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Long-term outcome of thyroid function after amiodarone-induced thyrotoxicosis, as compared to subacute thyroiditis

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ABSTRACT. ***Background:*** **Two main forms of amiodarone-induced thyrotoxicosis (AIT) exist: type 1 AIT is a condition of true hyperthyroidism developing in patients with pre-existing thyroid disorders, and usually requires thyroid ablative treatment. On the other hand, type 2 AIT is a form of destructive thyroiditis occurring in normal thyroids, the management of which usually consists in glucocorticoid treatment.** ***Aim:*** **To assess the long-term outcome of thyroid function in a prospective study of type 2 AIT patients, as compared to patients with De Quervain's subacute thyroiditis (SAT).** ***Patients and Methods:*** **Sixty consecutive patients with type 2 AIT were evaluated during oral glucocorticoid treatment (oral prednisone 30 mg/day, gradually tapered and withdrawn over a 3-month period) and followed for 38±4 months (range 6-72) thereafter. Sixty consecutive patients with SAT, referred to our Institutes during the same period and treated with the same therapeutic schedule, served as controls.** ***Results:*** **Type 2 AIT patients were older ($p<0.0001$) and showed a larger male preponderance (M:F 3.6:1 *vs* 0.5:1, $p<0.0001$) than SAT patients. Mean serum free T_4 (FT_4) and free T_3 (FT_3) concentrations at diagnosis were increased in both conditions, but higher in type 2 AIT than in SAT (FT_4 47.6±18.8 and 29.6±8.3 pmol/l, respectively, $p<0.0001$; FT_3 15.4±7.0 and 11.2±3.0 pmol/l, respectively, $p<0.001$). Correction of thyrotoxicosis was obtained in all patients in both groups, but restoration of euthyroidism occurred earlier in SAT than in type 2 AIT ($p=0.006$). Ten type 2 AIT patients (17%) and 3 SAT patients (5%, $p<0.03$) became permanently hypothyroid after glucocorticoid withdrawal and required levothyroxine replacement.** ***Conclusions:*** **A relevant proportion of type 2 AIT patients develop permanent hypothyroidism after correction of thyrotoxicosis. Thus, periodic surveillance of thyroid status is required after type 2 AIT.**

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INTRODUCTION

Amiodarone is an iodine-rich drug widely used and very effective in the management of tachyarrhythmias and, to a lesser extent, severe heart failure (1, 2). The drug causes changes in thyroid function tests, namely an increase in serum T_4 and a relative decrease in serum T_4, even in euthyroid subjects, mostly due to inhibition of T_4 peripheral monodeiodination (1-4). Overt thyroid dysfunction, either hypothyroidism or thyrotoxicosis, occurs in about 15% of subjects under chronic amiodarone therapy (1-5). Amiodarone-induced hypothyroidism is relatively more frequent in iodine-sufficient areas, amiodarone-induced thyrotoxicosis (AIT) in iodine-deficient areas (6).

Treatment of AIT is a difficult challenge (7-9). Two main forms of AIT exist: type 1 occurs in patients with pre-existing thyroid disorders (usually autonomous nodular goiter or subclinical Graves' disease) and is a true form of iodine-induced hyperthyroidism. At variance, type 2 AIT is a form of drug-induced destructive thyroiditis apparently occurring in the absence of intrinsic thyroid gland abnormalities. Differentiation of the two main forms can often be made by conventional thyroid ultrasonography,

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color flow Doppler sonography (CFDS), thyroidal radioactive iodine uptake (RAIU), serum interleukin-6 levels, presence/absence of circulating thyroid autoantibodies (10-12). However, mixed (or indefinite) forms, in which both pathogenic mechanisms (thyroid hormone hypersecretion and destructive processes) intervene, are likely more frequent than previously believed (1, 9). While type 1 AIT and mixed forms are usually initially treated with a combination of thionamides and potassium perchlorate (and, in many instances, glucocorticoids), type 2 AIT is generally and effectively managed by glucocorticoids alone (1, 9). Because type 1 AIT occurs in an abnormal thyroid gland, thyroid ablation by either thyroidectomy or radioactive iodine (after removal of iodine contamination) is often required after correction of thyrotoxicosis (1, 9).

On the other hand, further treatments are rarely needed in type 2 AIT due to the absence of intrinsic abnormalities of the thyroid gland in this condition (1, 9). However, the long-term outcome of thyroid function and, in particular, the possible late consequences of thyroid damage after type 2 AIT, are largely unknown. The aim of the present study was to assess the long-term outcome of thyroid function in a large series of prospectively followed type 2 AIT patients.

MATERIALS AND METHODS

Subjects

The study included 60 consecutive, untreated patients with type 2 AIT [47 men, 13 women, mean (+SD) age 67±13yr, range 33-84 yr] seen at the Department of Endocrinology, University of Pisa and Department of Clinical Medicine, University of Insubria at Varese from 1998 to 2004. The first 60 consecutive patients with subacute thyroiditis (SAT) (19 men, 41 women, age 49±11yr, range 30-76 yr) referred to our departments during the same period served as controls. During the same period, 33 patients with type 1/mixed forms of AIT were observed.

Diagnosis of AIT was based on clinical and laboratory features, including increased free T_4 (FT_4) and free T_3 (FT_3) concentrations and undetectable serum TSH levels in patients chronically treated with amiodarone. Duration of amiodarone therapy ranged from 2-148 months (mean+SD, 26±24) and the cumulative dose of amiodarone ranged from 9-434 g (mean+SD, 113±83). Diagnosis of type 2 AIT was based on the following criteria: normal thyroid gland at conventional ultrasonography, absent hypervascularity at CFDS, absence of circulating thyroid autoantibodies [anti-thyroglobulin (Tg), anti-thyroid peroxidase (TPO), anti-TSH receptor (TRAb)], and low (≤3%)/undetectable RAIU values.

Diagnosis of SAT was made according to clinical and biochemical findings, including anterior neck pain with or without systemic symptoms, low-grade fever, sore throat or upper respiratory tract infection, elevated erythrocyte sedimentation rate, increased serum FT_4 and FT_3 levels and undetectable TSH concentrations, absent vascularity at CFDS, and low/undetectable thyroidal RAIU values.

Conventional and color flow Doppler sonography

Thyroid volume was measured by ultrasound and calculated by the ellipsoid model (width x length x thickness x 0.52 for each lobe) as previously described (13). CFDS was performed as previously reported (14).

Assays

Serum FT_4, FT_3 (Technogenetics, Milan, Italy), TSH (Delphia, hTSH ultra kit; Pharmacia, Turku, Finland), TRAb (TRAK assay, Henning, Berlin, Germany), anti-Tg (Serodia, Tokio, Japan) anti-TPO (Sorin Biomedica, Saluggia, Italy) were measured by commercial kits. Normal values in our laboratory are as follows: FT_4, 8.3-21.2 pmol/l; FT_3, 3.8-8.4 pmol/l; TSH, 0.4-3.7 mU/l; anti-Tg and anti-TPO, negative; TRAb, <1U/l.

Thyroidal RAIU

Thyroidal RAIU values were measured 3 and 24 h after the administration of a tracer dose (5 μCi) of 131-I. Normal 3-h and 24-h RAIU values in our area are 10-20 and 30-45%, respectively.

Urinary iodine excretion

Morning random urinary samples were collected for iodine measurements using an autoanalyzer apparatus (Technicon, Rome, Italy). The median urinary iodine excretion in our area is 110 μg/l.

Treatment

Amiodarone treatment was withdrawn in all patients. All patients were treated with oral prednisone (starting dose, 30 mg/day). The drug was gradually tapered and withdrawn after three months. Cure of thyrotoxicosis was defined by normalization of both serum FT_4 and FT_3, as previously reported (15). Hypothyroidism was considered permanent when serum TSH concentrations remained higher than normal (with a concomitant decrease in serum free thyroid hormone concentrations in 3 subsequent determinations after at least 6 months from glucocorticoid withdrawal). Mean follow-up period was 38+4 months (range 6-72 months) in type 2 AIT and 40+5 months (range 9-76 months) in SAT.

Statistical analysis

Results were expressed as mean+SD. Comparison of FT_4, FT_3, RAIU and thyroid volume between the study groups was performed by the analysis of variance (ANOVA); differences in the occurrence of hypothyroidism in the two groups was evaluated by chi-square and the Fisher's exact test.

RESULTS

Clinical and biochemical features of the study groups at baseline are shown in Table 1. Patients with type 2 AIT were older than those with SAT ($p<0.001$), with prevalence of male gender (M:F 3.6:1); at variance, most patients with SAT were women (M:F 0.5:1, $p<0.0001$; Table 1).

Mean serum FT_4 and FT_3 concentrations at diagnosis were increased in both groups, but higher in type 2 AIT than in SAT (FT_4 47.6±18.8 and 29.6± 8.3 pmol/l, respectively, $p<0.0001$; FT_3 15.4±7.0 and 11.2±3.0

Table 1 - *Clinical and biochemical features of the study groups at baseline.*

	Type 2 AIT	SAT	*p*
Patients (no.)	60	60	
Sex (M/F) M:F	47/13 3.6:1	19/41 0.5:1	<0.0001
Age (yr) Range	67±13 33-84	49±11 30-76	<0.0001
FT_4 (pmol/l) Range	47.6±18.8 22.3-90.1	29.6±8.3 22.4-61.9	<0.0001
FT_3 (pmol/l) Range	15.4±7.0 8.9-30.8	11.2±3.0 8.7-22.7	<0.001
Thyroid volume (ml) Range	16±10 6-31	12±5 5-28	<0.001
Thyroidal RAIU (%) 3-h 24-h	1.8±1.4 2.1±2.1	2.9±2.2 4.2±1.1	<0.01 <0.0001
UIE (µg/l)	4.455±3.791 430-14880	79±59 <25-239	<0.0001

Data are expressed as mean±SD. RAIU: radioactive iodine uptake; UIE: urinary iodine excretion; M: male; F: female; FT_3: free T_3; FT_4: free T_4. For normal ranges see text.

pmol/l, respectively, $p<0.001$) (Fig. 1). No patient in either group had positive serum anti-Tg, anti-TPO or TRAb tests.

Mean estimated thyroid volume at ultrasonography was slightly higher in type 2 AIT than in SAT ($p<0.001$) (Table 1); all patients in both groups had CFDS pattern 0, indicating the absence of thyroid hypervascularity. As expected, type 2 AIT patients had markedly higher urinary iodine excretion levels (4.455±3.791 µg/l) than SAT patients (79±59 µg/l) ($p<0.0001$) (Table 1).

Glucocorticoids restored euthyroidism in all patients in both groups in 10-150 days; three patients had thyrotoxicosis recurrence while on glucocorticoid therapy. Euthyroidism was restored earlier in patients with SAT (43±41 days) than in those with AIT (23±9 days, $p=0.006$).

Thereafter, 10 type 2 AIT patients (17%) and 3 SAT patients (5%) developed permanent hypothyroidism ($p<0.03$) (Fig. 2). Hypothyroidism occurred 10±6.5 months (range 6-24) after attainment of euthyroidism in type 2 AIT patients and 14.7±2.7 months (range

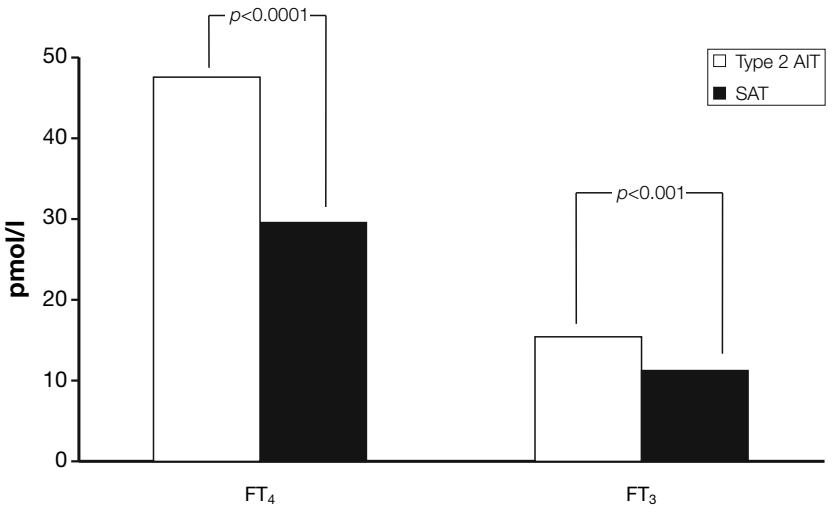

Fig. 1 - *Serum free T_4 (FT_4) and free T_3 (FT_3) concentrations in patients with type 2 amiodarone-induced thyrotoxicosis (type 2 AIT) and subacute thyroiditis (SAT) at baseline. Upper normal range values in our laboratory are: FT_4, 21.2 pmol/l; FT_3, 8.4 pmol/l. All patients in both groups had increased serum FT_4 and FT_3 concentrations at baseline.*

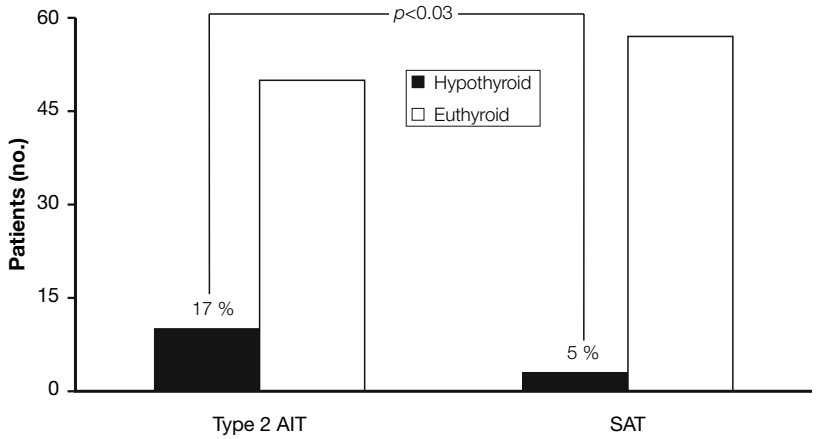

Fig. 2 - *Progression to permanent hypothyroidism after type 2 amiodarone-induced thyrotoxicosis (type 2 AIT) or subacute thyroiditis (SAT).*

12-18) in SAT patients (p=0.2). When hypothyroidsm was diagnosed, iodine urinary excretion was normal (data not shown). Hypothyroidism was treated with replacement doses of levothyroxine. No patients with type 2 AIT or SAT had detectable anti-Tg or Anti-TPO levels when hypothyroid. Type 2 AIT patients who developed hypothyroidism did not differ from those who remained euthyroid in terms of baseline serum FT_4 or FT_3 concentrations, thyroidal RAIU values, thyroid volume, average dose of administered amiodarone, duration of amidarone therapy, duration of glucocorticoid treatment, and UIE values (Table 2). No patients were re-exposed to further iodine (or amiodarone) load nor were they treated

Table 2 - *Clinical and biochemical features (at baseline) of type 2 amiodarone-induced thyrotoxicosis (AIT) patients, who after treatment remained euthyroid or become hypothyroid.*

	Euthyroid	Hypothyroid	p
(No.)	(50)	(10)	
Sex (M/F) M:F	39/11 3.5:1	8/2 4.0:1	 0.8
Age (yr) Range	67±13 33-84	66±11 51-78	 0.9
FT_4 (pmol/l) Range	45.2±17.4 22.3-88.3	53.9±21.2 30.5-90.1	0.2
FT_3 (pmol/l) Range	14.9±6.9 8.9-30.8	16.9±6.7 9.7-28.7	0.4
Thyroid volume (ml) Range	17.5±10.1 6-31	20.7±6.1 12-20	0.5
Thyroidal RAIU (%) 3-h 24-h	1.9±1.5 2.1±2.2	1.8±0.8 1.9±1.2	0.8 0.8
Amiodarone Cumulative dose (g) Range	110±84 9-434	110±77 28-243	0.9
Duration (months) Range	27±25 2-149	24±15 5-48	0.8
Time to cure thyrotoxicosis (days) Range	43±45 10-150	41±29 14-90	0.9

Data are expressed as mean±SD. RAIU: radioiodine uptake; UIE: urinary iodine excretion; M: male; F: female; FT_3: free T_3; FT_4: free T_4. For normal ranges see text.

with interferons. Likewise, SAT patients who became hypothyroid did not differ from those remaining euthyroid in terms of baseline serum FT_4 and FT_3 levels, thyroid volume, thyroidal RAIU values and duration of glucocorticoid therapy (data not shown).

DISCUSSION

Amiodarone is a very effective anti-arrhythmic drug, but causes thyroid dysfunction, either hypothyroidism or thyrotoxicosis, in a significant proportion of patients (1, 16, 17). AIT poses a diagnostic and therapeutic challenge (8), and results of different treatment modalities have often proven unsatisfactory due to heterogeneity and complexity of AIT patients, to incomplete understanding of the underlying mechanisms of disease and difficulties in the differentiation of the two main forms, also due to the existence of mixed (undefined) forms (9, 18-24).
In addition, the fact that the 2 main forms of AIT occur in patients with underlying thyroid abnormalities (type 1 AIT) or normal thyroid gland (type 2 AIT) raises the question of how patients should be treated and followed after initial correction of thyrotoxicosis. Pre-existence of thyroid disorders, as in type 1 and mixed (undefined) AIT, usually suggests that thyroid ablation be strongly considered at least after restoration of euthyroidism (1, 9). On the contrary, type 2 AIT, due to its transient destructive feature occurring in a normal thyroid gland, is generally assumed not to require any further treatment after resolution of thyrotoxicosis (1, 9, 25). This is particularly relevant considering the results of the present study. No type 2 AIT patients had recurrence of thyrotoxicosis after restoration of euthyroidism. More important, 17% developed permanent hypothyroidism, a proportion significantly higher than that observed in SAT (5%) during the same period of follow-up. We included in our study a group of patients with SAT as controls of a spontaneous-occurring destructive thyroiditis. The group of SAT patients consecutively enrolled during the study period was not age- and sex-matched. This is not surprising, because it is well known that SAT occurs in younger patients than AIT (25) and, at variance with the latter, shows a higher prevalence in women than in men (26). Despite this limitation, it was interesting to compare the outcome of these two thyroid-destructive processes. Previous studies reported permanent hypothyroidism after SAT in 5-15% of cases (26, 27). The much higher prevalence of permanent hypothyroidism in type 2 AIT than in SAT in our study is likely due to the greater degree (and probably duration in pre-clinical phases of the disease) of thyroid destruction in the former group. The higher serum FT_4 and FT_3 concentrations and the more marked clinical signs of thyrotoxicosis in type 2 AIT than in SAT lend further support to this notion.
In conclusion, prolonged follow-up of type 2 AIT after correction of thyrotoxicosis shows that a substantial proportion of these patients spontaneously progress to hypothyroidism, depending on the degree of thyroid damage by the destructive process. Accordingly, thyroid function of type 2 AIT patients should periodically be monitored after recovery from thyrotoxicosis in order to disclose the development of thyroid failure. While previous data of the literature showed that evolution to hypothyroidism is rather frequent after re-exposure of AIT patients (or patients with thyroid-destructive processes) to iodine load (28-30), our study demonstrates that this outcome is relatively frequent in type 2 AIT even in the absence of further iodine contamination.

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REFERENCES

1. Martino E, Bartalena L, Bogazzi F, Braverman LE. Amiodarone and the thyroid. Endocr Rev 2001, 22: 240-54.
2. Bartalena L, Bogazzi F, Braverman LE, Martino E. Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. J Endocrinol Invest 2001, 4: 116-30.
3. Wiersinga WM. Amiodarone and the thyroid. In: Weetman, AP, Grossman A eds. Pharmacotherapeutics of the Thyroid Gland. Berlin: Springer Verlag 1997, 225-87.
4. Iudica-Souza C, Burch HB. Amiodarone-induced thyroid dysfunction. The Endocrinologist 1999, 9: 216-27.
5. Thorne SA, Barnes I, Cullinan P, Somerville J. Amiodarone-induced thyroid dysfunction. Risk factors in adults with congenital heart disease. Circulation 1999, 100: 149-54.
6. Martino E, Safran M, Aghini-Lombardi F, et al. Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. Ann Intern Med 1984, 101: 28-34.
7. Bartalena L, Brogioni S, Grasso L, Bogazzi F, Burelli A, Martino E. Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results from a prospective study. J Clin Endocrinol Metab 1996, 81: 2930-3.
8. Bartalena L, Bogazzi F, Martino E. Amiodarone-induced thyrotoxicosis: a difficult diagnostic and therapeutic challenge. Clin Endocrinol (Oxf) 2002, 56: 23-4.
9. Bartalena L, Wiersinga WM, Tanda ML, et al. Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members

of the European Thyroid Association. Clin Endocrinol (Oxf) 2004, 61: 494-502.

10. Bogazzi F, Bartalena L, Brogioni S, et al. Color flow Doppler sonography rapidly differentiates type I and type II amiodarone-induced thyrotoxicosis. Thyroid 1997, 7: 541-5.
11. Eaton SEM, Euinton HA, Newman CM, Weetman AP, Bennet WM. Clinical experience of amiodarone-induced thyrotoxicosis over a 3-year period: role of colour-flow Doppler sonography. Clin Endocrinol (Oxf) 2002, 56: 33-8.
12. Bogazzi F, Martino E, Dell'Unto E, et al. Thyroid color flow Doppler sonography and radioiodine uptake in 51 consecutive patients with amiodarone-induced thyrotoxicosis. J Endocrinol Invest 2003, 26: 635-40.
13. Vitti P, Rago T. Thyroid ultrasound as a predictor of thyroid disease. J Endocrinol Invest 2003, 26: 686-9.
14. Bogazzi F, Bartalena L, Brogioni S, et al. Thyroid vascularity and blood flow are not dependent on serum thyroid hormone level: studies in vivo by color flow Doppler sonography. Eur J Endocrinol 1999, 140: 452-6.
15. Chopra IJ, Baber, K. Use of oral cholecystographic agents in the treatment of amiodarone-induced hyperthyroidism. J Clin Endocrinol Metab 2001, 86: 4707-10.
16. Trip MD, Wiersinga WM. Incidence, predictability, and pathogenesis of amiodarone-induced thyrotoxicosis and hypothyroidism. Am J Med 1991, 91: 603-6.
17. Leger AF, Massin JP, Laurent MF. Iodine-induced thyrotoxicosis: analysis of eighty-five consecutive cases. Eur J Clin Invest 1984, 14: 449-57.
18. Wimpfheimer C, Staubli M, Schadelin J, Studel H. Prednisone in amiodarone-induced thyrotoxicosis. Br Med J 1982, 284: 1835-6.
19. Broussolle C, Ducottet X, Martin C, et al. Rapid effectiveness of prednisone and thionamides combined therapy in severe amiodarone iodine-induced thyrotoxicosis. Comparison of two groups of patients with apparently normal thyroid glands. J Endocrinol Invest 1989, 12: 37-42.
20. Bonnyns M, Sterling I, Renard M. Dexamethasone treatment of amiodarone-induced thyrotoxicosis (AIT) with or without persistent administration of the drug. Acta Cardiol 1989, 44: 235-43.
21. Martino E, Aghini-Lombardi F, Mariotti S, et al. Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole. J Endocrinol Invest 1986, 9: 201-7.
22. Williams M, Lo Gerfo P. Thyrodectomy using local anesthesia in critically ill patients with amiodarone-induced thyrotoxicosis: a review and description of the technique. Thyroid 2002, 12: 523-5.
23. Bogazzi F, Miccoli P, Berti P, et al. Preparation with iopanoic acid rapidly controls thyrotoxicosis in patients with amiodarone induced thyrotoxicosis. Surgery 2002, 132: 1114-8.
24. Osman F, Franklyn JA, Sheppard MC, Gammage MD. Successful treatment of amiodarone-induced thyrotoxicosis. Circulation 2002, 105: 1275-7.
25. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med 2003, 348: 2646-51.
26. Fatourechi V, Aniszewski JP, Fatuorechi GP, Atkinson EJ, Jacobs SJ. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmstedt County, Minnesota. J Clin Endocrinol Metab 2003, 88: 2100-5.
27. Lio S, Pontecorvi A, Caruso M, Monaco F, D'Armiento M. Transitory subclinical or permanent hypothyroidism in the course of subacute (De Quervain) thyroiditis. Acta Endocrinol (Copenh) 1984, 106: 67-70.
28. Roti E, Minelli R, Gardini E, et al. Iodine-induced subclinical hypothyroidism in euthyroid subjects with a previous episode of amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab 1992, 75: 1273-7.
29. Roti E, Minelli R, Gardini E, et al. Impaired intrathyroidal iodine organification and iodine-induced hypothyroidim in euthyroid women with a previous episode of postpartum thyroiditis. J Clin Endocrinol Metab 1991, 73: 958-63.
30. Roti E, Minelli R, Gardini E, Bianconi L, Breverman LE. Iodine-induced hypothyroidism in euthyroid subjects with a previous episode of subacute thyroiditis. J Clin Endocrinol Metab 1990, 70: 1581-5.