4. Por eu ter o problema de não ser capaz de parar de comer quando quero, às vezes tenho que provocar o vômito, usar laxativos e/ou diuréticos para aliviar minha sensação de empanturramento.

#12
( ) 1. Parece que eu como tanto quando estou com os outros (reuniões familiares, sociais), como quando estou sozinho(a).
( ) 2. Às vezes, quando eu estou com outras pessoas, não como tanto quanto eu quero comer porque me sinto constrangido(a) com o meu comportamento alimentar.
( ) 3. Freqüentemente eu como só uma pequena quantidade de comida quando outros estão presentes, pois me sinto muito embaraçado(a) com o meu comportamento alimentar.
( ) 4. Eu me sinto tão envergonhado(a) por comer demais que escolho horas para comer demais quando sei que ninguém me verá. Eu me sinto como uma pessoa que se esconde para comer.

#13
( ) 1 Eu faço três refeições ao dia com apenas um lanche ocasional entre as refeições.
( ) 2. Eu faço três refeições ao dia mas, normalmente, também lancho entre as refeições.
( ) 3. Quando eu faço lanches pesados, tenho o hábito de pular as refeições regulares.
( ) 4. Há períodos regulares em que parece que eu estou continuamente comendo, sem refeições planejadas.

#14
( ) 1. Eu não penso muito em tentar controlar impulsos indesejáveis para comer.
( ) 2. Pelo menos, em algum momento, sinto que meus pensamentos estão "pré-ocupados" com tentar controlar meus impulsos para comer.
( ) 3. Freqüentemente, sinto que gasto muito tempo pensando no quanto comi ou tentando não comer mais.
( ) 4. Parece, para mim, que a maior parte das horas que passo acordado(a) estão "pré-ocupadas" por pensamentos sobre comer ou não comer. Sinto como se eu estivesse constantemente lutando para não comer.

#15
( ) 1. Eu não penso muito sobre comida.
( ) 2. Eu tenho fortes desejos por comida, mas eles só duram curtos períodos de tempo.
( ) 3. Há dias em que parece que eu não posso pensar em mais nada a não ser comida.
( ) 4. Na maioria dos dias, meus pensamentos parecem estar "pré-ocupados" com comida. Sinto como se eu vivesse para comer.

#16
( ) 1. Eu normalmente sei se estou ou não fisicamente com fome. Eu como a porção certa de comida para me satisfazer.
( ) 2. De vez em quando eu me sinto em dúvida para saber se estou ou não fisicamente com fome. Nessas ocasiões é difícil saber quanto eu deveria comer para me satisfazer.
( ) 3. Mesmo que se eu pudesse saber quantas calorias eu deveria ingerir, não teria idéia alguma de qual seria a quantidade "normal" de comida para mim.

Grade de correção da Escala de Compulsão Alimentar Periódica.

#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15	#16
1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0	1 = 0
2 = 0	2 = 1	2 = 1	2 = 0	2 = 1	2 = 1	2 = 2	2 = 1	2 = 1	2 = 1	2 = 1	2 = 1	2 = 0	2 = 1	2 = 1	2 = 1
3 = 1	3 = 2	3 = 3	3 = 0	3 = 2	3 = 3	3 = 3	3 = 2	3 = 2	3 = 2	3 = 2	3 =2	3 = 2	3 = 2	3 = 2	3 = 2
4 = 3	4 = 3	4 = 3	4 = 2	4 = 3	_	4 = 3	4 = 3	4 = 3	4 = 3	4 = 3	4 = 3	4 = 3	4 = 3	4 = 3	_

Ref (10)

References

1. Frank GKW, Shott ME, DeGuzman MC. The Neurobiology of Eating Disorders. Child Adolesc Psychiatr Clin N Am [Internet]. 2019;28(4):629–40. **Available at: https://doi.org/10.1016/j.chc.2019.05.007**
2. Wolf V, Abdul Y, Ergul A. Novel Targets and Interventions for Cognitive Complications of Diabetes. **Front Physiol**. 2022;12(January).
3. De Azevedo AP, Papelbaum M, D'Elia F. Diabetes and eating disorders: A high risk association. **Rev Bras Psiquiatr**. 2002;24(SUPPL. 3):77–80.
4. Jones JM, Lawson ML, Daneman D, Olmsted MP, Rodin G. Eating disorders in adolescent females with and without type 1 diabetes: Cross-sectional study. **Br Med J**. 2000;320(7249):1563-6.
5. Herpertz-Dahlmann B. Adolescent Eating Disorders: Update on Definitions, Symptomatology, Epidemiology, and Comorbidity. **Child Adolesc Psychiatr Clin N.Am** [Internet].2015;24(1):177–96. Available at http://dx.doi.org/10.1016/j.chc.2014.08.003
6. Ward A, Troop N, Cachia M, Watkins P, Treasure J. Double disabled: Diabetes in combination with an eating disorder. **Postgrad Med J**. 1995;71(839):546-50.
7. Garner DM, Garfinkel PE. The Eating Attitudes Test: an index of the symptoms of anorexia nervosa. **Psychol Med**. 1979 May;9(2):273-9.
8. Nunes MA, Bagatini LF, Abuchaim AL, Kunz A, Ramos D, Silva JÁ, Somenzi L, Pinheiro A. Eating disorders: considerations about the Eating Attitudes Test (EAT). **Rev. ABP-APAL**. 1994;16(1): 7-10.
9. Gormally, J. et al. The assessment of binge eating severity among obese persons. **Addict Behav, New York**, v. 7, n.1, p. 47-55, sept. 1982.
10. Freitas S, Lopesa CS, Coutinho W, Appolinario JC. Translation and adaptation to Portuguese of the Periodic Eating Compulsion Scale. **Brazil J. Psychiatry**. 2001; 23 (4).
11. Stunkard AJ, Sorensen T, Schulsinger F. Use of the Danish Adoption Register for the study of obesity and thinness. **Research Publication – Association for Research in Nervous and Mental Disease**. 1982; v. 60, p. 115-120.
12. .Conti MA et al. Stunkard figure rating scale for Brazilian men. Eating and Weight Disorders-Studies on Anorexia, **Bulimia and Obesity.** 2013; v.18, no.3, p. 317-322.
13. Coleman SE, Caswell N. Diabetes and eating disorders: an exploration of "Diabulimia". **BMC Psychol**. 2020;8(1):101.
14. Costa AF, Flor LS, Campos MR, de Oliveira AF, Costa M de F dos S, da Silva RS, et al. Burden of type 2 diabetes mellitus in Brazil. **Cad Health Publica**. 2017;33(2):1–14.
15. Sinclair A, Saeedi P, Kaundal A, Karuranga S, Malanda B, Williams R. Diabetes and global aging among 65–99-year-old adults: Findings from the International Diabetes Federation Diabetes Atlas, 9th edition. **Diabetes Res Clin Pract** [Internet].2020;162:108078. Available at: https://doi.org/10.1016/j.diabres.2020.108078
16. De Almeida-Pititto B, Dias ML, de Moraes ACF, Ferreira SRG, Franco DR, Eliaschewitz FG. Type 2 diabetes in Brazil: Epidemiology and management. Diabetes, **Metab Syndr Obes Targets Ther**. 2015;8:17–28.
17. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, et al. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. **Diabetes Res Clin Pract**. 2020;162.
18. Baker JH, Runfola CD. Eating disorders in midlife women: A perimenopausal eating disorder? Maturitas [Internet]. 2016;85:112–6. Available at: http://dx.doi.org/10.1016/j.maturitas.2015.12.017.
19. Melin P, Araújo AM. Diagnosing eating disorders in men: a clinical challenge. **Brazil J. Psychiatry**. 2002; 24 (suppl 3).

20. Biagio LD, Moreira P, Amaral CK. Eating behavior in obesity and its correlation with nutritional treatment. **J Bras Psiquiatr**. 2020;69(3):171–8.

21. Dias Santana D, Mitchison D, Gonzalez-Chica D, Touyz S, Stocks N, Apolinario JC, et al. Associations between self-reported diabetes mellitus, disordered eating behaviors, weight/shape overvaluation, and health-related quality of life. **J Eat Disord**. 2019;7(1):1–9.

22. Verbist IL, Condon L. Disordered eating behaviors, body image and social networking in a type 1 diabetes population. **J Health Psychol**. 2021;26(11):1791–802.

23. Winston AP. Eating Disorders and Diabetes. **Curr Diab Rep**. 2020;20(8):1–6.

ORIGINAL ARTICLE
IMPACT OF INSULIN THERAPY EDUCATION ON GLYCATED HEMOGLOBIN IN PATIENTS WITH TYPE 2 DIABETES

IMPACTO NA HEMOGLOBINA GLICADA PELA EDUCAÇÃO EM INSULINOTERAPIA NOS PACIENTES COM DIABETES TIPO 2

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TACIANE ELISABETH CESCA**
THIELSEN CARDOSO DA SILVA**

Abstract

Introduction: Diabetes Mellitus is an important cause of morbidity and mortality worldwide. Blood glucose control is essential for these patients due to the high incidence of micro and macrovascular complications, often associated with loss of quality of life and increased mortality. In patients undergoing diabetes education training, improvement in HbA1C, weight, BP, total and HDL cholesterol is observed. **Objective:** To assess the perception and prior knowledge of insulin-dependent patients about their condition, severity and importance of adherence to treatment for glycemic control. To evaluate the effects of insulin application training on diabetes perception and knowledge in this group of patients. To evaluate the effects of training on insulin use on glycated hemoglobin in this group of patients. **Methods:** This is a prospective study with a descriptive interventionist character with a quantitative approach, which was carried out at the Hospital Universitário Evangélico Mackenzie - HUEM, from March to December 2021. 14 hospitalized patients, previously diagnosed with DM II, were recruited in use of insulin therapy or hospitalized patients with or without a previous diagnosis of DM II who will start insulin therapy. A survey was applied to diabetic patients undergoing treatment with insulin, structured for data collection provided theoretical didactic material printed or *online*, for those who have access to the internet, and practical training was carried out demonstrating the correct technique of application of the insulin therapy. After the training, the survey was performed again and the scores were compared. **Results:** Before the training, the total average of correct answers was 13.7 points (up to 32). After theoretical and practical training on insulin treatment, the total average of correct answers was 25.4 points. The average score of the post-training survey showed an increase of 11.7 points in relation to the pre-training survey (increase of 85%). **Conclusion:** In our study, there was a significant improvement in the score in the self-administered survey on knowledge of insulin therapy after training with printed visual material and practical demonstration. Training for insulin-dependent patients makes it possible to improve self-knowledge in diabetes and, possibly, improve glycemic control. Further studies are needed to establish a standardized training program for insulin treatment in patients with type 2 diabetes mellitus. **Endocrinol diabetes clin exp 2021 / 2283 - 2290.**

associado à perda de qualidade de vida e aumento da mortalidade. Em pacientes submetidos a treinamentos de educação em diabetes é verificado melhora dos aspectos de HbA1C, peso, PA, colesterol total e HDL. **Objetivo:** Avaliar a percepção e o conhecimento prévio do paciente insulinodependente sobre sua condição, gravidade e importância da adesão ao tratamento para controle glicêmico. Avaliar os efeitos do treinamento de aplicação de insulina na percepção e conhecimento do diabetes neste grupo de pacientes. Avaliar os efeitos do treinamento no uso de insulina na hemoglobina glicada neste grupo de pacientes. **Métodos:** Trata-se de um estudo prospectivo com caráter intervencionista descritivo de abordagem quantitativa, que foi realizado no Hospital Universitário Evangélico Mackenzie – HUEM, no período de março a dezembro de 2021. Foram recrutados 14 pacientes internados, previamente diagnosticados com DM II, em uso de insulinoterapia ou pacientes internados com diagnóstico prévio ou não de DM II que iniciarão insulinoterapia. Foi aplicado um inquérito para pacientes diabéticos que fazem tratamento com insulina, estruturado para levantamento de dados fornecido material didático teórico impresso ou online, para aqueles que possuem acesso à internet, e realizado um treinamento prático demonstrando a correta técnica de aplicação da insulinoterapia. Após a realização do treinamento, foi realizado novamente o inquerito e comparados as pontuações. **Resultados:** Antes da realização do treinamento, a média total de acertos foi de 13,7 pontos (até 32). Após a realização do treinamento teórico e prático sobre o tratamento com insulina, a média total de acertos foi de 25,4 pontos. A pontuação média do inquérito pós treinamento apresentou aumento de 11,7 pontos em relação ao inquérito pré treinamento (aumento de 85%). **Conclusão:** Em nosso estudo, houve melhora significativa na pontuação no inquerito auto-aplicável sobre o conhecimento em insulinoterapia após a realização de treinamento com o material visual impresso e demonstração prática. O treinamento para pacientes insulinodepentes possibilita a melhora do auto-conhecimento em Diabetes e, possivelmente, melhora nos controles glicêmicos. Novos estudos são necessários para estabelecer um programa de treinamento padronizado para o tratamento com insulina em paciente com *Diabetes Mellitus tipo 2*. **Endocrinol diabetes clin exp 2021 / 2283 - 2290.**

INTRODUCTION

Diabetes Mellitus (DM) is an important cause of morbidity and mortality worldwide. According to the IBGE, 6.2% of the Brazilian population over 18 years old declared a diagnosis of diabetes. Of these, a higher prevalence in women than in men

Resumo

Introdução: O Diabetes Mellitus é uma importante causa de morbimortalidade no contexto mundial. O controle da glicemia é essencial para esses pacientes devido à grande incidência de complicações micro e macrovasculares, frequentemente

and in people with incomplete primary education (1).

The significant impact of this pathology on the costs of the Unified Health System (SUS) in Brazil is mainly related to hospitalizations resulting from complications of the disease, which require highly complex procedures and generate costs of approximately 39 million reais per year (2).

For the control of the disease, which is carried out through glycemic adjustment in the normal ranges, an adequate therapy is essential, that the patient is informed and well guided by a professional regarding the correct application and use of insulin. To perform the correct technique, material, quantity and correct location are necessary (3).

The ideal route of application is subcutaneous. If there is an application error, in the intradermal route for example, the patient may have hyperglycemia, due to the slower absorption of insulin and if it is applied in the intramuscular route, there is a risk of hypoglycemia due to faster absorption. The places indicated for insulin application are: arm, buttocks, thigh and abdomen. It is necessary to emphasize that the rotation of the application points is a decisive factor for the prevention of lipohypertrophy and glycemic lack of control (3).

Blood glucose control is essential for these patients, since, compared to non-diabetic individuals of the same age and with the same risk factors, individuals with poor glycemic control are two to four times more likely to develop coronary heart disease and stroke. brain (2).

In this way, the correct use of insulin therapy benefits not only through the control of comorbidities and complications related to DM, but also helps in the reduction of hospitalizations, in the reduction of public expenses and considerably increases the life expectancy of the affected population.

HYPOTHESIS

The adherence and participation of diabetic patients using insulin in the treatment of their disease is essential for therapeutic success. According to the literature, with the accomplishment of this work, it is expected to find a significant improvement in the results of the surveys and a reduction in glycated hemoglobin after training the patients.

GOALS

To assess the perception and prior knowledge of insulin-dependent patients about their condition, severity and importance of adherence to treatment for glycemic control.

To evaluate the effects of insulin application training on diabetes perception and knowledge in this group of patients.

To evaluate the effects of training on insulin use on glycated hemoglobin in this group of patients.

LITERATURE REVIEW

Diabetes Mellitus (DM) is a metabolic disease characterized by a state of hyperglycemia with impaired release and/or action of insulin secreted by the pancreas. DM has several etiologies, associated with genetic and environmental factors. The disease forms are diabetes type I, type II (DM II), gestational diabetes and other subtypes (3).

DM II is a disease with a multifactorial etiology and corresponds to 90% of diabetes cases today and affects mainly adults from the fourth decade of life. The pathophysiology involved in this case derives from a lower responsiveness of peripheral tissues to insulin action and from the inefficient response of β cells to circulating glucose. As a compensatory mechanism, β cells increase insulin secretion to regulate blood glucose levels. This initial condition is called insulin resistance and as the disease progresses, over the years, there is an impairment of β cells that can decrease insulin secretion and progress to complete exhaustion. Patients often have the metabolic syndrome, characterized by central obesity, dyslipidemia, and hypertension. (3,4)

Epidemiological studies point to the environment as an im-portant role in relation to DM II. Low birth weight individuals have higher plasma proinsulin, which suggests a higher risk for the development of DM II or some metabolic syndrome in the future. Furthermore, in developed countries, the increase in prevalence is more frequent in older age groups due to the increase in life expectancy and population growth. In developing countries, there will be an increase in prevalence in all age groups. (5)

In Brazil, in recent studies carried out in six capitals, it was found that the age group most affected is between 35 and 74 years old. In another study carried out by the IBGE, it was identified that 6.2% of the Brazilian population over 18 years old declared diabetes diagnosis. Of these 6.2%, a higher prevalence, was found in women than in men and a higher rate in people with incomplete primary education. (6)

For the control of the disease, which is carried out through glycemic adjustment in the normal ranges, an adequate therapy is essential, that the patient is informed and well guided by a professional regarding the correct application and use of insulin. To perform the correct technique, material, quantity and correct location are necessary. (3)

MATERIAL AND METHODS

This is a prospective study with a descriptive interventionist character with a quantitative approach, which was carried out at the Hospital Universitário Evangélico Mackenzie - HUEM, from March to December 2021, approved by the ethics committee of the institution. We recruited 14 hospitalized patients, previously diagnosed with DM II, using insulin therapy or hospitalized patients with or without a previous diagnosis of DM II who will start insulin therapy (HbA1C greater than or equal to 9.0% or who, during hospitalization, required the use of more than 30IU (total dose of insulin per day to adjust blood glucose levels). Patients diagnosed with DM I, patients with DM II controlled with the use of oral hypoglycemic agents, patients who refused to sign the Free and Informed Consent Form, illiterate patients and/or patients with disabling mental or physical limitations were excluded.

A survey (Annex 1) was applied to diabetic patients undergoing insulin treatment, structured to collect data on the profile of patients, knowledge of diabetes and the use of insulin, which contains 47 questions related to socioeconomic aspects, age, weight, height, time of illness, time of use and types of treatment in use for diabetes, in addition to pharmacological characteristics, correct methods of use, packaging, application sites, care with use and ways of disposing of insulin, as well as knowledge and management of hypoglycemia and frequency of hyperglycemia. Of the total of 47 questions, 32 were analyzed objectively, with 1 point being counted for each correct alternative (maximum score of 32 points).

After the application of the survey, printed or online theoretical didactic material was provided for those who have access to the internet, and practical training was carried out demonstrating the correct technique of application and handling of insulin. The topics covered in the theoretical material and in the practical training consisted of: (a) Review of the definition, characteristics, types of diabetes and complications associated with the disease; (b) Presentation of the materials used for insulin application, types of syringes, needle size, materials for asepsis, types of insulin and pharmacological characteristics of each type; (c) Demonstration of the technique for homogenizing insulin vials and pens, guidelines on the correct way and place of storage, transport and expiration dates of insulins; (d) Demonstration of the correct places for insulin application and rotation, skinfold technique, aspiration of insulin in the bottle and guidance on lipodystrophy and ways of prevention; (e) Simulation of insulin application in a human skin simulator device; (f) Guidance on hypoglycemia and demonstration of correct management in this situation. For the control group, usual guidelines on insulinization were offered.

After carrying out the practical training and the usual guidelines on insulinization, the survey was applied again and the scores were then compared at the end of the study (**Table 1**).

RESULTS

The study sample consisted of 14 patients who met the inclusion criteria.

It was also seen that most patients, 71.4% of the sample, were male (frequency 10/14).

Among the patients in the sample, the mean hemoglobin was 13.3 g/dL, the mean plasma creatinine was 0.94 mg/dL and the mean HbA1C was 10.58%.

Analyzing the patients through the score in the Survey for diabetic patients undergoing treatment with insulin, structured for a survey (Appendix 1), before the training, the total average of correct answers was 13.7 points. The mean score for patients with HbA1C less than or equal to 9.9% (frequency 5/14) was 17.8 points. The mean score for patients with HbA1C greater than or equal to 10.0% (frequency 9/14) was 11.4 points. Among male participants, the average of correct answers was 13.2 points. Among female participants, the average of correct answers was 15 points (Table 1).

When the patients were analyzed after theoretical and practical training on insulin treatment, the total average of correct answers was 25.4 points. The mean score for patients with HbA1C less than or equal to 9.9% (frequency 5/14) was 28 points. The mean score for patients with HbA1C greater than or equal to 10.0% (frequency 9/14) was 23.8 points. Among male participants, the average of correct answers was 26.4 points. Among female participants, the average of correct answers was 22.7 points (**Table 1**).

The average score of the post-training survey showed an increase of 11.7 points in relation to the pre-training survey (increase of 85%) (**Table 1**).

	Patient	**Age (years)**	**Hemoglobin (g/dL)**	**Creatinine (mg/dL)**	**HbA1C (%)**	**Pre training survey (up to 32 points)**	**Post training survey (up to 32 points)**
1	D. L. S.	56	12,4	0,77	10,7	15	29
2	J. C. M	73	14,0	0,68	10,5	10	26
3	E. L. M.	47	11,6	1,47	12,7	9	23
4	V. B.	63	16,2	0,89	14,7	11	21
5	M. A. F.	54	13,6	0,56	9,3	14	26
6	G. A. C	74	10,7	1,14	8,3	18	32
7	M. D. R.	46	15,3	0,86	10,2	14	29
8	F. P. N.	82	12,3	1,34	11,3	12	26
9	M.F.	82	11,5	1,12	10,7	12	22
10	J. B. E. S.	38	16,5	0,76	9,1	16	27
11	S. M. B.	56	14,8	0,84	8,3	17	24
12	V. S. M.	56	12,4	0,63	7,4	24	31
13	E. M. A.	58	14,0	0,94	13,8	7	14
14	S. M.	54	11,6	1,23	11,2	13	25
					AVERAGE	**13,7**	**25,4**

DISCUSSION

Diabetes Mellitus is an important cause of morbidity and mortality worldwide. Blood glucose control is essential for these patients due to the high incidence of micro and macrovascular complications, often associated with loss of quality of life and increased mortality (1).

It is important to homogenize the insulin suspension, verify that the conservation is being adequate, observe the validity and pay attention to which device is being used for application. The places indicated for insulin application are: arm, buttocks, thigh and abdomen. It is necessary to emphasize that the rotation of the application points is a decisive factor for the prevention of lipohypertrophy and glycemic lack of control (3).

The main cutaneous complications related to insulin therapy include an erythematous and edematous reaction at the application sites, which may be related to the use of so-called impure insulins; lipohypertrophy which is characterized by subcutaneous masses that can lead to incorrect insulin absorption; and insulin lipodystrophy. (7).

In a study by Marcia Eiko Karino et. al., on the mistakes and successes of self-administration of insulin in diabetic adolescents carried out with 47 individuals, found that 29.8%

of diabetic patients had lipodystrophy, probably caused by the lack of rotation of insulin application sites, which reinforces the importance of correct orientation and reassessment of diabetic patients. Furthermore, this study also showed that 77.27% of the patients reuse the syringe for self-application and that only 29.8% of the patients correctly developed the technique of self-administration of insulin. (8).

The American Diabetes Association recommends that individuals with DM receive education and support for the self-management of the disease, since this has been identified as the most effective measure for the control and improvement of the quality of life (9).

Glycated hemoglobin (HbA1c) is considered the gold standard test to assess the metabolic control of diabetic individuals. This test, which is made from a blood sample, allows you to assess the average blood glucose over the last 3 months. Its values, if they are high, are related to the risk of macro-microvascular complications (3).

Studies have found that diabetes education programs that include nutritional therapy and individualized care plans are associated with a decrease in glycated hemoglobin (HbA1c) in people with DM (10-12).

In a randomized study involving 104 type 2 diabetic patients, of which 52 of them received diabetes training and education, a significant improvement in glycated hemoglobin, weight, blood pressure, total and HDL cholesterol was observed in the group submitted to training, in a period of 12 months (13).

In patients undergoing diabetes education training, improvement in HbA1C, weight, BP, total and HDL cholesterol is observed.

In our study, patients with worse scores on the pre-training survey also had higher means of HbA1C. There was a significant improvement in the scores of surveys on knowledge of insulin therapy after training with theoretical printed material and practical training.

CONCLUSION

Training for insulin-dependent patients makes it possible to improve self-knowledge in diabetes and, possibly, improve glycemic control.

Further studies are needed to establish a standardized training program for insulin treatment in patients with type 2 diabetes mellitus.

This survey is voluntary and completely anonymous. If you choose not to participate, your treatment will not be affected in any way. People who use insulin or other diabetes medication are invited to participate. The information you provide will be used to improve the training and education of everyone who uses insulin to manage their diabetes

Annex 1

Survey for diabetic patients undergoing insulin treatment

1.Sex
(   ) Female
(   ) Male

2. Age? _____ years old
3. Weight? _____ kg
4. Height? _____ cm

5. How long have you had diabetes?
(   ) less than 1 year - indicate number of days/months: _____
(   ) more than 1 year – indicate the number of years: _____ year(s)

6. What type of treatment are you currently taking for your diabetes (and for how long)? (Check all that apply)
(   ) Pills (_____years or _____months)
(   ) Insulin (_____years or _____months)

7. What device do you normally use to inject insulin? (Check all that apply)
(   ) Syringe
(   ) Pen
(   ) Other (eg insulin pump)

8. How many injections do you have per day?
(   ) 1
(   ) 2
(   ) 3
(   ) 4
(   ) 5
(   ) 6
(   ) 7
(   ) More than 7
9. What type of insulin is considered Fast?
(   ) NPH (milky)
(   ) Regular
(   ) I don't know

10. What type of insulin is considered Slow?
(   ) NPH (milky)
(   ) Regular
(   ) I don't know

11. If you use milky insulin (NPH, N or premix insulin), do you homogenize the insulin before use?
(   ) Yes
(   ) No

12. If yes, before the injection, how many times on average do you roll and/or tilt the insulin vial or pen? _____ times

13. Where do you store your insulin before you start using the insulin vial or pen?

(   ) Refrigerator

(   ) Bathroom, bag, drawer or others – room temperature

14. Where do you store your insulin after you start using the insulin vial or pen?

(   ) Refrigerator

(   ) Bathroom, bag, drawer or others – room temperature

15. Do you keep track of the expiration date of the insulin in use?

(   ) Yes

(   ) No

16. On average, what is the shelf life of insulin after opening?

(   ) Up to 7 days

(   ) Between 7-15 days

(   ) Between 30-45 days

(   ) Between 2-6 months

(   ) I don't know

17. How can closed insulins be transported?

(   ) At room temperature, exposed to the sun and heat

(   ) At room temperature, sheltered from the sun and heat

(   ) In thermal bag

(   ) I don't know

18. How can open insulins be transported?

(   ) At room temperature, exposed to the sun and heat

(   ) At room temperature, sheltered from the sun and heat

(   ) In thermal bag

(   ) I don't know

19. What needle length do you currently use to deliver insulin? (Check all that apply)

(   ) 13mm

(   ) 12.7mm

(   ) 12mm

(   ) 10mm

(   ) 8mm

(   ) 6mm

(   ) 5mm

(   ) 4mm

(   ) I don't know

20. What is the correct angle to apply insulin?

(   ) Between 0 and 15

(   ) Between 45 and 90

(   ) Between 90 and 180

(   ) I don't know

21. What are the correct places to apply insulin (Check all that apply)?

(   ) abdomen

(   ) Thighs

(   ) Buttocks

(   ) Arm

(   ) I don't know

22. Do you rotate injection sites?

(   ) Yes

(   ) No

23. How do you choose the place to inject?
( ) I always inject in the same place at the same time of day (eg, in the morning, always injection in the abdomen)
( ) I inject in the same place for a whole day
( ) I inject in the same place for a few days
( ) I choose the location according to my physics activity
( ) I choose the location according to my rotation program (or plan)
( ) I do not have a specific injection routine regarding the site
( ) I choose the place that hurts the least

24. Before the injection do you clean the skin with disinfectant (eg alcohol)?
( ) Yes
( ) No

25. Before inserting the needle into the insulin vial, do you clean the rubber with disinfectant (eg alcohol)?
( ) Yes
( ) No

26. Do you inject through your clothes?
( ) Yes
( ) No

27. How should the skin fold be done?
( ) Use all fingers and apply strong pressure to the skin
( ) Use all fingers and apply light pressure to the skin
( ) Use only index finger and thumb and apply strong pressure to the skin
( ) Use only index finger and thumb and apply light pressure to the skin
( ) I don't know

28. How long should the skin fold be maintained?
( ) Just to mark the insulin application site
( ) Keep only until the needle is inserted into the skin
( ) Hold until insulin is fully injected
( ) Hold until the insulin is fully injected and release after removing the needle from the skin
( ) I don't know

29. Do you have any swelling or lumps (lipodystrophy) under the skin at the usual injection sites?
( ) Yes
( ) No

30. If yes, in which location(s)?
( ) abdomen
( ) Thighs
( ) Buttocks
( ) Arms

31. Do you inject these bumps or lumps?
( ) Ever
( ) Sometimes
( ) Never

32. What should be done to avoid lipodystrophy (more than one possible alternative) ?
( ) Always apply insulin in the same place at all times
( ) Always use the same syringe and needle
( ) Rotate the application site, keeping at least 1 cm of distance between each one and wait at least 7 days to reapply in the same place
( ) Do not reuse syringes and needles
( ) I don't know

33. If you use a syringe, do you apply insulin with it more than once?
( ) Yes
( ) No

34. Are your injections always painful?
( ) Yes
( ) No

35. If yes, how would you best describe your injections?
( ) Always painful
( ) Often painful (a few times a week)

( ) Sometimes painful (a few times a month)
( ) Almost never painful (a few times a year)

36. Does insulin usually leak at the injection site on the skin?
( ) Yes
( ) No

37. If yes, how often does the fluid leak from the skin at the application site?
( ) Ever
( ) Often (several times a week)
( ) Sometimes (a few times a month)
( ) Almost never (a few times a year)

38. At least how long do you have to wait to remove the needle from the skin after injecting the insulin?
( ) No need to wait
( ) 1 second
( ) 5 seconds
( ) 15 seconds
( ) I don't know

39. How do you dispose of your pen needle/syringes?
( ) In a special container for sharps
( ) In a homemade container like an empty bottle
( ) In the common trash

40. If you discard it in a container, what do you do with the container?
( ) Dispose of in the common trash
( ) Dispose of in recyclable trash
( ) Takes you to the basic health unit
( ) Take it to the pharmacy
( ) Takes you to the doctor's office
( ) Takes it to the laboratory
( ) Takes you to the hospital or clinic
( ) None of the above alternatives

41. Do you know what hypoglycemia is?
( ) Yes
( ) No

42. What is the blood sugar value that defines hypoglycemia?
( ) Less than 100 mg/dL
( ) Less than 70 mg/dL
( ) Less than 50 mg/dL
( ) I don't know

43. In the last 6 months have you had hypoglycemia?
( ) Yes
( ) No

44. Did you need medical or hospital care during any of these hypoglycemic episodes?
( ) Yes
( ) No

45. In case of hypoglycemia, what should be done (more than one option possible)?
( ) Wait until it improves
( ) Communicate close people or friends/family
( ) Ingesting complex foods (eg. Cereal bar, cookies, chocolate)
( ) Drink a glass of water with a tablespoon of sugar
( ) I don't know

46. Do you have frequent hyperglycemia (blood glucose value greater than 180 mg/dL)?
( ) Yes
( ) No

47. If yes, indicate the frequency of hyperglycemia?
( ) More than 5 times/week
( ) 3 to 5 times/week
( ) 1 to 2 times/week
( ) An occasional episode (less than 4 times/month)

References

1. Brasil. IBGE - **Instituto Brasileiro de Geografia e Estatística**. Pesquisa de Orçamentos Familiares 2008-2009. Rio de Janeiro; 2013.
2. GUIDONI, C.M. et al. Assistência ao diabetes no Sistema Único de Saúde: Análise do modelo atual. BRAZ. **J.Pharm.Sci**., São Paulo, v.45, n.1, p. 37-48, Mar.2009.
3. Diretrizes - **Sociedade Brasileira de Diabetes** - 2019-2020. p. 1-491, 2020.
4. LONG, Dan L. et al. **Medicina Interna de Harrison**. 18 ed. Porto Alegre, RS: AMGH Ed., 2013. 2v.
5. BARKER, D. J. P.; HALES, C. N.; FALL, C. H. D.; OSMOND, C.; PHIPPS, K.; CLARK, P. M. S.. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. **Diabetologia**, 1993\; v. 36, n. 1, p. 62-67
6. IBGE - **INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTAT[ISTICA**. Pesquisa Nacional de Saúde - Pesquisa Nacional de saúde 2013, estilos de vida e doenças crônicas - Brasil, Grandes Regiões e Unidades da Federação - Rio de Janeiro, 2014: 40
7. SUZA, C.R.; ZANETTI, M.L. Administração de. insulina: uma abordagem fundamental na educação em diabetes. **Rev.Esc.Enf**. USP, v.34, n.3, p. 264-70, set. 2000.
8. KARINO, M. E. et al. / UNOPAR Cient., **Ciênc. Biol. Saúde**, 2002; v. 4, n. 1, p. 7-19
9. American Diabetes Association (ADA). Standards of medical care in diabetes-2015. **Diabetes Care**, 2016; 39(Supl.):1-112.
10. ESTRUCH R., Ros E, Salas-Salvado J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. **N Engl J Med** 2013; 368(25):1279-1290.
11. TEIXEIRA-LEMOS E., Nunes S, Teixeira F, Reis F. Regular physical exercise training assists in preventing type 2 diabetes development: focus on its antioxidant and anti-inflammatory properties. **Cardiovasc Diabetol** 2011; 10(1):1-12.
12. UMPIERRE D., Ribeiro PA, Kramer CK, Leitao CB, Zucatti AT, Azevedo MJ, Gross JL, Ribeiro JP, Schaan BD. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. **JAMA** 2011; 305(17):1790-1799.
13. SCAIN, S.F. et al. A Structured Educational Program Improves Metabolic Control in Patients With Type 2 Diabetes: A Randomized Controlled Trial. **The Diabetes Educator**, v. 35, n. 4, 603-611, July/August 2009.

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TOPICS IN MEDICAL CLINIC
CASE REPORT

VOGT-KOYANAGI-HARADA SYNDROME INDUCED BY CHEMOTHERAPY USED FOR THE TREATMENT OF MELANOMA: CASE REPORT

SÍNDROME DE VOGT-KOYANAGI-HARADA INDUZIDA POR QUIMIOTERÁPICO PARA TRATAMENTO DE MELANOMA: DESCRIÇÃO DE CASO

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Key words: Panuveitis; Vitiligo; Melanoma.
Descritores: Pan- Uveite; Vitiligo; Melanoma

Abstract

Herein, a case of Vogt-Koyanagi-Harada syndrome (VKH) induced by chemotherapy with Dacarbazine (DTIC) for malignant melanoma in the right thigh region is described. The patient presented with severe bilateral panuveitis requiring glucocorticoid and immunosuppressants **Endocrinol diabetes clin exp 2021 / 2291 - 2292.**

Resumo

Presentemente é descrito um caso de síndrome de Vogt-Koyanagi-Harada (VKH) induzida pelo uso de Dacarbazina para melanoma maligno da coxa direito. A paciente apresentou-se com panuveite bilateral e prejuízo grave da visão necessitando uso de corticoide e imunossupressores. **Endocrinol diabetes clin exp 2021 / 2291 - 2292.**

INTRODUCTION

Melanoma is a very aggressive tumor with 5 years estimated survival of 6 to 8% when it reaches stage 4 (1). Several chemotherapy and immunotherapy have been used as a treatment for this entity and often such treatments lead to the appearance of depigmenting diseases since autoimmunity directed against melanocytes is considered an important form of defense against this tumor (2). In fact, the onset of vitiligo, for example, has been associated with better response to therapy and longer survival in this context (3).

Vogt-Koyanagi-Harada Syndrome (VKH) is an autoimmune disorder against a melanocytic antigen, generating a rare multisystemic disease that reaches particularity organs or tissues containing melanocytes such as the eyes, meninges, central nervous system, skin, mucous membranes and inner ear (4). Its etiology is related to an autoimmune process against antigens on the surface of melanocytes (5), which can be triggered by infections, trauma or even medications (6-9).

The description of VKH syndrome after melanoma treatment is a complication already described (6-9) although considered rare and therefore not always recognized in the medical setting. This entity can lead to serious consequences for eye function; if not properly treated can cause amaurosis, which brings loss of autonomy to the affected individual as well as great damage to their quality of life. Early recognition and prompt treatment of VKH can avoid such consequences.

We describe here a case of VKH after treatment of melanoma in order to alert health professionals to the occurrence of this syndrome, whose incorrect diagnosis and therapeutic error may lead to severe complications.

CASE DESCRIPTION

A 51 year-old female comes to the Ophthalmology outpatient clinic reporting loss of visual acuity in both eyes beginning 04 months before. She had been undergoing chemotherapy with Dacarbazine (DTIC) for malignant melanoma in the right thigh region for the last 4 months. After the appearance of ocular symptoms, hypochromic spots were found in the upper eyelid bilaterally associated with poliosis. She denied photophobia, eye pain and ear complaints. No signs of central nervous system alteration were observed and cranial nerves examination were also normal.

The ophthalmologic examination showed a vision of "counting fingers" at 2m in both eyes. Biomicroscopy revealed bilateral vitreitis and the eye fundus was difficult to visualize due to the opacity of the means. There were keratic precipitates and posterior sinechia bilaterally. Intra ocular pressure (IOP) was 14mmHg in both eyes.

Severe panuveitis with vitiligo and poliosis was diagnosed suggesting the diagnosis of VKH Syndrome.

Treatment was done with local corticosteroids (eye drops and subconjunctival injections) and oral corticosteroids. Attempts to remove the oral corticoid caused new flares, so oral cyclosporine was associated with decreased inflammatory activity.

Her vision stabilized between 20/200 - 20/300, in both eyes, without new complaints. Cancer treatment was maintained.

DISCUSSION

In the present case, bilateral and acute pan uveitis was observed, associated with poliosis and vitiligo, which are typical findings of VKH Syndrome. There are no specific laboratory tests that allow diagnosis confirmation (4). The diagnosis of this syndrome is given by the combination of signs and symptoms such as: (a) the absence of a history of penetrating eye trauma or surgery preceding the onset of uveitis; (b) absence of a clinical or laboratory history of another eye disease; (c) bilateral ocular involvement; (d) presence of neurological/auditory findings

(which may have already disappeared in the middle of clinical presentation) or; (e) dermatological findings, which should never precede eye disease or neurological manifestations.

In the case reported, the patient had no history of ocular trauma, as well as no previous surgery or eye disease. She presented with bilateral ocular involvement of uveitis with severe low visual acuity and skin involvement (poliosis and vitiligo) of subsequent appearance to such ocular symptoms. The appearance of VKH syndrome in this context has been credited to auto-immunity against melanocytes released during chemotherapy induced tumor lysis. In the reported case it would be interesting to know if the patient had any genetic predisposition to VKH – that is brought by class II histocompatibility antigens - such as some subtypes of DR4. The HLADRB1*0405 alleles are considered the most expressive and predominant in Brazilian cases (10,11). A genetic predisposition could have favored the appearance of this complication. Unfortunately, this study was not done as it is not easily performed.

Another mechanism for the onset of VKH after melanoma treatment have been proposed, especially when so-called check point inhibitors are used. This group of drugs favors the action of cytotoxic T lymphocytes that would destroy the tumor. However, the enhancement of T cells action also favors the appearance of autoimmunity diseases such as VKH syndrome. However, this was not the case as the used medication had a different mechanism of action.

CONCLUSION

Readily recognizing this complication is of fundamental importance for both the oncologist and the ophthalmologist who act in the care of these individuals. Early institution of treatment may prevent visual loss in a patient already so affected by an aggressive neoplasm.

References

1. Crosson JN, Laird PW, Debiec M, Bergstrom CS, Lawson DH, Yeh S. Vogt-Koyanagi-Harada-like Syndrome Following CTLA-4 Inhibition with Ipilimumab for Metastatic Melanoma. **J Immunother**. 2015; 38(2): 80–84.
2. Fusumae T, Kamiya K, Maekawa T, Komine M, Murata S, Inoda S, et al. Vogt–Koyanagi–Harada disease-like uveitis induced by vemurafenib for metastatic cutaneous malignant melanoma **J.Dermatol**. 2018; 45: e159–e160
3. Bystryn, JC, Friedman RJ, Kopf A. Prognostic significance of hypopigmentation in malignant melanoma. **Arch. Dermatol**., 1987; 123 :1053- 1055.
4. Matiello M, Carvalho HC, Alvarenga H. Síndrome de Vogt-Koyanagi-Harada. **Cad Bras Méd**. 2004, 17:50-8.
5. Choe CH, McArthur GA, Caro I, Kempen JH, Amaravadi RK. Ocular toxicity in BRAF mutant cutaneous melanoma patients treated with vemurafenib. **Am J Ophthalmol**. 2014; 158(4): 831–837. e2
6. Shinzato M, Yamamoto J, Hirata CE, Goldberg AC, Yoshinari NH, Bonfá E. Eye disease in a patient with rheumatoid arthritis. **Postgrad Med J**. 1999, 75:676-7.
7. Ishikawa A, Shiono T, Uchida S. Vogt-Koyanagi-Harada disease in identical twins. **Retina**. 1994, 14:435-7.
8. Zaoutis LB, Rose CD, McKay CP. Intrafamilial occurrence of tubulointerstitial nephritis with uveitis and Vogt-Koyanagi Harada syndrome. **J Rheumatol**. 1999, 26:2496-8.
9. Levinson RD, See RF, Rajalingam R, et al. HLA-DRB1 and -DQB1 alleles in mestizo patients with Vogt-KoyanagiHaradas disease in Southern California. **Hum Immunol**. 2004, 65(12):1477-82.
10. Yamamoto JH, Damico FM, Cunha-Neto E. Update on autoimmune mechanisms and pathogenesis in Vogt Koyanagi-Harada disease, a model of an autoimmune uveitis: From laboratory to reality. **Módulo Temático e Simpósio Imunologia da cornea.** Universidade de São Paulo. São Paulo: 2005.
11. Gocho K, Kondo I, Yamaki K. Identification of specific antigen for Vogt-Koyanagi-Harada disease: lymphocyte reactivity against the tyrosinase family proteins. **Invest Ophthalmol Vis Sci**. 1999, 40:204.

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