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ORIGINAL ARTICLE

The prevalence of post-thyroidectomy chronic asthenia: a prospective cohort study

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Abstract
Purpose Chronic asthenia (CA) is complained by some patients that have undergone thyroid surgery. We evaluate its impact in patients undergoing unilateral or bilateral thyroidectomy, the trend during a 1-year follow-up, and the possible risk factors.
Methods A prospective, cohort study was carried out on 263 patients scheduled for thyroidectomy from 2012 and 2014. Exclusion criteria were as follows: Graves' disease, malignancies requiring radioiodine therapy, post-surgical hypoparathyroidism, laryngeal nerve palsy, abnormal pre- and post-operative thyroid hormone levels, and BMI outside the normal range. Demographics; smoking and alcoholism addiction; cardiac, pulmonary, renal, and hepatic failure; diabetes; anxiety; and depression were recorded. The Brief Fatigue Inventory (BFI) was used to evaluate CA and its possible association with these comorbidities 6 and 12 months after thyroidectomy.
Results One hundred seventy-seven patients underwent total thyroidectomy (TT), 54 hemithyroidectomy (HT). Thirty-two patients were not recorded because of the onset of exclusion criteria. In the 6 months after thyroidectomy, in the TT group, 64 patients (36.16%) reported an impairment in the BFI score and only 1 in the TL group. The mean BFI score changed from 1.663(±1.191) to 2.16 (±11.148) in the TT group, from 1.584 (±1.371) to 1.171 (±1.093) in the TL group ($p < 0.001$). No further significant variations in BFI were reported 1 year after surgery.
Conclusions CA worsened after TT, but not after HT. Apart from operative procedure itself, no other risk factor was found be significantly associated with post-thyroidectomy asthenia. Further investigation is needed to determine the causes of CA.

Keywords Total thyroidectomy · Hemithyroidectomy · Chronic asthenia · Fatigue

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Introduction

Total thyroidectomy (TT) was previously considered the treatment of choice for benign diseases and malignancies [1–5]. As a result, this surgical procedure has widespread indications at our institution [6, 7]. Several studies have examined patient quality of life (QoL) related to the thyroid disorders and evaluated this aspect before and after treatment. The majority of studies investigated the correlation between QoL and hormone changes [8–10]. One study highlighted the psychological changes rather than appearance or worsening of the tiredness or asthenia [11]. Another study showed the advantages of thyroidectomy in reducing post-operative fatigue by evaluating a cohort of patients with various hormone levels [8]. A recent study [12] reported that TT is frequently accompanied by chronic low-moderate asthenia. The asthenia can result in impaired QoL due to feelings of tiredness and a reduced ability to perform physical or mental tasks. These symptoms have

not been evaluated in specific clinical trials despite being widely suspected and commonly observed.

The aim of the present study is to evaluate the real impact of post-thyroidectomy chronic asthenia (PTCA) in patients undergoing unilateral or bilateral excision of the thyroid gland. We also evaluated the trends after a 1-year post-operative follow-up period.

In this study, we assessed whether PTCA is induced or worsened in the presence of specific habits (smoking, alcohol), chronic diseases (cardiac, pulmonary, hepatic, renal, metabolic), or mental disorders such as anxiety or depression.

Materials and methods

Patient population

This study involved 263 consecutive consenting patients from a homogeneous area (three western areas of Sicily: Palermo, Trapani, Agrigento) scheduled for thyroidectomy at the Unit of General and Emergency Surgery of "Policlinico Paolo Giaccone" University Hospital, in Palermo from January 2012 to December 2014. We included all patients with the benign nodular thyroid disease euthyroid at the time of enrollment and throughout the study. All patients had a BMI within the normal range for Caucasians based on WHO criteria [13]. The patients were traceable during all the fixed stages of the follow-up (pre-operative, 6 months, and 1 year after surgery).

Exclusion criteria

The following exclusion criteria were used in this study: thyroid carcinoma (except low-risk papillary microcarcinoma) (seven patients), Graves' disease due to its negative impact on health-related QoL [14, 15], chronic anemia (including thalassemia), chronic disease (cardiac, pulmonary, hepatic, renal) in advanced stage, type 1 diabetes mellitus or type 2 diabetes requiring insulin treatment for control, inflammatory bowel diseases, hyperparathyroidism, functional adrenal diseases, personal history of cancer, and all diseases interfering with performance status. Chronic diseases were evaluated in all study periods. If a chronic disease worsened during the follow-up period, the patients were excluded (two patients). We used the New York Heart Association (NYHA) criteria to evaluate and measure chronic heart failure [16], and the patients in class III or IV were excluded. Chronic respiratory failure severity was evaluated in accordance with GOLD criteria [17]. The patients classified as level II or III were excluded. We also excluded patients with hepatic failure in Child and Pugh C-class [18] and those with stage III (or more advanced) chronic renal failure in accordance with KDOQI guidelines [19]. The diagnosis of diabetes mellitus was established in accordance with the American Diabetes Association criteria [20]. All mental disorders were evaluated in the pre-operative period and at the 6- and 12-month follow-up evaluations. Anxiety was evaluated using a common seven-item self-administered questionnaire (available online) [21] investigating generalized anxiety disorders (GAD-7). The patients with a score ≥10 in one of the three follow-up steps were excluded from the study (four patients). The Hamilton Depression Rating Scale (HAM-D) [22] was used to exclude patients suffering from depression. The patients with more than moderate depression (score ≥19) were also excluded (one patient).

Asthenia was assessed and measured by the Brief Fatigue Inventory (BFI), which is a nine-item visual analog score system (Fig. 1). This system is reliable and is validated for a wide range of diseases (both benign and malignant) [23, 24]. The tool investigates the current level of asthenia in patients for the last 24 h and any interference with general activity, work, and relationships with other people [12, 24]. We obtained permission to use this tool (Italian version) online. The results of the questionnaire are used to classify asthenia as mild (score <3), moderate (scores between 4 and 6), or severe (scores between 7 and 10). The patients with severe asthenia were previously excluded.

We also excluded all patients that complained post-operative complications: inferior laryngeal nerve palsy (three patients), persistent hypoparathyroidism (two patients). Seven patients did not meet the inclusion criteria concerning the BMI. Finally, we lost two patients during the follow-up.

Indications for surgery

The recommended surgical procedure (unilateral or bilateral resection of thyroid gland) was consistent with our internal protocols and was chosen definitively on the basis of informed consent. These protocols indicated resection extent in accordance with the Bethesda system for reporting thyroid cytopathology [25]. The patients with unilateral benign cytology diagnosis, indeterminate, or suspicious lesions were offered hemithyroidectomy (HT). The patients with bilateral nodules were offered total thyroidectomy (TT). After the cytology results were obtained, the patients were informed of the risks and advantages of each surgical procedure with respect to potential complications and recurrence rate. The resection extent was finally chosen in accordance with their wishes. The surgical procedure was a total extracapsular, unilateral or bilateral resection of thyroid gland with systematic identification of the inferior laryngeal nerve and the parathyroid glands. A complete removal of the isthmus of the gland was always achieved during the thyroid lobectomy.

Post-operative treatment

The blood calcium levels were measured on the first post-operative day in accordance with institutional protocols. If the calcium value was less than 8 mg, then an empirical

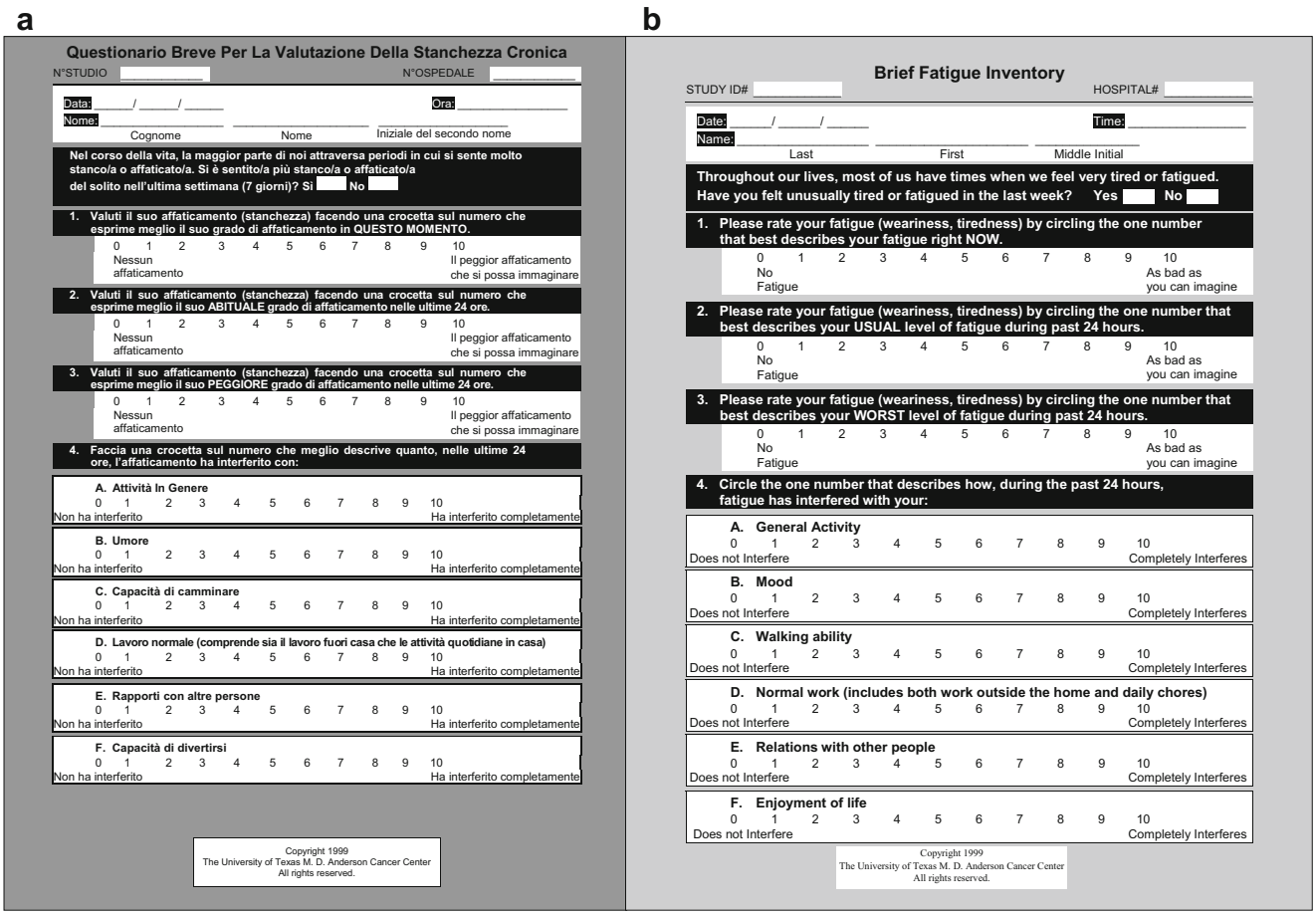

Fig. 1 Questionnaire used for asthenia evaluation: Italian version (**a**) is a psychometrically and linguistically validated version obtained from "MD Anderson Assessment Tool Distribution"; we submitted this version to our patients; English version (**b**)

daily oral supplementation of calcium (1000–4000 mg, in accordance with needs) and calcitriol (0.50–1.25 mcg) was administered for progressive low values of calcemia. The supplementation was gradually reduced in outpatient management as calcium values improved. Levothyroxine was systematically prescribed to optimize supplementary (for the patients in the HT group) or substitutive (for the TT group) treatment at discharge on the first or second post-operative day. The treatment adjustments were made during post-operative examinations. The thyroid-stimulating hormone (TSH) value was maintained at approximately 1 mIU/L. If the TSH value was lower than 0.5 mIU/L or higher than 1.9 mIU/L, then the L-thyroxine dosage was adjusted to approach the target values throughout follow-up. If patients showed TSH values ≤0.4 or >4 mIU/L at any stage of the follow-up, then they were excluded from the study (four patients). Table 1 shows the TSH mean values during the three periods in both groups. A histological examination confirmed the complete removal of the thyroid tissue in all cases, the absence of a cancer >1 cm, and the nature of the lesion.

Statistical analysis We used two-way ANOVA to analyze depression and asthenia because these variables were surveyed three times. The test was used to verify whether the two groups differ regarding surgical technique (TT, HT) or survey time (preoperative, 6 months after the thyroidectomy, 1 year after the thyroidectomy). Patient anxiety was analyzed as a dichotomous variable. Anxiety was evaluated with the Mantel-Haenszel test to verify the hypothesis of equality between the odds ratios (ORs) for the three results in the TT and HT patients. A multiple logistic regression for dichotomous dummy variables was used to analyze the effects of other variables relative to the BFI (evaluated three times). The analysis was conducted using IDE RStudio (version 0.98.945, RStudio, Boston, MA, USA) with R software (3.1.0, 2014-04-10).

Results

Excluding the 32 patients from the definitive record, we then analyzed 231 patients, which were divided into the TT group (177 patients) treated with surgery for a multinodular goiter, euthyroid or toxic, ± Hashimoto's thyroiditis or the HT group (54 patients) that had undergone surgery for a single nontoxic nodule (compressive or needing bioptic examination), or

Table 1 Enrolled patients' TSH mean values (mIU/L) during the study

	TSH values (mean)			*p* values
	Pre-operative	6 months after surgery	1 year after surgery	
TT	1.39 ± 0,32	1.29 ± 0.41	1.47 ± 0.44	0.22[a] 0.36[b]
HT	1.19 ± 0.44	1.39 ± 0.45	1.54 ± 0.6	0.51[a] 0.45[b]
p value	0.44	0.29	0.36	

[a] Pre-operative TSH values vs 6 months after surgery TSH values

[b] Pre-operative TSH values vs 1 year after surgery TSH values

Plummer's disease. Table 2 shows the demographic and clinical data for both patient groups. The groups were balanced with respect to patient gender. However, the patient age in the TT group was slightly higher due to the higher concentration of young patients in the HT group. Other variables that were not well-balanced between two groups were hepatic disease and smoking. It is possible that multinodular goiter is more frequent in the context of chronic hepatitis and its evolutions. The reason for a relatively higher prevalence of smoker subjects in the HT group is not clear. Table 3 analyzes the balance of anxiety, depression, and fatigue in the two groups at the three observation time points using ANOVA. The anxiety was similar in the TT and HT groups in the three periods of observation. However, the prevalence of depression was different based on value medians. The values did not change during the follow-up or improved similarly in each group and were not statistically significant. Asthenia was similar in the two groups at the pre-operative evaluation but changed significantly in the next two post-operative periods. We analyzed the impact of each variable including the extent of surgical resection on post-operative asthenia once the initial differences between the two groups had been evaluated with respect to habits and comorbidities. The results of our multivariate logistic regression analysis are summarized in Table 4. The data indicate that only the variable "surgical technique" (TT, HT) determines significant changes in the onset or worsening of the asthenia. The HT group showed that the asthenia did not appear or worsen during the follow-up. Conversely, the asthenia improved in several cases and this change was clear when comparing the pre-operative results with the 6-month follow-up. The findings are represented in the box-plot graphs (Fig. 2a, b) and show the trend of the CA over time in TT and HT groups.

Table 2 Balancement of sex, age, thyroid disease, habits, and comorbidities in the two groups

Variables		TT	HT	*p* value
Gender	Male Female	36 (20.3%) 141 (79.7%)	7 (13%) 47 (87%)	0.30
Age	Average (years)	54.50 (13.08)	48.94 (15.62)	0.0094*
Thyroid diseases	MNG/single nodule (euthyroid patients)	136 (77%)	38 (70%)	0.43
	MNTG/Plummer's disease[a]	17 (10%)	13 (24%)	0.01*
	Nodule(s) + Hashimoto's thyroiditis	24 (13%)	3 (6%)	0.17
Smoking	No Yes	141 (79.7%) 36 (20.3%)	35 (65%) 19 (35%)	0.039*
Alcohol	No Yes	171 (96.6%) 6 (3.4%)	54 (100%) 0 (0%)	0.34
Cardiac disease	No Yes	104 (58.8%) 73 (41.2%)	34 (63%) 20 (37%)	0.69
Pulmonary disease	No Yes	155 (87.6%) 22 (12.4%)	47 (87%) 7 (13%)	0.99
Hepatic disease	No Yes	160 (90.4%) 17 (9.6%)	54 (100%) 0 (0%)	0.014*
Renal disease	No Yes	162 (91.5%) 15 (8.5%)	53 (98.1%) 1 (1.9%)	0.13
Diabetes mellitus	No Yes	141 (79.7%) 36 (20.3%)	48 (88.9%) 6 (11.1%)	0.18

Chronic diseases leading to a functional organ insufficiency such as heart failure (inability of the heart to pump enough blood to meet the body's needs), respiratory insufficiency (inability of the lungs to maintain an adequate gas exchange), liver failure (cirrhosis), renal insufficiency

MNG multinodular goiter, *MNTG* multinodular toxic goiter

*Differences statistically significant

[a] Since the Plummer's disease was a standard indication for hemithyroidectomy, its proportional prevalence in the HT group resulted statistically significant

Table 3 Analysis of anxiety (Mantel-Haenszel test), depression and asthenia (two-way ANOVA test) in the three periods of observation

Variables	Period	T.T. *n* (%/SD)	H.T. *n* (%/SD)	*p* value
Anxiety	Pre-operative	20 (11.3)	5 (9.3)	0.652
	6 months after surgery	14 (7.9)	6 (11.1)	
	1 year after surgery	12 (6.7)	3 (5.5)	
Depression	Pre-operative	3.09 (±2.69)	3.03 (±2.53)	0.00021 (group)
	6 months after surgery	2.65 (±2.55)	2.01 (±2.09)	0.798 (time)
	1 year after surgery	2.73 (±2.97)	1.83 (±1.97)	
Asthenia	Pre-operative	1.663 (±1.191)	1.584 (±1.371)	<0.0001 (group)
	6 months after surgery	2.16 (±1.148)	1.171 (±1.093)	
	1 year after surgery	2.106 (±1.235)	1.021 (±1.08)	<0.0001 (time)

Discussion

TT was used as a surgical treatment for a wide range of thyroid diseases including solitary benign nodules [6, 26, 27]. Several assumptions led to this widely shared behavior. The major reasons included the following: low complication rate associated with TT (as reported by several authors) [27–29], risk of relapse after hemithyroidectomy [5, 7], risk of an occult malignancy [30] that makes follow-up complex, and/or greater difficulty in performing the revision surgery after thyroid lobectomy. Several recent studies have emphasized various advantages of hemithyroidectomy [31, 32] in selected cases of malignancy [33, 34]. Further observations may reinforce the support of HT such as voice and swallowing disorders that have been evaluated in association with TT [35, 36]. However, the data concerning these complaints after HT are limited [37]. Another important issue that could modify/influence both surgeon and patient choice in favor of a surgical option is the assessment of the QoL after thyroidectomy. Prior studies indicated that surgery extent does not influence the QoL [38] and the specific symptom "tiredness" remains one of the most affected domains [39–41] after thyroidectomy. It should be noted that in these studies both TT and HT are considered together. Furthermore, the rate of unilateral compared to bilateral thyroidectomies in these studies (34.8, 54, and 53%, respectively) is high. Additionally, Grave's disease was not an exclusion criterion. The method used for evaluating the QoL was the ThyPRO, which is a validated and standardized questionnaire in which tiredness is assessed once in a general context of complaints referable to a thyroid disease. Conversely, the BFI assesses the severity of fatigue and its impact on daily activities by using nine items that are rated with a 0–10 scale [24]. Thus, it is plausible that the more careful method of analyzing various aspects of fatigue might result in more precise and reproducible answers.

Table 4 Factors affecting post-thyroidectomy chronic asthenia

Coefficients	Estimate	*Z* value	*p* value
Intercept	0.771	1.076	0.281
Sex	−0.865	−1.931	0.053
Age	−0.017	−1.212	0.225
Surgical procedure (HT)	−3.866	−3.716	0.000203*
Smoking	−0.036	−0.036	0.971
Alcohol	0.544	1.269	0.204
Heart disease	0.135	0.350	0.726
Pulmonary disease	−0.246	−0.043	0.662
Liver disease	0.665	1.133	0.257
Renal disease	0.765	1.071	0.284
Diabetes disease	0.349	0.666	0.505
Anxiety	−0.564	−1.014	0.310
Depression	−0.093	−1.332	0.182

The position of empirical values in theoretical distribution is used to calculate the *p* value

Estimate = empirical values; *Z* value = theoretical values

*Differences statistically significant

A previous study that specifically analyzed the correlation between chronic asthenia and thyroidectomy found patients who had undergone TT frequently complained of tiredness or asthenia in performing physical tasks and mental work [12]. It is well known that hypothyroidism, hyperthyroidism, and Hashimoto's thyroiditis may be associated with chronic asthenia [39, 42]. However, thyroid surgery itself does not improve QoL except for specific symptoms such as compression. The same study demonstrated that total or near-TT led to a lower QoL for several items including "physical functioning," "physical role," and "vitality" [43]. In our study, we evaluated the real impact of chronic asthenia in a cohort of patients undergoing thyroidectomy for diseases with limited association to asthenia or tiredness. Therefore, we excluded cases with Grave's disease or thyroid cancer because these patients require particular treatment and not merely a follow-up exam. We excluded the patients suffering from general comorbidities (cardiac, pulmonary, hepatic, renal, metabolic) that could be associated with a severe impairment of their performance status. Furthermore, when comorbidities were present, we evaluated the impact in determining or worsening the chronic asthenia.

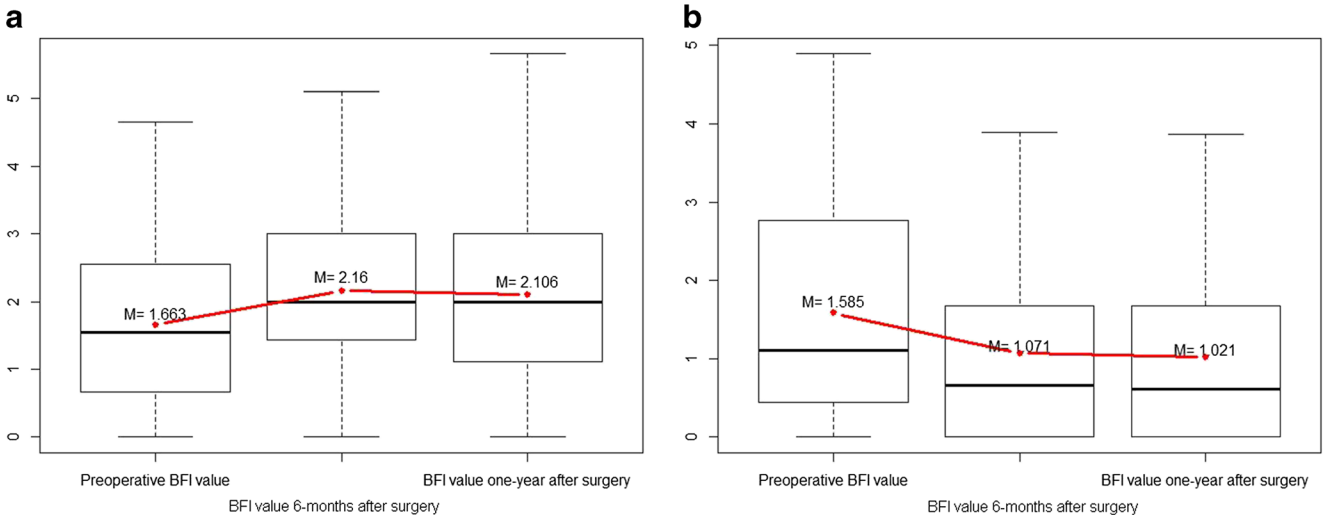

Fig. 2 The *box-plot graphics* show the increase of BFI in the first post-operative period (6 months after surgery) in TT group and its decrease in HT one. In the second post-operative period, (1 year after surgery) trends in two groups do not change more. Both trends are statistically significant (see Table 3)

Although this study has some limitations correlated with small sample size, our results confirm that chronic fatigue is one of the significant sequelae of TT and does not depend on a lack of balance of (commonly evaluable) thyroid hormones. Moreover, it seems to be independent of habits and comorbidities that we did not consider as exclusion criteria. The reasons for why this effect is correlated to total thyroidectomy and not hemithyroidectomy are unexplained. It is possible that there is an important role for unknown thyroid hormone imbalanced in the appearance or worsening of chronic fatigue. In our study, we excluded any patient with a TSH, fT3, or fT4 outside the normal respective ranges. However, there was no evaluation concerning "nonclassical" thyroid hormones performed. These hormones are produced by deiodination and other biochemical pathways in peripheral tissues and the thyroid gland itself [44]. In particular, 3,5-diiodothyronine (T2) showed intense activity in stimulating mitochondrial calcium uptake and increasing mitochondrial dehydrogenase activity. These changes can increase the resting metabolic rate (RMR) and an intense and rapid stimulation of oxygen consumption in experimental models. The pathways involved in the formation and clearance of the T2 are currently unknown [45–47]. Previous studies showed that T2 production from the T3 hormone might be less prominent in hypothyroid patients treated with L-T4 [48]. These data could suggest a possible involvement of changes in T2 levels in PTCA if the decrease after TT is proven. These findings were linked to other studies performed in an experimental animal model that demonstrated the effect of TT in altering the contractility of the diaphragm muscle [49]. Thus, it appears reasonable that supplemental treatment with desiccated thyroid extract (DTE) could improve asthenia in patients with this symptom. One study reported improved scores in a thyroid-specific questionnaire given to a group of patients who had undergone treatment with DTE [50]. Unfortunately, the DTE is not commonly available and substances other than T3 and T4 are excluded by official pharmacopeia [12].

Conclusion

Although the cause of the PTCA remains unexplained, the evidence seems to be indisputable. We have not identified any risk factors in this study, which suggests that the variable is independent of several habits and diseases that might be considered as risk factors. Additional clinical and experimental studies should be performed to clarify the mechanisms involved in the initiation and development of this underestimated sequelae.

TT was widely accepted as the treatment of choice for thyroid cancer and for preventing recurrence in benign thyroid diseases until recently. Moreover, many endocrinologists considered the follow-up after TT to be easy and safe.

The lack of an explanation for PTCA and the absence of instruments for efficacious resistance suggest that it might by valuable to reconsider of the indications of total thyroidectomy, which should be used only in the presence of strict and highly selective criteria.

Compliance with ethical standards The Institutional Ethics Board (Comitato Etico - Policlinico "P. Giaccone" - Palermo) approved the present study that has been performed in accordance with the ethical standards of the 1964 Helsinki declaration. Informed consent was obtained from patients acting as subjects in our investigation.

No author has received funds for the implementation of this study.

Conflict of interest The authors declare that they have no conflict of interest.

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