Contribution of radioiodine uptake measurement and thyroid scintigraphy to the differential diagnosis of thyrotoxicosis

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Abstract

Both clinical and subclinical thyrotoxicosis can result from a wide range of disorders. Establishing the correct etiology underlying thyrotoxicosis is essential to direct treatment towards its specific pathophysiologic process. Based on clinical experience and guideline recommendations, radioiodine iodine uptake (RAIU) measurement and scintigraphy are often requested as the first-line investigation in thyrotoxic patients; however, their specific individual contribution to the differential diagnosis of thyrotoxicosis has not been previously investigated. In our study *we aimed* at evaluating the diagnostic role of RAIU measurement and scintigraphy in the management of thyrotoxicosis. *A total of 108 patients with clinical and 42* patients with subclinical thyrotoxicosis were included in this retrospective study. All patients had RAIU measured at 24 hours after ^{131}I-iodide administration, followed by thyroid scintigraphy. Based on the combination of RAIU and scintigraphy, patients were classified as having diffuse toxic goiter (DTG) in 44% (the most common diagnosis), toxic adenoma in 15.9%, thyroiditis in 14%, and toxic multinodular goiter in 2.7%, while the pattern was inconclusive in 22.7% of all patients. *When considering only patients* with clinical thyrotoxicosis, the scan was inconclusive in 12.9% of patients whereas it was inconclusive in 47.6% of patients with subclinical thyrotoxicosis. There was a highly significant association between thyrotoxic status and scan result, with a statistically significant better performance of RAIU and scintigraphy in patients with clinical thyrotoxicosis when compared to patients with subclinical thyrotoxicosis considered as a whole (P<0.001). Instead, no statistically significant difference was observed between patients with subclinical thyrotoxicosis and TSH <0.1 mU/L and patients with TSH between 0.1 mU/L and 0.4 mU/L (P=0.191). *In conclusion*, we confirm the key role of RAIU and scintigraphy in the management of thyrotoxicosis and document its better performance in patients with clinical thyrotoxic status.

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Introduction

The term *thyrotoxicosis* refers to all causes of elevated levels of circulating thyroid hormones, whereas the term *hyperthyroidism* refers to production and secretion of excessive amounts of thyroid hormones by the thyroid gland [1-3]. Considering that the clinical manifestations of thyrotoxicosis are largely independent of its cause and that several different disorders can cause hyperthyroidism, it is crucial to identify the correct cause, because appropriate therapy depends upon the underlying pathophysiologic mechanism of the disease.

Overt thyrotoxicosis is usually obvious on clinical grounds, biochemical confirmation being based on suppressed serum levels of thyroid stimulating hormone (TSH), elevated serum levels of free thyroxine (fT4), and/or free triiodothyronine (fT3). Subclinical thyrotoxicosis is characterized by partially suppressed serum levels of TSH associated with normal fT3 and fT4 concentrations [1-3]. Both thyrotoxicosis and subclinical thyrotoxicosis may result from a wide range of disorders, such as Graves' disease (the most common cause of thyrotoxicosis, accounting for 60% to 80% of cases of hyperthyroidism in the United States), thyroiditis, toxic adenoma, toxic multinodular goiter, and factitious suppression of the gland [1-4].

Final diagnosis and appropriate treatment are based on a combination of morpho-functional data such as thyroid-related hormone levels (TSH, fT3, fT4), thyroid autoimmunity (including stimulating antibodies against the TSH receptor), ultrasound findings, and radioiodine thyroidal uptake (RAIU) and scintigraphy (or scintigraphy with ^{99m}Tc-pertechnetate as a surrogate for radioiodine).

After confirmation of thyroid hyperfunction by assaying the TSH and thyroid hormone levels, radioiodine uptake measurement and radioiodine thyroid scintigraphy are often recommended as the first-line investigation in thyrotoxic patients [1-3]. Especially in countries with limited health care resources (where the assay of thyroid auto-antibodies - particularly stimulating antibodies - is not routinely available), RAIU and scintigraphy play a key role in discriminating various causes of clinical and subclinical thyrotoxicosis, this

practice being consistent with widely accepted clinical guidelines for the management of thyrotoxicosis [5].

Although RAIU measurement and thyroid scintigraphy have been clinically available for several decades (so that their combined application is taken for granted in any clinical setting), their specific individual contribution to the management of thyrotoxicosis has not been previously investigated. For this retrospective study, we reviewed the patterns of radioiodine uptake and scintigraphy in patients referred to a single center because of clinical or subclinical thyrotoxicosis, in order to comparatively assess their separate contribution to clinical decision making.

Materials and methods

Study population

We retrospectively reviewed the clinical and laboratory records of all patients referred to the National Center for Diabetes, Endocrinology and Genetics of Amman (Jordan) for management of recent-onset clinical and subclinical thyrotoxicosis during the period from December 2005 till February 2009; patients with subclinical disease only had vague, nonspecific symptoms that the referring physician wanted to clarify with a routine check-up. Pregnant women (for whom administration of radioiodine is contraindicated), patients with prior thyroid disease, pituitary disease, and patients who were receiving antithyroid medications or any drugs known to affect thyroid function (such as thyroxine or amiodarone) were excluded from the study.

A total of 150 patients (110 women and 40 men) met the selection criteria. Their age ranged from 15 to 77 years (mean 42.4 ± 15.6). There were 108 patients with clinical and 42 patients with subclinical thyrotoxicosis.

A final diagnosis of the specific disorder causing subclinical or clinical thyrotoxicosis was reached on the basis of a combination of parameters including RAIU, radioiodine thyroid scintigraphy, response to treatment, and follow-up. $^{99m}TcO_4^-$ thyroid scintigraphy and ultrasound eximaniation were employed in few selected cases.

Laboratory tests

Thyroid stimulating hormone serum levels were measured using third-generation microparticle enzyme immunoassay (MEIA, Abbott, normal range: 0.4-4.2 mIU/L); fT3 (normal range: 2.23-5.35 pmol/L) and fT4 (normal range 9.14-23.81 pmol/L) serum levels were also measured using MEIA (Abbott).

Radionuclide evaluation

Radioiodine uptake (RAIU) was measured 24h after oral administration of a capsule containing 1.85-3.7MBq ^{131}I-iodide (Izotop, Hungary) in the fasting state. A dedicated thyroid uptake system (Veenstra, Netherlands) uptake system was employed, and capsules were counted using a neck phantom prior to the administration to the patient. Uptake values were corrected for background activity (mid-thigh), but not for physical decay; in fact, the normal range for thyroid uptake defined in our institution replicates the condition utilized by our Medical Physics Department for calculating the effective residence time of radioiodine in the gland for dosimetric purposes, when radiometabolic therapy is considered for treatment. All patients were advised to follow a standard low iodine diet for 7-10 days prior to scan and none had received iodine contrast medium during the prior month.

Uptake values were reported as low (<10%), within normal limits (between 10%-30%), or high (>30%) according to reference values previously obtained in a group of subjects with normal thyroid function. Immediately after the 24-hour RAIU measurement, a thyroid scan was performed using a single-head Meridian gamma camera (Philips, USA) fitted with pinhole collimator, setting the photon peak at 365keV with a 20% energy window. Images were acquired for 10min in all patients. Images were then classified as: a) diffuse homogeneous, b) presence of hot area(s), and c) inhomogeneous without well-defined nodular areas of abnormally increased or decreased uptake.

Interpretation criteria

The RAIU and thyroid scan were considered diagnostic of: (a) diffuse toxic goiter (DTG) in patients with increased uptake and diffuse homogeneous pattern, (b) hot nodule(s) in patients with definite area(s) of abnormally increased uptake (uptake in the remaining parenchyma being significantly reduced), and (c) thyroiditis in patients with reduced uptake and inhomogeneous scan; the latter condition was most often attributed to autoimmune or to subacute thyroiditis (thereafter referred to simply as “thyroiditis” considering that the various forms of thyroiditis share the same clinical management). The pattern was considered inconclusive in patients with normal uptake and diffuse homogenous pattern, as well as in patients with normal uptake and inhomogeneous pattern without well defined areas of abnormally increased or decreased activity [6-8] (Fig. 1).

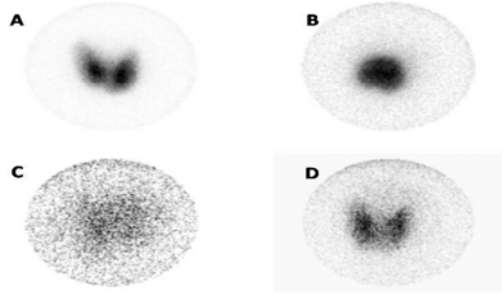

Figure 1. Examples of different scintigraphic patterns, correlated with the corresponding RAIU values. Panel A: ^{131}I-iodide scintigraphy and RAIU (65%) suggestive of diffuse toxic goiter. Panel B: ^{131}I-iodide scintigraphy and RAIU (25%) suggestive of hot thyroid nodule. Panel C: ^{131}I-iodide scintigraphy and RAIU (4%) suggestive of thyroiditis. Panel D: inconclusive ^{131}I-iodide scintigraphy and RAIU (15%).

Statistical analysis

Besides simple descriptive statistics, the data was analyzed by using SPSS version 11.0 for Windows. Cross-tabulation and chi-square test were employed to assess association between thyrotoxic status and radioiodine evaluation patterns, setting the statistical significance level at $P<0.05$.

Results

Measurement of radioiodine uptake and thyroid scintigraphy

The most common classification reached on the basis of combined RAIU and thyroid scan was DTG (44%), followed by toxic adenoma (15.9%), thyroiditis (14%), and toxic multinodular goiter (2.7%). The pattern was inconclusive in 22.7% of all patients. The RAIU and scintigraphic patterns were further analyzed after stratifying the patients into two subgroups, with clinical and subclinical thyrotoxicosis.

The most common classification in patients with clinical thyrotoxicosis was DTG (61%), followed by thyroiditis (13%), toxic adenoma (11.1%), and toxic multinodular goiter (1.9%); 12.9% of the clinically thyrotoxic patients exhibited an inconclusive pattern (Fig. 2).

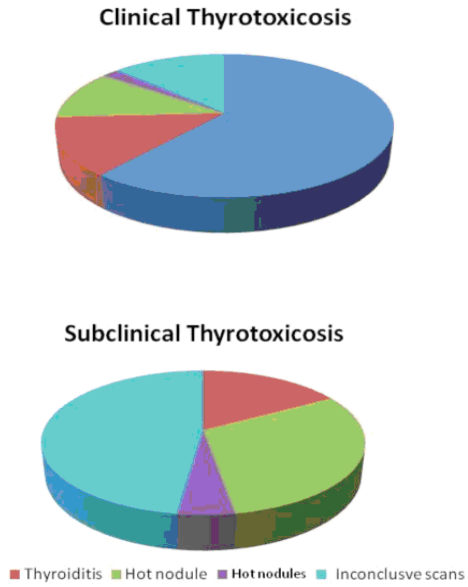

Figure 2. Pie-chart representation of the distribution of combined RAIU and scintigraphic classification in the two subgroups of patients, respectively with overt and with subclinical hyper-thyroidism.

All patients with subclinical thyrotoxicosis had either normal or decreased uptake, the majority of them being classified as inconclusive (47.6%), followed by single hot nodule (30.4%), thyroiditis (16.7%), and multiple hot nodules (4.8%).

The 42 patients with subclinical thyrotoxicosis were further stratified according to their TSH serum levels: <0.1mU/L (n=27), and between 0.1 and 0.4mU/L (n=15). According to our interpretation criteria, the majority of the patients with serum TSH<0.1 mU/L exhibited an inconclusive RAIU and scintigraphic pattern (40.7%), followed by single hot nodule (29.6%), thyroiditis (22.2%), and multiple hot nodules (7.4%). In patients with serum TSH between 0.1 and 0.4mU/L an inconclusive pattern was the most frequent finding (60.7%), followed by single hot nodule (32.6%), and thyroiditis (one patient only, 6.7%) (Fig. 3).

A highly significant association was found between thyrotoxic status (in terms of clinical *versus* subclinical thyrotoxicosis) and scan results (Table 1). In particular, the percentage of inconclusive scans was higher in patients with subclinical than in those with overt thyrotoxicosis (P<0.001). On the other hand, no statistically significant difference of RAIU and scan performance was observed between the two subclinical thyrotoxic subgroups, with serum TSH levels <0.1mU/L and with serum TSH levels in the 0.1-0.4mU/L range, respectively (P=0.191, see Table 1).

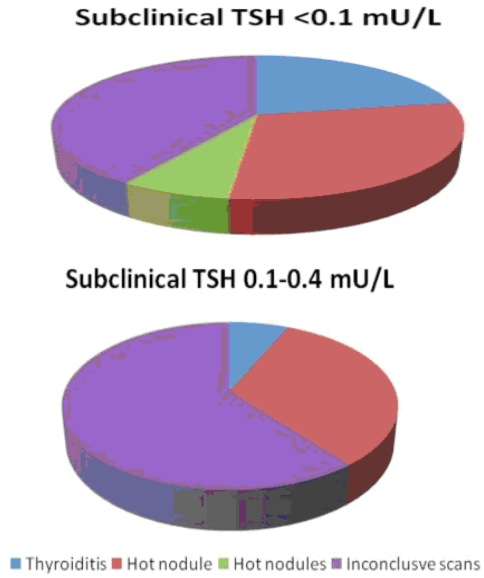

Figure 3. Radioiodine uptake and scintigraphic classification in the two categories of patients with subclinical thyrotoxicosis, with serum TSH<1mU/L and with serum TSH between 0.1 and 0.4mU/L, respectively.

Table 1. *Comparison of the fraction of inconclusive RAIU and scan patterns observed in patients with clinical versus subclinical thyrotoxicosis as well as, in the subclinical thyrotoxicosis group, between patients with TSH serum levels <0.1mU/L and patients with TSH in the 0.1-0.4mU/L range.*

Thyrotoxic status	No. of patients	Inconclusive scans	P-value
Clinical thyrotoxicosis	108	12.9%	<0.001*
Subclinical thyrotoxicosis	42	47.6%	
Sublinical with TSH 0.1-0.4	15	60.7%	0.191**
Subclinical with TSH <0.1	27	40.7%	

(*) Comparison between the clinical and the subclinical thyrotoxicosis groups.(**) Comparison between patients with subclinical thyrotoxicosis and serum TSH <0.1mU/L and those with subclinical thyrotoxicosis and serum TSH in the 0.1-0.4mU/L range.

Impact of RAIU and scintigraphic pattern on patient management

Twenty six of the 150 patients were lost to follow-up after the radionuclide evaluation. Average follow-up for the remaining 124 patients was 17 months (range 1-37 months, 4 patients with DTG had a follow-up shorter than 3 months). In the patients with complete follow-up, 61 had a scintigraphic diagnosis of DTG (all had clinical thyrotoxicosis) and were either treated medically, had received radioiodine treatment, or had been referred for surgery.

Twenty-one patients were classified as having a single hot thyroid nodule (11 of them had subclinical

thyro-toxicosis); the presence of nodules was confirmed by neck palpation and/or ultrasound in all patients but one case with clinical thyrotoxicosis, whose final classification as thyroiditis was based on normalization of thyroid function and absence of nodules on ultrasound. Four patients were classified as having multiple hot nodules (2 of them had subclinical thyrotoxicosis). Patients with hot thyroid nodules were referred for either radioiodine ablation or surgery. Sixteen patients were classified as having thyroiditis (4 of them had subclinical thyrotoxicosis); they all progressed into euthyroidism or hypothyroidism without medical intervention, thus confirming the scintigraphic diagnosis, except in one patient whose subclinical thyrotoxicosis persisted at the 2-year follow-up visit; at this time, the $^{99m}TcO_4^-$ scan suggested small multiple autonomous nodules, consistent with the persistence of subclinical thyrotoxicosis.

Of the 22 patients who had inconclusive RAIU and scintigraphic patterns (10 of them had subclinical thyrotoxicosis), 10 patients were ultimately diagnosed with thyroiditis, 4 patients had a hot thyroid nodule and 3 patients had multiple hot nodules. Five patients with inconclusive scans and clinical thyrotoxicosis were managed as DTG after the persistence of thyrotoxicosis for more than 4 months and absent thyroid nodules on ultrasound examination (Fig. 4).

It is worth mentioning that 10 of the patients (35.7%) who were lost to follow-up had a combination of inconclusive scans and subclinical thyrotoxicosis.

Discussion

The development of sensitive assays for serum TSH has considerably facilitated the diagnosis of hyperthyroidism and revealed that thyrotoxicosis is a relatively common condition; in fact, thyrotoxicosis has been diagnosed in 0.5% of a 'disease-free' U.S. population, subclinical thyrotoxicosis in 0.7% of the same study population [9]. The most common cause of thyrotoxicosis is

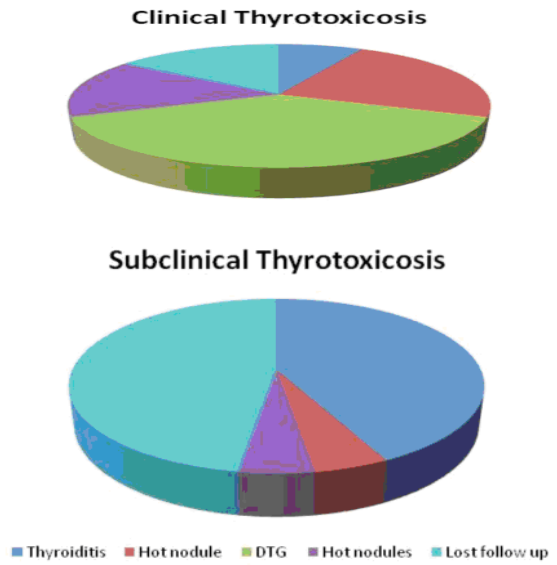

Figure 4. Long-term clinical outcomes in the patients with inconclusive RAIU and scintigraphic patterns.

Graves' disease, followed by toxic multinodular goiter, then solitary hyperfunctioning nodules; hyperfunctioning nodules are more common in iodine-deficient areas [10]. Concerning in particular the latter condition, although the typical Jordanian diet does not include seafood (an important source of iodine intake), specific public health legislation has introduced iodized salt in Jordan over 20 years ago. Various forms of thyroiditis that result in destruction of thyroid follicles and release of thyroid hormones into the blood represent another clinically important entity. This term refers generically to any inflammatory condition of the thyroid (whether autoimmune, infectious, or toxic) that activates apoptotic pathways leading to death of the thyroid follicular cells [1]. Especially in case of subacute thyroiditis (most frequently caused by a viral infection), follicular disruption, with the consequent release of colloid-stored hormones into the circulation, results in transient hyperthyroidism; after the inflammatory process subsides, mild to moderate hypothyroidism generally follows, before complete recovery. Other conditions that can cause thyrotoxicosis include thyrotropin producing pituitary tumours, struma ovarii, hyperthyroidism mediated by human chorionic gonadotropin**,** iodine-induced hyperthyroidism (Jod-Basedow), metastatic follicular thyroid cancer, and factitious thyrotoxicosis [11]. Clearly, the underlying pathophysiology and therefore clinical management and treatment strategies differ markedly among these different conditions.

In addition to TSH serum levels, laboratory tests routinely include assays of free and total thyroxine and tri-iodothyronine. The assay of anti-TSH-receptor antibodies (TRAb, also called thyroid-stimulating immunoglobulins, TSI) is not available in Jordan; although in routine clinical practice they are not necessary (e.g., for treatment), such tests may be helpful in selected cases, such as in patients with hyperthyroidism during pregnancy [5].

It should be emphasized that radioiodine uptake measurement and thyroid scan merely provide estimates of iodine avidity of the thyroid gland, and not of thyroid function; they may also be useful for assessing the functional status of any palpable and/or thyroid nodules detected by ultrasound. Nevertheless, radioiodine uptake measurement and scan are often recommended as the first investigation of thyrotoxicosis in patients with suppressed TSH levels, and they actually constitute the first investigation ordered in our clinical practice [1-3, 5].

Diffuse toxic goiter was the most common scintigraphic diagnosis in our patient population, accounting for 49.2% of cases with completed follow-up. There were 5 patients with inconclusive scans whose clinical thyrotoxicosis persisted more than 4 months after presentation. They were diagnosed clinically as having diffuse toxic goiter and might represent a mild or early onset disease. Alternative explanations would be non-adherence to the low iodine diet, or rapid washout of iodine. DTG usually accounts for 60% to 80% of thyrotoxicosis; when including these 5 patients in our study population, the prevalence of DTG rises to 51.6%. This discrepancy in prevalence is expected, since DTG due to Graves' disease is often clinically obvious**.** In cases with associated ophtalmopathy. RAIU and thyroid scan are often not requested, except for confirming the clinical diagnosis or prior to treatment with radioiodine.

The thyroid scan reveals a (hyper) functioning nodule and suppression to a varying degree of the extranodular thyroid tissue in patients with autonomous thyroid nodules. Autonomous thyroid nodule was the second most common diagnosis, confirmed in 25 patients with completed follow-up (20.2%); 50% of these patients

had subclinical thyrotoxicosis. In 4 of these patients the RAIU and scan pattern was inconclusive, and a diagnosis was obtained after correlation with the ^{99m}Tc-O_4^- scan and with neck ultrasound. The inconclusive pattern was probably due to the poor imaging characteristics of ^{131}I and incomplete suppression of the normally functioning glandular parenchyma, resulting in an apparently inhomogeneous pattern. One patient with scintigraphic diagnosis of hot thyroid nodule progressed spontaneously into euthyroidism. This case was diagnosed clinically as thyroiditis, where uninflammed thyroid tissue demonstrated normal uptake and caused a misleading RAIU scan.

A total of 26 out of the 124 patients with adequate follow-up were ultimately diagnosed with thyroiditis (corresponding to 21%). These patients developed euthyroidism or hypothyroidism on follow-up; 15 of these 26 patients had a scan suggestive of diffuse thyroiditis, while in 10 cases the scan was not conclusive, probably because the thyroid was in the recovery phase.

Poor specificity is a reported limitation of low RAIU in thyrotoxic patients, whereas the scintigraphic pattern is identical in different disease entities such as thyroiditis, factitious thyrotoxicosis and Jod-Basedow [1]. In these subjects detailed history of dietary iodine intake, blood tests for thyroglobulin, and often simple clinical follow-up are sufficient to establish a clinical diagnosis [1, 2, 5]. In our population, one patient persisted to have subclinical thyrotoxicosis and was shown on follow-up to have multiple small autonomous thyroid nodules [11].

Clinical versus subclinical thyrotoxicosis

The clinical significance of subclinical hyperthyroidism relates to the risk of progression to overt hyperthyroidism, to its cardiac and skeletal effects and to its prevalence, which is increasing in parallel with increasing sensitivity of the serum TSH assays [12-16]. A panel of experts recently suggested to classify patients with subclinical hyper-thyroidism into two categories: patients with low but detectable serum TSH levels (0.1-0.4mU/L), and patients with undetectable TSH (<0.1mU/L) [17].

No consensus exists on the management of subclinical hyperthyroidism. It is suggested that treatment is unnecessary, except in elderly patients with undetectable TSH and in patients with nodular thyroid disease [5, 12, 17]. Once TSH suppression is present, a clear clinical diagnosis is warranted to guide the treatment strategy. Although thyroid radioiodine uptake measurement and scan are often recommended as the first investigation in patients with low TSH [1-3], the role of the scan and its contribution to the management of subclinical thyrotoxicosis has not been thoroughly investigated, with a single study only dealing with the subclinical condition [18].

Endogenous causes of subclinical hyperthyroidism include Graves' disease, autonomously functioning nodule or multiple autonomous thyroid nodules, and thyroiditis [19-22]. It is interesting to notice that all patients with subclinical thyrotoxicosis in our study had either normal or low radioiodine uptake values; consequently, none of our patients with subclinical thyrotoxicosis met the scintigraphic criteria for DTG. We suggest that patients with subclinical thyrotoxicosis and inconclusive scans might benefit from including TSH receptor antibodies (TRAb) or thyroid-stimulating immunoglobulins (TSI) tests in their workup [23-25].

As reported in Table 1, there was a statistically significant lower fraction of inconclusive RAIU and scans in patients with clinical thyrotoxicosis than in those with subclinical thyrotoxicosis as a whole group. No statistically significant difference was instead observed when comparing patients with subclinical thyrotoxicosis and TSH levels <0.1 mU/L to patients with TSH levels between 0.1 mU/L and 0.4 mU/L.

In conclusion, RAIU and thyroid scan play a key role in the differential diagnosis of thyrotoxicosis. In this paper we report our experience regarding the contribution of RAIU and scan to the management of clinical and subclinical thyrotoxicosis and document its better performance in patients with clinical thyrotoxic states. Nevertheless, we are aware that such conclusions might be biased because of the limitations affecting a retrospective study such as the one presented here. For this reason and thanks to the collaboration established between our two centers, we are now planning a double-blind, prospective, multi-center study addressing to elucidate this issue in deeper details.

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