Is There a Correlation of TSI Levels and Incidental Papillary Thyroid Carcinoma in Graves Disease? A Review of the Latest Evidence

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ABSTRACT

Purpose: Our aim is to clarify if there is an association between the TSI levels and the development of thyroid carcinoma in patients with Grave's disease.

Methods: A systematic search concerning original studies from 2010 to 2020 was carried out through the databases PubMed, EMBASE and Cochrane, according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. The terms used are 'Graves' disease' and /or 'Incidental Papillary thyroid cancer' and 'TSI' levels. Retrospective studies upon the subject were concluded in the analysis.

Results: Only three retrospective studies were found involving 916 patients with Graves' disease and Euthyroid goiter. No significant correlation has been found between TSI and the occurrence of thyroid carcinoma in patients with Graves' disease.

Conclusion: Very little research has been conducted upon the subject. More assays are required in order to identify a possible prognostic role of TSI levels in Papillary thyroid carcinoma in patients with Graves disease.

KEYWORDS

TSI; papillary; thyroid; cancer; Graves disease

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Tab. 1 The data of the current study.

Study		Patients (n)	Method	Results
1	Ergin et al., (2014) (4)	248 EG + 245 GD	Total thyroidectomy	PTMC was found in 28% in EG group, as compared to 26% in GD group. PTC Patients with GD were significantly younger (44 vs 59) and less likely to have compressive symptoms than with EG before surgery ($p < 0.001$). In GD group, patients with PTMC were also significantly older ($p = 0.009$) than those without, were more likely to have symptomatic goiter ($p < 0.001$), and to have a nodular disease ($p < 0.001$). TSI ab titer did not predict PTMC in GD group. Among patients with GD and incidental PTMC, 58% of patients had at least one nodule.
2	Menon et al., (2018) (6)	308	Primary surgery	Significant incidences of disease progression in patients with PTC associated with GD ($p = 0.034$; OR 2.747, CI 1.078–7.004). Disease progression as new distant metastases mostly in skeletal locations was high in this group compared to euthyroid group ($p = 0.027$; OR 4.121, CI 1.008–15.600). There was higher incidence of cumulative metastatic diseases in PTC associated with GD.
3	Boutzios et al., (2019) (5)	115	Total thyroidectomy	The mean TSI antibodies levels were 4.14 IU/L compared with patients who had not developed cancer, whose mean TSI antibodies levels were 9.26 IU/L ($p = 0.31$). Patients with GD and TC had lower mean levels of TSI antibodies, though statistically not significant, in comparison with patients without TC.

EG: Euthyroid Goiter; PTMC: Papillary thyroid microcarcinoma; GD: Grave's Disease; PTC: Papillary thyroid cancer; TC: Thyroid Cancer; TSI: Thyroid Stimulating Immunoglobulin

INTRODUCTION

Graves' disease (GD) is an immune system disorder resulting in the overproduction of thyroid hormones and thyrotoxicosis as a result of binding of circulating antibodies to certain thyrotropin receptors. Thyroid-stimulating immunoglobulins (TSI) are immunoglobulins G that bind to and activate the G-protein coupled thyrotropin receptors causing the growth of the thyroid gland and the increased synthesis of thyroid hormones. TSIs mimic the action of thyroid stimulating hormone (TSH) and their levels are high in persons with hyperthyroidism due to GD. In fact, GD is the most common cause of hyperthyroidism (50–80%) (1).

TSI levels are suspected to be responsible for the potentially increased incidence or aggressiveness of papillary carcinoma in that setting. The diagnosis of incidental papillary carcinoma in patients submitted to thyroidectomy for a benign disease is quite frequent. According to Pezolla et al., 75% of patients undergoing thyroidectomy for benign disease were diagnosed with thyroid cancer and 18 out of 30 were papillary carcinomas (60%) (2).

The aim of this review is to investigate possible correlation of TSI levels in patients with GD to incidental papillary thyroid cancer (PTC) and assess the ability to predict PTC.

METHODS

A systematic search was conducted using three electronic databases (EMBASE, PubMed and Cochrane library) for retrieval of potentially relevant articles published from 2010 through 2020. The search comprised the following terms "thyroid cancer", "incidental thyroid papillary carcinoma", "TSI levels" and "Grave's Disease". Articles were also searched from references of the original papers and review articles. Inclusion criteria were for the articles to be retrospective studies and follow a surgical approach. All duplicates were removed, and the remained records were screened for eligibility criteria. Studies suspected of bias were excluded. The research was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines as shown in Figure 1.

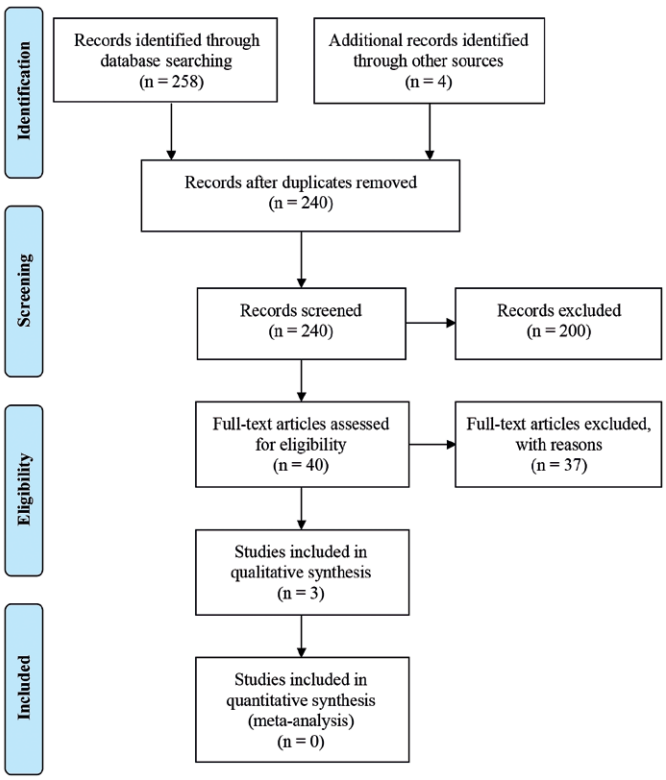

Fig. 1 PRISMA flow diagram for the current study.

RESULTS

The database search resulted in only 3 studies that met the inclusion criteria of relating the incidental PTC and TSI levels in patients with GD. A total of 916 patients with GD and euthyroid goiter were analysed in those studies. The data of the analysis can be seen in Table 1.

According to Ergin et al. (2014), the prevalence of incidental papillary carcinoma of the thyroid gland in GD is comparable to euthyroid patients with goiter (3). Each is increased compared to the general population. The age of papillary carcinoma presentation is lower in GD suggesting increased risk for patients with GD. Nodules >1 cm predict incidental papillary carcinoma. On the contrary disease duration and TSI titters do not. Boutzios et al. (2019), studied the association between the levels of TSI antibodies and thyroid cancer and found that among patients with cancer, the mean TSI antibodies levels were 4.14 IU/L compared with patients who had not developed cancer, whose mean TSI antibodies levels were 9.26 IU/L ($p = 0.31$). Those levels were not statistically significant (4).

Menon et al. (2018), conclude that papillary carcinomas in GD are more aggressive even when tumor characteristics are favorable. Aggressive progression with osseous metastases is also more frequent in PTC when GD is associated (13.6% in GD whereas the overall reported incidence ranges from 1.7–7%). TSI levels are elevated in GD raising the suspicion of potential relation with both the higher incidence and/or the aggressiveness of PTC in this setting. According to Menon et al., aggressive treatment and close follow-up are important in patients with GD compared to euthyroid counterparts diagnosed with PTC (5).

DISCUSSION

Thyroid carcinoma is the commonest endocrine cancer (6) and PTC – a well-differentiated thyroid cancer – usually appears as nodule or irregular mass, solid or cystic, in a normal parenchyma (7, 8). 11% of PTC patients present with metastases outside the neck and the mediastinum (9–12). Although thyroid carcinoma was originally thought to be rare in GD there are certain studies that have suggested an increased risk of thyroid malignancy in GD (13–15). Hypotheses about the carcinogenesis mechanisms centre around binding of thyroid stimulating antibodies and activating pathways of growth, invasion and angiogenesis (16). The American Thyroid Association states a frequency of < 2% of thyroid cancer in GD (17). Thyroid cancer may be associated with a nodule, detectable in 30–70% of the population on ultrasound (18). A fine needle aspiration (FNA) biopsy is always recommended in all detectable nodules, especially in high-risk patients (17, 18).

Thyroid cancer may occur concomitantly in GD. Its frequency varies from 0.15 to 15%. GD seems to be associated with larger, multifocal, and potentially more aggressive thyroid cancer compared to single hot nodules or multinodular toxic goiter. Patients with GD and nodules are at higher risk for thyroid cancer compared to patients with diffuse goiter (15).

Papillary thyroid microcarcinoma (PTMC) is a distinct entity; a thyroid carcinoma of ≤ 10 mm diameter usually an incidental finding during FNA biopsy or thyroidectomy for benign disease of the gland (19). Its prevalence in GD is estimated at 4.1% (20–22). Though rare, a small portion of microcarcinomas give distant metastases. The well-known prognostic biomarkers for thyroid cancer (BRAF and/or TERT) do not have an established role in PTMC patients (23). TSH has no prognostic value either in PTMC progression (24). No data exist concerning TSI levels in GD and their relationship with PTMC. Thus, further research is needed since both autoimmunity and inflammation are considered as independent risk factors for thyroid cancer (25).

Incidental thyroid carcinoma is considered the one occurring in patients with no suspicious features in any exam that may suggest the presence of cancer and no previous FNA biopsy (18). Both the prevalence and the clinical significance of incidental PTC in patients with GD remain uncertain.

The majority of thyroid cancers are PTMC. The prevalence and clinical significance of incidental PTC, which is well-differentiated thyroid cancer, in GD are uncertain but comparable to euthyroid patients with goiter and increased compared to the general population (3).

Papillary carcinomas of the thyroid express TSH receptors. The binding of the TSH to its receptors promotes the progression of cancer through growth of tumor cells (1). Similarly, TSI, present in GD, act through TSH receptor stimulating tumor cell growth. This may explain the higher incidence and/or the aggressiveness of PTC in patients with GD but no direct relationship between TSI levels and PTC has been established yet. It is also unclear whether concomitant GD affects the prognosis of papillary thyroid malignancy.

CONCLUSIONS

The conclusions of this review cannot be considered solid since the number of studies upon the subject is very limited. Further research is needed to understand the connections between cancer and thyroid autoimmunity, to correlate TSI levels with prediction or prognosis of papillary carcinoma and design a tailored therapy for these patients since both autoimmunity and inflammation are defined as independent risk factors for thyroid cancer.

CONFLICTS OF INTEREST

All the authors declare that there is no conflict of interest.

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