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Insulin resistance and hyperinsulinemia as pathophysiological links between thyroid cancer and obesity. Review

G. Brenta

Univetsity of Buenos Aires, Argentina
Dr Cesar Milstein Hospital, Buenos Aires, Argentina

In recent decades, there has been a notable increase in the prevalence of thyroid cancer, although the specific reasons for this have not yet been well defined [1, 2]. Early detection and over-detection are considered to be major reasons for the increase, as mirrored in the detection of microcarcinomas [3].

Environmental factors (radiation exposure, iodine intake) and lifestyle factors are thought to be associated with the increase in prevalence [4].

Papillary and follicular carcinomas of the thyroid fall under the category of well-differentiated thyroid cancers, and form the bulk of thyroid malignancies [5]. Although obesity is known to be a risk factor for several types of cancer (oesophagus, colon, kidney, breast, and skin), the association between thyroid cancer and obesity remains controversial [6, 7].

Thyroid cancer was shown to be correlated with body mass index (BMI) mainly in females. Obesity, which is defined as excess bodyweight, or a BMI > 30 kg/m^2, is associated with an increased risk of diabetes, dyslipidemia, kidney disease, cardiovascular disease, all-cause-mortality and cancer [7].

Insulin resistance (IR) is associated with a cluster of risk factors for coronary artery disease, and it has been recently implicated as an important factor for cell proliferation [7]. Physiologically, insulin stimulates the mitogenic pathway. Insulin is not only a metabolic hormone but is also a growth factor [8]. The mitogenic pathway provides evidence as to why obese people with high levels of insulin have an increased prevalence of cancer [8]. Insulin triggers and stimulates cells to grow. Individuals who suffer from hyperinsulinemia have stable growth of cells, which leads to an increased risk of mutations and cancer [8].

IR is characterized by an inadequate physiological response of peripheral tissues to circulating insulin and results in metabolic and hemodynamic disturbances [8]. IR usually leads to type 2 diabetes mellitus [9], while hemodynamic instabilities comply with the theory that hyperinsulinemia and insulin resistance participate early in the development of tissue damage and a progressive decrease in the elasticity of small arteries [9]. Furthermore, hyperinsulinemia tends to increase the activity of the sympathetic nervous system, presenting as a high pulse rate [10].

To identify eligible studies, the main search was conducted in the electronic databases PubMed and EMBASE, covering the period from conception until 2019 and using combinations of the key terms «thyroid cancer», «obesity», «insulin resistance», «hyperinsulinemia». The main search was completed independently by two investigators.

Three of the studies showed that there was a significant increase in the incidence of (TC) [11, 12]. However, one study showed that when papillary microcarcinomas (PMCs) were excluded there was no such increase

Brenta Gabriela, MD, PhD, Prof., Faculty of Medical Sciences; Chief of the Thyroid Division of the Endocrinology Department. E-mail: gbrenta@gmail.com. ORCID: http://orcid.org/0000-0001-5531-7652

[11]. It also indicated that the increase in diagnosis of PMCs was associated with increased sampling of resected specimens [12]. Conversely, other studies indicated that the incidence of large well-differentiated thyroid cancers (WDTCs) and cancers with extrathyroidal and cervical extension had doubled [12, 13]. Tumours > 4 cm and those of distant Surveillance, Epidemiology, and End Results (SEER) stage disease had also increased [12, 13].

Furthermore, other studies showed a significant increase in TC prevalence with increasing BMI [14, 15].

Some srudies showed that this relationship was significant only in women, not in men [16, 17], while others showed that it was significant in both genders [15, 16]. It is important to note that one of the studies showed that in women above the age of 50, there was no association between TC incidence and increased BMI [14].

Another study tested the association between obesity and TC by studying the expression of leptin and its receptor in papillary thyroid cancer (PTC) [18]. It showed that expression of both proteins was associated with greater tumor size and that their coexpression was associated with a greater incidence of lymph node metastasis [19]. On the other hand, another study indicated that there was no significant association between increased BMI and the risk of TC [20].

Some studies indicated that IR was positively associated with an increase in TC prevalence [21, 22]. They showed that diabetes and IR were significantly more common in patients with differentiated thyroid cancer (DTC), respectively, compared with controls [23]. In addition to this, another study showed that the increased prevalence of PTC was positively associated with IR [24]. One other study indicated that remission was more likely to occur in patients without IR, and IR patients were more likely to have structurally persistent disease [25].

The incidence of thyroid malignancy has increased over the last 40 years. It has been suggested that this increase is apparent rather than real, and a result of a greater number of histological samples being analysed. Similarly, the use of high-resolution cervical US and FNA has increased over the years, and this has likely led to increased diagnosis of PTC, reflected in the current increased incidence of all types of thyroid cancer [11].

Improved detection does not entirely explain the growing incidence of thyroid cancer, however. If the increase in thyroid cancer is solely based on better diagnostic practices, there would be an increase only in the identification of small tumors and subclinical disease, as the detection of large tumors does not require the use of advanced screening technologies [10, 14]. In addition, there is a difference in the incidence trend between various racial/ethnic groups. If the increase in incidence is purely based on improved diagnostic practices, such a difference would not exist [25].

Other data also suggests that patients diagnosed with benign conditions (hyperthyroidism, thyroiditis, goiter, and adenoma) have significantly elevated risks of DTC [26]. Thus, there could be a detection bias (incidental detection) during the follow-up of these patients, which could also explain the increase in incidence [27]. Various factors, such as environmental influences and molecular pathways, could also be causing this rise in incidence. Hence, improved detection is not sufficient to explain the increase in the incidence of thyroid cancer, although it certainly has played an important role in relation to small thyroid cancers.

There is a suggestive positive correlation between obesity and thyroid cancer that could be explained by several mechanisms, including gender, age, white adipose tissue expansion, hyperinsulinemia, and hormonal dysregulation [15, 16]. Another indirect link in the association between obesity and thyroid cancer is the presence of thyroid nodules. Age, gender, BMI, and diabetes were independently positively correlated with the presence of thyroid nodules [28].

The histological analyses revealed that relative risk of follicular carcinoma was higher than that of papillary carcinoma with increasing BMI [29]. Other data also suggest positive associations with thyroid cancer risk for waist circumference, young-adult BMI, and adulthood BMI gain [27]. There is a positive association between thyroid cancer and high BMI in females under 50 years old, suggesting that age group has a higher risk of thyroid cancer [4]. Adipose tissue is known to have a relation with the hormone estradiol, and this hormone increases cell proliferation in PTC, which plays a significant role in menopausal women.

BMI, as an index, cannot distinguish fat from muscle mass, which explains why some studies have not found a correlation between BMI and thyroid cancer [28]. It is also suggested that BMI is not reliable when it comes to the elderly population. In older women (post-menopause) there is a change in body composition — decreased bone density and muscle mass, and increased fat mass (increased central adiposity) — that may be masked by a normal BMI [29]. Many people lose height in older age, due to kyphosis, shortening of the vertebrae, or thinning of cartilage [30]. Hence, the inclusion of height in the calculation of BMI can lead to

an overestimation of obesity for this group [30]. Other factors such as hypothyroidism can cause accumulation of water and salts, which can increase the individual's weight. Because an increase in BMI is not always related to excess fat accumulation and is not necessarily correlated with obesity it is an unreliable measure [30].

IR was also found to be an important risk factor for the development of DTC. Chronic subclinical inflammation caused by obesity is another factor that contributes to carcinogenesis and to the pathogenesis of IR [31].

To conclude, there is a suggestive correlation between thyroid cancer, obesity, and insulin resistance. These associations may be explained by various proposed pathophysiological mechanisms. The increased prevalence of thyroid cancer is not only due to improved detection. Novel research should include various anthropometric parameters, adipose tissue measurements and genetics for a complete understanding of the pathophysiological associations.

Conflicts of interest: none.

ЛІТЕРАТУРА/REFERENCES

1. Kaliszewski K, Diakowska D, Miciak M, et al. The Incidence Trend and Management of Thyroid Cancer-What Has Changed in the Past Years: Own Experience and Literature Review. Cancers (Basel). 2023 Oct 11;15(20):4941. doi: 10.3390/cancers15204941. PMID: 37894308; PMCID: PMC10605595.
2. Rossi ED, Faquin WC, Baloch Z, Fadda G, Thompson L, Larocca LM, Pantanowitz L. Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP): Update and Diagnostic Considerations-a Review. Endocr Pathol. 2019 Jun;30(2):155-162. doi: 10.1007/s12022-019-9574-7. PMID: 30953289; PMCID: PMC7477663.
3. Vlassopoulou V, Vryonidou A, Paschou SA, et al. No considerable changes in papillary thyroid microcarcinoma characteristics over a 30-year time period. BMC Res Notes. 2016 Apr 29;9:252. doi: 10.1186/s13104-016-2018-2. PMID: 27129971; PMCID: PMC4850716.
4. Shin HY, Jee YH, Cho ER. Body mass index and incidence of thyroid cancer in Korea: the Korean Cancer Prevention Study-II. J Cancer Res Clin Oncol. 2017 Jan;143(1):143-9. doi: 10.1007/s00432-016-2261-x. Epub 2016 Sep 23. PMID: 27662845.
5. Boucai L, Zafereo M, Cabanillas ME. Thyroid cancer: a review. JAMA. 2024 Feb 6;331(5):425-35. doi: 10.1001/jama.2023.26348. PMID: 38319329.
6. Haddad RI, Bischoff L, Ball D, Bernet V, Blomain E, Busaidy NL, Campbell M, Dickson P, Duh QY, Ehya H, Goldner WS, Guo T, Haymart M, Holt S, Hunt JP, Iagaru A, Kandeel F, Lamonica DM, Mandel S, Markovina S, McIver B, Raeburn CD, Rezaee R, Ridge JA, Roth MY, Scheri RP, Shah JP, Sipos JA, Sippel R, Sturgeon C, Wang TN, Wirth LJ, Wong RJ, Yeh M, Cassara CJ, Darlow S. Thyroid Carcinoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022 Aug;20(8):925-951. doi: 10.6004/jnccn.2022.0040. PMID: 35948029.
7. Franchini F, Palatucci G, Colao A, Ungaro P, Macchia PE, Nettore IC. Obesity and thyroid cancer risk: an update. Int J Environ Res Public Health. 2022 Jan 20;19(3):1116. doi: 10.3390/ijerph19031116. PMID: 35162142; PMCID: PMC8834607.
8. Xu N, Liu H, Wang Y, Xue Y. Relationship between insulin resistance and thyroid cancer in Chinese euthyroid subjects without conditions affecting insulin resistance. BMC Endocr Disord. 2022 Mar 7;22(1):58. doi: 10.1186/s12902-022-00943-6. PMID: 35255873; PMCID: PMC8903656.
9. Li LR, Song JL, Liu HQ, Chen C. Metabolic syndrome and thyroid Cancer: risk, prognosis, and mechanism. Discov Oncol. 2023 Feb 22;14(1):23. doi: 10.1007/s12672-022-00599-7. PMID: 36811728; PMCID: PMC9947216.
10. Heidari Z, Abdani M, Mansournia MA. Insulin resistance associated with differentiated thyroid carcinoma: penalized conditional logistic regression analysis of a matched case-control study data. Int J Endocrinol Metab. 2017 Oct 25;16(1):e14545. doi: 10.5812/ijem.14545. PMID: 29696038; PMCID: PMC5903382.
11. Morris LG, Myssiorek D. Improved detection does not fully explain the rising incidence of well-differentiated thyroid cancer: a population-based analysis. Am J Surg. 2010 Oct;200(4):454-61. doi: 10.1016/j.amjsurg.2009.11.008. Epub 2010 Jun 18. PMID: 20561605; PMCID: PMC2943969.
12. Grodski S, Brown T, Sidhu S, et al. Increasing incidence of thyroid cancer is due to increased pathologic detection. Surgery. 2008 Dec;144(6):1038-43; discussion 1043. doi: 10.1016/j.surg.2008.08.023. PMID: 19041015.
13. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer. 2009 Aug 15;115(16):3801-7. doi: 10.1002/cncr.24416. PMID: 19598221.
14. Singh Ospina N, Iñiguez-Ariza NM, Castro MR. Thyroid nodules: diagnostic evaluation based on thyroid cancer risk assessment. BMJ. 2020 Jan 7;368:l6670. doi: 10.1136/bmj.l6670. PMID: 31911452.
15. Valderrabano P, McIver B. Evaluation and management of indeterminate thyroid nodules: the revolution of risk stratification beyond cytological diagnosis. Cancer Control. 2017 Oct-Dec;24(5):1073274817729231. doi: 10.1177/1073274817729231. PMID: 28975825; PMCID: PMC5937245.
16. Pasternak B, Wintzell V, Hviid A, et al. Glucagon-like peptide 1 receptor agonist use and risk of thyroid cancer: Scandinavian cohort study. BMJ. 2024 Apr 10;385:e078225. doi: 10.1136/bmj-2023-078225. PMID: 38683947; PMCID: PMC11004669.
17. Buscemi S, Massenti FM, Vasto S, et al. Association of obesity and diabetes with thyroid nodules. Endocrine. 2018 May;60(2):339-47. doi: 10.1007/s12020-017-1394-2. Epub 2017 Aug 23. PMID: 28836113.
18. Cheng SP, Chi CW, Tzen CY, et al. Clinicopathologic significance of leptin and leptin receptor expressions in papillary thyroid carcinoma. Surgery. 2010 Jun;147(6):847-53. doi: 10.1016/j.surg.2009.11.004. Epub 2009 Dec 31. PMID: 20045163.
19. Refahi R, Heidari Z, Mashhadi M. Association of high serum leptin level with papillary thyroid carcinoma: a case-control study. Int J Hematol Oncol Stem Cell Res. 2023 Jul 1;17(3):210-9. doi: 10.18502/ijhoscr.v17i3.13311. PMID: 37817973; PMCID: PMC10560642.

20. Abdel-Aziz TE, Rehem RA, Elwafa WA. Serum leptin levels and well-differentiated thyroid cancer: a true association: reply. World J Surg. 2015 Sep;39(9):2367. doi: 10.1007/s00268-015-3120-7. PMID: 26103957.
21. Brenta G, Di Fermo F. Thyroid cancer and insulin resistance. Rev Endocr Metab Disord. 2024 Feb;25(1):19-34. doi: 10.1007/s11154-023-09849-7. Epub 2023 Nov 14. PMID: 37957487.
22. Yin DT, He H, Yu K, et al. The association between thyroid cancer and insulin resistance, metabolic syndrome and its components: A systematic review and meta-analysis. Int J Surg. 2018 Sep;57:66-75. doi: 10.1016/j.ijsu.2018.07.013. Epub 2018 Aug 3. PMID: 30081182.
23. Xu N, Liu H, Wang Y, Xue Y. Relationship between insulin resistance and thyroid cancer in Chinese euthyroid subjects without conditions affecting insulin resistance. BMC Endocr Disord. 2022 Mar 7;22(1):58. doi: 10.1186/s12902-022-00943-6. PMID: 35255873; PMCID: PMC8903656.
24. Zhao J, Zhang Q, Yang Y, Yao J, Liao L, Dong J. High prevalence of thyroid carcinoma in patients with insulin resistance: a meta-analysis of case-control studies. Aging (Albany NY). 2021 Sep 22;13(18):22232-41. doi: 10.18632/aging.203529. Epub 2021 Sep 22. PMID: 34550096; PMCID: PMC8507263.
25. Pitoia F, Abelleira E, Bueno F, Urciuoli C, Schmidt A, Niepomniszcze H. Insulin resistance is another factor that increases the risk of recurrence in patients with thyroid cancer. Endocrine. 2015 Apr;48(3):894-901. doi: 10.1007/s12020-014-0416-6. Epub 2014 Sep 11. PMID: 25209891.
26. Pazaitou-Panayiotou K, Michalakis K, Paschke R. Thyroid cancer in patients with hyperthyroidism. Horm Metab Res. 2012 Apr;44(4):255-62. doi: 10.1055/s-0031-1299741. Epub 2012 Feb 14. PMID: 22334393.
27. Kunjumohamed FP, Al-Busaidi NB, Al-Musalhi HN, Al-Shereiqi SZ, Al-Salmi IS. The prevalence of thyroid cancer in patients with hyperthyroidism. Saudi Med J. 2015 Jul;36(7):874-7. doi: 10.15537/smj.2015.7.11463. PMID: 26108596; PMCID: PMC4503911.
28. Smith JJ, Chen X, Schneider DF, et al. Toxic nodular goiter and cancer: a compelling case for thyroidectomy. Ann Surg Oncol. 2013 Apr;20(4):1336-40. doi: 10.1245/s10434-012-2725-4. Epub 2012 Oct 30. PMID: 23108556.
29. Kitahara CM, Platz EA, Freeman LE, Hsing AW, Linet MS, Park Y, Schairer C, Schatzkin A, Shikany JM, Berrington de González A. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. Cancer Epidemiol Biomarkers Prev. 2011 Mar;20(3):464-72. doi: 10.1158/1055-9965.EPI-10-1220. Epub 2011 Jan 25. PMID: 21266520; PMCID: PMC3079276.
30. Kitahara CM, McCullough ML, Franceschi S, Rinaldi S, Wolk A, Neta G, Olov Adami H, Anderson K, Andreotti G, Beane Freeman LE, Bernstein L, Buring JE, Clavel-Chapelon F, De Roo LA, Gao YT, Gaziano JM, Giles GG, Håkansson N, Horn-Ross PL, Kirsh VA, Linet MS, MacInnis RJ, Orsini N, Park Y, Patel AV, Purdue MP, Riboli E, Robien K, Rohan T, Sandler DP, Schairer C, Schneider AB, Sesso HD, Shu XO, Singh PN, van den Brandt PA, Ward E, Weiderpass E, White E, Xiang YB, Zeleniuch-Jacquotte A, Zheng W, Hartge P, Berrington de González A. Anthropometric Factors and Thyroid Cancer Risk by Histological Subtype: Pooled Analysis of 22 Prospective Studies. Thyroid. 2016 Feb;26(2):306-18. doi: 10.1089/thy.2015.0319. PMID: 26756356; PMCID: PMC4754509.
31. Spira D, Buchmann N, Dörr M, Markus MRP, Nauck M, Schipf S, Spranger J, Demuth I, Steinhagen-Thiessen E, Völzke H, Ittermann T. Association of thyroid function with insulin resistance: data from two population-based studies. Eur Thyroid J. 2022 Feb 28;11(2):e210063. doi: 10.1530/ETJ-21-0063. PMID: 35085102; PMCID: PMC8963174.

ABSTRACT

In recent decades, there has been a marked increase in the prevalence of thyroid cancer. The incidence of well-differentiated thyroid cancer (TC) has been increasing dramatically over the last 20 years worldwide, and TC is expected to be the fourth most common cancer by 2030. The rapid increase in the detection rate of TC in recent years has caused many changes in the management of these malignancies. TC accounts for 3.4 % of all cancers diagnosed annually worldwide. Some data suggest that TC is increasing globally much faster than other malignant lesions. This might be a consequence of the widespread use of ultrasonography (US) examination and ultrasound guided fine needle aspiration biopsy (UG-FNAB) procedures. Generally, this observation led to a globally highlighted discussion about the causes of such a situation. Some authors say that the higher incidence of TC is due to overdiagnosis. Others believe that various additional factors may play a role in this observation, such as obesity and an increased exposure to ionizing radiation. This phenomenon has paralleled the increase in the prevalence of obesity worldwide, which is associated with insulin resistance. Associations between these entities have been hypothesized, mainly for older and female populations, but they remain unclear. The aim of this review article was to systematically review the literature in an attempt to determine whether the increase in the prevalence of thyroid cancer is due to obesity or due only to improved detection with the better imaging techniques available. A thorough literature search on PubMed and application of selection criteria identified 14 appropriate studies. The detailed analysis of the data from these studies indicated that there is a suggestive association between thyroid cancer, obesity, insulin resistance and hyperinsulinemia for both genders. Therefore, the increased prevalence of thyroid cancer is not dependent on improved detection only. Further research should be performed for complete understanding of the pathophysiological associations, especially regarding adipose tissue and genetics, but also for the improvement of preventive public health policies.

Keywords: thyroid cancer, obesity, insulin resistance, prevalence, diagnostics, nodules.

РЕЗЮМЕ

Інсулінорезистентність та гіперінсулінемія як патофізіологічний зв'язок між раком щитоподібної залози та ожирінням. Огляд

Г. Брента

Університет Буенос-Айреса, Аргентина
Лікарня доктора Сезара Мільштейна, Буенос-Айрес, Аргентина

Упродовж останніх десятиліть спостерігається зростання поширеності раку щитоподібної залози. Захворюваність на диференційований рак щитоподібної залози (РЩЗ) різко зросла протягом останніх 20 років у всьому світі. Очікується, що до 2030 р. РЩЗ стане четвертим за поширеністю раком. Швидке збільшення частоти виявлення РЩЗ останніми роками спричинило багато змін у лікуванні цих злоякісних пухлин. На частку РЩЗ припадає 3,4 % від усіх онкологічних захворювань, які щорічно діагностують у світі. Деякі дані свідчать, що поширеність РЩЗ зростає в усьому світі набагато швидше, ніж інших злоякісних уражень. Це може бути наслідком широкого використання ультразвукового дослідження (УЗД) і тонкоголкової аспіраційної біопсії під контролем УЗД. Результати багатьох досліджень призвели до глобальної дискусії про причини такої ситуації. Деякі автори стверджують, що вища частота РЩЗ пояснюється гіпердіагностикою. Інші вважають, що додаткові чинники можуть відігравати роль у цьому процесі, наприклад, ожиріння та підвищений вплив іонізувального випромінювання. Зростання поширеності ожиріння в усьому світі пов'язане з резистентністю до інсуліну. Запропоновано гіпотези про зв'язки між цими явищами, переважно в осіб похилого віку та жінок, але вони не доведені.

Проведено систематичний огляд літератури, щоб визначити, чи пов'язане збільшення поширеності раку щитоподібної залози з ожирінням чи лише з поліпшенням виявлення за допомогою кращих доступних методів візуалізації. Ретельний пошук літератури в базі даних PubMed і застосування критеріїв відбору дали змогу виявити 14 відповідних досліджень. Детальний аналіз даних цих досліджень показав існування зв'язку між раком щитоподібної залози, ожирінням, інсулінорезистентністю та гіперінсулінемією для осіб обох статей. Таким чином, зростання поширеності раку щитоподібної залози не залежить лише від поліпшеного виявлення. Необхідно провести дослідження для повного розуміння патофізіологічних зв'язків, особливо щодо жирової тканини та генетики, а також для поліпшення політики профілактики громадського здоров'я.

Ключові слова: рак щитоподібної залози, ожиріння, інсулінорезистентність, поширеність, діагностика, вузлові утворення.

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