2002 Italy
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actual dose of I- not stated.
Source is "iodized salt" which provides 180 mcg I- in 4 gm salt.

discussion

nodules

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Iodized salt improves the effectiveness of L-thyroxine therapy after surgery for nontoxic goitre: a prospective and randomized study

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Summary

OBJECTIVE To investigate whether the addition of iodized salt to daily diet in thyroidectomized patients for nontoxic goitre could influence the effectiveness of nonsuppressive L-thyroxine (L-T4) therapy on thyroid remnant size, during 12 months' follow-up after thyroid surgery.

DESIGN AND PATIENTS A consecutive series of selected 139 patients (26 males, 113 females; median age 45 years, range 30–69 years) living in a moderate iodine-deficient area, and undergoing thyroid surgery for nontoxic multinodular goitre, was enrolled. Patients were assigned randomly to two different therapeutic regimens: 70 patients received L-T4 therapy alone (Gr. L-T4), while the remaining 69 patients took iodized salt on a daily basis in addition to L-T4 treatment (Gr. L-T4 + I). In both groups, the initial L-T4 dose was 1·5 µg/kg/day, which, in our experience, has been shown to be intermediate between suppressive and replacement doses. To avoid the risks of mild thyrotoxicosis and to limit the excessive TSH stimulation of the thyroid remnant, the L-T4 dose was adjusted in those patients with serum TSH levels outside the lowest two-thirds of the normal range (0·3–2·5 mU/l). An ultrasound evaluation of thyroid remnant size was performed after thyroid surgery and 12 months later.

RESULTS After surgery, the median thyroid remnant volume was 3·5 ml (range 0·4–13·9 ml) in Gr. L-T4 and 4·6 ml (range 0·5–12·7 ml) in Gr. L-T4 + I (*P* = 0·06). After 1 year of follow-up, the patients treated with L-T4 + I obtained a remnant volume reduction (–39·7%, range –87·0% to +91·2%) significantly (*P* = 0·006) greater than that observed in patients assuming L-T4 alone (–10·2%, range –89·4% to +85·0%). However, the percentage of patients showing an increase in remnant size in the months following surgery was higher in Gr. L-T4 than in Gr. L-T4 + I (22/60 *vs.* 9/66; *P* = 0·01).

In Gr. L-T4 patients the thyroid remnant volume variation throughout 12 months of treatment was correlated significantly with the size of the thyroid remnant found at the first ultrasound evaluation (R^2 = 0·3; *P* < 0·001). No such correlation was found in Gr. L-T4 + I patients, for whom the therapy maintains a similar effectiveness in patients with either a large or a small postsurgery thyroid remnant.

In patients treated with L-T4 alone, the remnant volume variation was correlated significantly with the median serum TSH values attained in the course of treatment (R^2 = 0·4; *P* < 0·001). The highest reduction in remnant volume was observed only by lowering the serum TSH concentrations. In patients treated with L-T4 plus iodine, instead, the thyroid remnant volume reduction occurred independently of the plasma TSH levels attained in the course of treatment.

CONCLUSIONS Our short-term prospective and randomized study leads us to conclude that, in patients living in a moderate iodine-deficient area and undergoing thyroid surgery for nontoxic goitre: (1) the iodine prophylaxis improves the effects of postsurgery nonsuppressive L-T4 therapy on thyroid remnant size. (2) In patients treated with L-T4 alone the therapeutic effectiveness decreases in the presence of a large postsurgery thyroid remnant. With the addition of iodine, the L-T4 maintains a similar efficacy in patients with either a large or a small remnant. (3) During treatment with L-T4 alone the highest therapeutic effectiveness is attained by lowering the plasma TSH concentration. With the addition of iodized salt to the daily diet the effects of L-T4 on remnant size are relevant independently of the TSH levels.

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Postsurgery recurrence of nontoxic nodular goitre is a common problem for endocrinologists, especially in iodine-deficient regions (Gaitan *et al*., 1991).

Many factors contribute to goitre recurrence and the prophylactic efficacy of postsurgery L-thyroxine (L-T4) therapy is controversial (Gharib & Mazzaferri, 1998). Most studies from iodine-sufficient areas deny the effectiveness of L-T4 therapy (Persson *et al*., 1982; Geerdsen & Frolund, 1984; Berghout *et al*., 1989; Berglund *et al*., 1990; Bistrup *et al*., 1994), whereas other studies regarding endemic areas are fairly uniform in assessing the need for this treatment (Ibis *et al*., 1991; Miccoli *et al*., 1993; Kulacoglu *et al*., 2000). Iodine supplementation has been compared with L-T4 therapy in the prevention of goitre recurrence (Feldkamp *et al*., 1997), without, however, taking into account that the effectiveness of L-T4 varies according to both the extent of the surgical resection and the degree of TSH suppression (Rotondi *et al*., 2000). The risk of goitre recurrence is correlated strictly with the size of the thyroid remnant and suppressive L-T4 therapy has been advocated as the only therapeutic regimen able to prevent postintervention recurrences, especially in patients with large remnants (Ibis *et al*., 1991; Miccoli *et al*., 1993; Rotondi *et al*., 2000), despite the widely described side-effects (Biondi *et al*., 1993; Sawin *et al*., 1994; Uzzan *et al*., 1996; Parle *et al*., 2001).

In patients affected by endemic nontoxic goitre, iodine alone or in combination with L-T4 has been proposed as an efficient alternative therapeutic tool to treatment with L-T4 alone (Hintze *et al*., 1989; Einenkel *et al*., 1992; La Rosa *et al*., 1995). Among the advantages derived from this combination is the possibility of using lower doses of L-T4 with less TSH suppression than that attained in the course of L-T4 monotherapy (Nauman *et al*., 1996). It is not clear whether the iodized salt prophylaxis could guarantee the same effectiveness produced by the iodine substances used in the previous studies (Hintze *et al*., 1989; Einenkel *et al*., 1992). Moreover, the literature lacks data on the possibility of performing the iodized salt prophylaxis in addition to L-T4 for the prevention of postsurgery nodular goitre recurrence in thyroidectomized patients living in iodine-deficient areas.

The aim of this prospective and randomized study was to investigate whether the simple addition of iodized salt to daily diet could influence the effectiveness of nonsuppressive L-T4 therapy on thyroid remnant size, during 1-year of follow-up after thyroid surgery for nontoxic goitre.

Patients and methods

Patients

From January 1997 to January 2000 a consecutive series of selected 139 patients (26 males, 113 females; median age 45 years, range 30–69 years) undergoing thyroid surgery for multinodular goitre at the Second University of Naples was enrolled. All patients live in the surrounding areas of Naples, a region known to be moderately iodine deficient (Nasti *et al*., 1998). Fifty-two patients underwent a near-total thyroidectomy, whereas in the remaining 87 patients different degrees of bilateral thyroidectomy were performed. All patients gave informed consent to the study, and the protocol was approved by the local ethical committee. At the study entry, the exclusion criteria were: (1) presurgical diagnosis of toxic goitre; (2) clinical and/or histological diagnosis of thyroid autoimmunity; (3) histological diagnosis of thyroid cancer; (4) assumption of iodized salt before thyroid surgery; and (5) urinary iodine excretion above 100 µg/l.

Design

At discharge, the patients were assigned randomly to two different therapeutic regimens (L-T4 alone or L-T4 + I) by a centralized computer algorithm that stratified enrolment according to the sex of the patient. Seventy patients (15 M, 55 F) received L-T4 therapy alone (Gr. L-T4), while the remaining 69 patients (11 M, 58 F) took iodized salt on a daily basis in addition to L-T4 treatment (Gr. L-T4 + I). The starting L-T4 dose was 1·5 µg/kg/day, which in our experience has been shown to be intermediate between suppressive and replacement doses (Rotondi *et al*., 2000). Levels of serum free T3 (FT3), free T4 (FT4) and TSH were evaluated 1, 2, 6 and 12 months after surgery. To avoid the risks of mild thyrotoxicosis and to limit the excessive TSH stimulation of thyroid remnants, the L-T4 dose was adjusted in those patients of both groups with serum TSH levels outside the lowest two-thirds of the normal range (0·3–2·5 mU/l). No significant difference in L-T4 final doses was demonstrated between the two therapeutic groups (Table 1).

At 30–60 days after surgery an ultrasound evaluation of thyroid remnant size was performed. At this time none of the patients showed thyroid nodules in the postsurgical remnant. The estimation of remnant size was repeated after 12 months.

At the end of the follow-up, urinary iodine excretion was evaluated and an appropriate questionnaire was distributed to all patients to determine the compliance to treatment. Three Gr. L-T4 + I patients were lost to follow-up. The remaining 66 Gr. L-T4 + I patients had used iodized salt regularly and showed urinary iodine above 100 µg/l at the end of the study. Ten Gr. L-T4 patients were excluded from the study because seven of them had consumed iodized substances in the 12 months following thyroid surgery, and the other three patients showed urinary iodine above 100 µg/l at the end of the study. The remaining 60 patients showed urinary iodine below 100 µg/l at the end of the study. Therefore, 126 patients (66 in group L-T4 + I and 60 patients in group L-T4) were considered for the clinical evaluation. The two therapeutic groups maintained the characteristics determined by the stratified randomization (Table 1).

Table 1 Baseline and post-therapy characteristics of Gr. L-T4 and Gr. L-T4 + I patients

Variable	Gr. L-T4	Gr. L-T4 + I
No. cases	60	66
Age (years)	43 (34–69)	47 (30–57)
Females/males	45/15	58/8
Thyroid remnant size (ml)		
At the first ultrasound scan	3·5 (0·4–13·9)	4·6 (0·5–12·7)
At the end of follow-up	2·2 (0·2–18·5)	2·4 (0·3–20·8)
Change in remnant volume in course of therapy (%)	−10·2 (−89·4 to +85·0)	−39·7 (−87·0 to +91·2)*
Serum TSH values (mU/l) in course of treatment	0·9 (0·3–2·4)	1·0 (0·3–2·2)
Serum FT3 values (pmol/l) in course of treatment	4·6 (3·1–5·8)	4·8 (3·5–6·0)
Serum FT4 values (pmol/l) in course of treatment	16·7 (11·6–22·3)	18·0 (14·1–21·9)
L-T4 dose (μg/kg/day)	1·5 (1·0–1·9)	1·4 (0·8–1·8)

The values are expressed as median and range.
*$P = 0{\cdot}006$ for the comparison with the patients in Gr. L-T4.

Biochemical assays

Serum FT3 and FT4 were assayed by double antibody radioimmunoassay (RIA) using commercial kits from Technogenetics, Milan, Italy, and TSH was assayed by an immunoradiometric method using a commercial kit from Dia-Sorin, Saluggia, Italy. Samples were assayed in duplicate for each hormone. Quality control pools at low, normal and high for all hormones were present in each assay. The detection limit of the assays and the intra- and interassay coefficients of variation were, respectively: 1·2 pmol/l, 2·9% and 4·7% for FT3; 1·3 pmol/l, 3·0% and 5·7% for FT4; 0·05 mU/l, 3·1% and 4·2% for TSH. In our laboratory, normal values were 3·8–7·7 pmol/l for FT3, 9·0–23·1 pmol/l for FT4 and 0·3–3·5 mU/l for TSH. Urinary iodine excretion was assayed in extemporary samples by a colorimetric rapid test (Urojod-Test, Merk KgaA, Germany) with a semiquantitative determination of iodide. This method classifies the urinary iodine values in three groups: < 100 μg/l, 100–300 μg/l, and > 300 μg/l.

Ultrasound evaluation

The instrument used was a Toshiba 250, with a 7·5 MHz transducer. All ultrasound evaluations were performed by the same operator (G.Z.) ‘blinded’ with regard to the group to which the patient belonged. Thyroid volume was calculated using the formula of a rotation ellipsoid model: width × length × thickness × 0·52 for each lobe. The coefficient of variation for repeated measurements, in a series of 10 triplicate scans in a period of less than 1 month, was not higher than 9·5%. Thyroid remnant volume variation of at least 10% was regarded as significant.

Statistical methods

Results are expressed as medians and ranges. Paired and unpaired data were compared by Wilcoxon and Mann–Whitney tests, respectively. Linear regression analysis was performed to evaluate the correlation between two continuous variables. Frequencies among different groups were compared by χ^2 and Fisher’s exact tests. A P-value < 0·05 was considered significant.

Results

The postintervention median thyroid remnant volume of the entire group was 4·1 ml (range 0·4–13·9 ml). After 1 year of follow-up, it decreased to 2·4 ml (range 0·2–20·8 ml) with a median change of −21·7% (range −89·4% to +91·2%). Seventy-nine patients (30 of Gr. L-T4, 49 of Gr. L-T4 + I) were responders to treatment with median reduction of thyroid remnant size of −49·0% (range −10·2% to −89·4%). On the contrary, 47 patients were nonresponders (30 of Gr. L-T4, 17 of Gr. L-T4 + I): in particular, 31 patients, despite therapy, demonstrated a significant increase in remnant size (ranging from +10·0% to +91·2%), whereas in 16 patients no variation in thyroid remnant volume was observed throughout the follow-up.

Taking into account the different therapeutic regimens, after 1 year of follow-up the patients treated with L-T4 + I showed a remnant volume reduction (−39·7%, range −87·0% to +91·2%), significantly ($P = 0{\cdot}006$) greater than that observed in patients taking L-T4 alone (−10·2%, range −89·4% to +85·0%) (Table 1, Fig. 1). The percentage of responder patients was significantly lower in Gr. L-T4 than in Gr. L-T4 + I (30/60 *vs.* 49/66; $P = 0{\cdot}006$). However, the percentage of patients showing an increase in remnant size in the months following surgery was higher in Gr. L-T4 than in Gr. L-T4 + I (22/60 *vs.* 9/66; $P = 0{\cdot}01$).

Figure 2a,b show the results of the linear regression analysis performed separately for the two therapeutic groups to demonstrate whether the percentage of variation in remnant volume was correlated with the remnant size estimated at the first ultrasound evaluation. In Gr. L-T4 patients the thyroid remnant volume variation during the treatment correlated significantly with the size

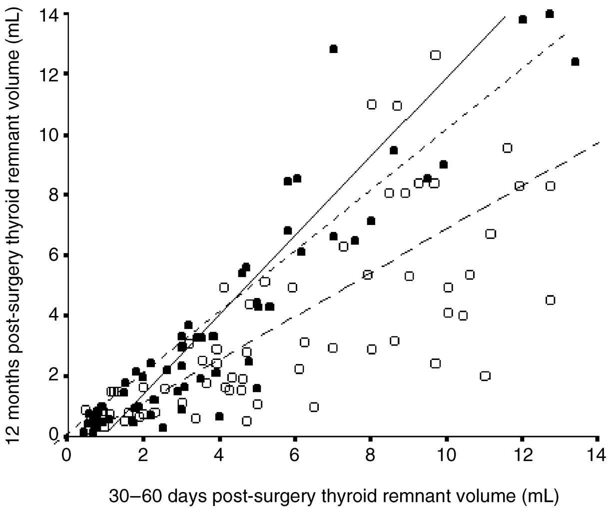

Fig. 1 Individual scatter plots of remnant volume (ml) 30–60 days postsurgery and at the end of 12 months' follow-up in 126 patients undergoing surgery for nontoxic goitre. The broken line going through the origin is an expression of the predicted values in the absence of any volume variation occurring during the 12 months of treatment. The values on the left and on the right of this line indicate an increase and a reduction in remnant size, respectively, in the course of treatment. For each therapeutic group (●, Gr. L-T4; ○, Gr. L-T4 + I) a graphical representation of the linear regression analysis is presented (dashed line, Gr. L-T4; solid line, Gr. L-T4 + I).

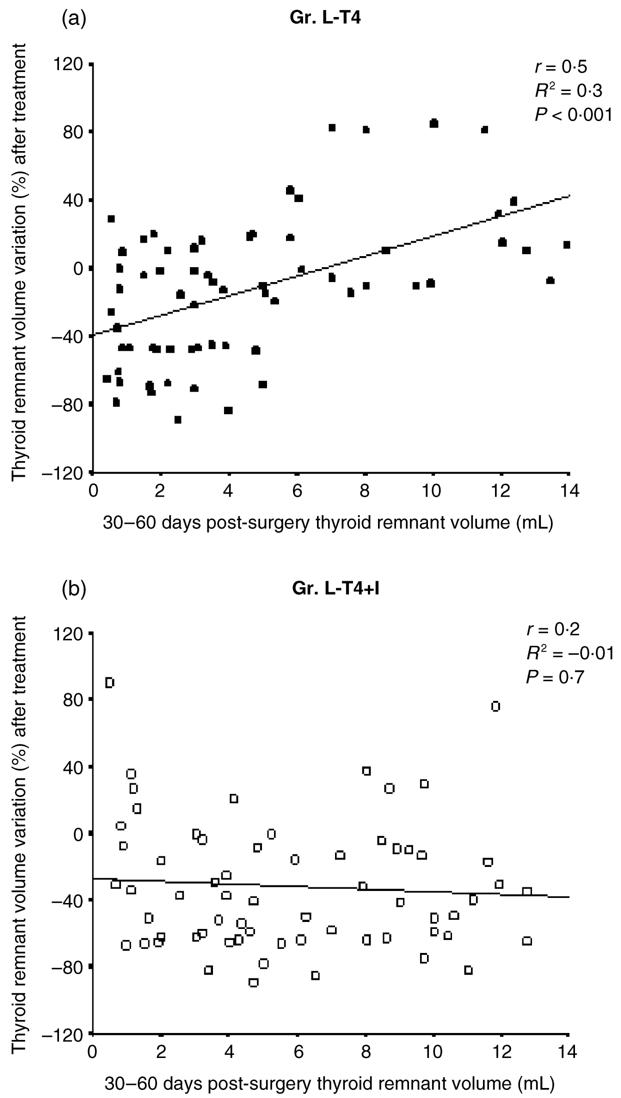

Fig. 2 Linear regression analysis performed separately for therapeutic groups (a) (●, Gr. L-T4) and (b) (○, Gr. L-T4 + I) to evaluate whether the percentage of thyroid remnant variation in the course of treatment was correlated with the thyroid remnant size estimated 30–60 days after surgery.

of the thyroid remnant at the first ultrasound evaluation ($R^2 = 0{\cdot}3$; $P < 0{\cdot}001$) (Fig. 2a). No such correlation was not found in Gr. L-T4 + I patients, in whom the therapy maintains a similar effectiveness in patients with either a large or a small postsurgery thyroid remnant (Fig. 2b).

Figure 3a,b shows the results of the linear regression analysis performed separately for the two therapeutic groups to demonstrate whether the percentage of variation in remnant volume was correlated with the serum TSH values attained in the course of therapy. In patients treated with L-T4 alone, the remnant volume variation correlated significantly with the median serum TSH values attained in the course of treatment ($R^2 = 0{\cdot}4$; $P < 0{\cdot}001$) (Fig. 3a). In fact, the highest reduction in remnant volume was observed only by lowering the serum TSH concentrations. In patients treated with L-T4 plus iodine, instead, the thyroid remnant volume reduction occurred independently from the median TSH levels attained in the course of treatment (Fig. 3b).

Discussion

This prospective and randomized study shows that in patients thyroidectomized for nontoxic goitre the combination of iodized salt prophylaxis with L-T4 therapy induces a significantly higher remnant volume reduction, regardless of serum TSH values, than that observed in the course of treatment with L-T4 alone. The therapeutic effectiveness of L-T4 decreases in the presence of a large postsurgical thyroid remnant; such impairment is reversed by the addition of iodine to L-T4 treatment.

The prevention of goitre recurrence is of great clinical concern, especially in iodine-deficient areas (Gaitan *et al.*, 1991; Miccoli *et al.*, 1993; Feldkamp *et al.*, 1997; Kulacoglu *et al.*, 2000; Rotondi *et al.*, 2000). In cases of goitre recurrence, a second surgical intervention is often required, with increased risk

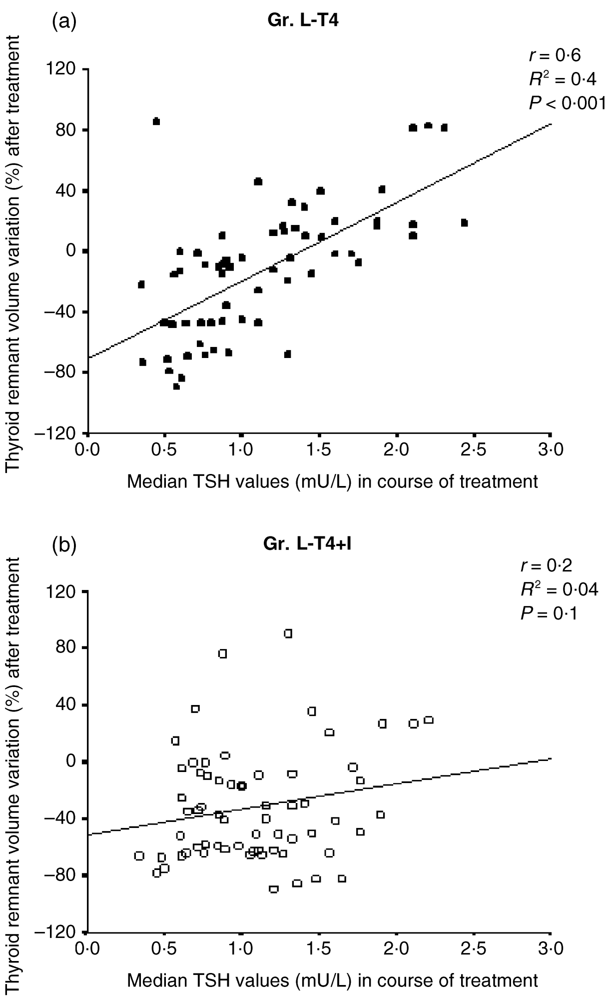

Fig. 3 Linear regression analysis performed separately for therapeutic groups (a) (●, Gr. L-T4) and (b) (○, Gr. L-T4 + I) to evaluate whether the percentage of thyroid remnant variation in the course of treatment was correlated with the median TSH levels attained in the course of treatment (evaluations after 1, 2, 6 and 12 months of treatment).

of serious complications (Reeve *et al*., 1988). Different criteria for the definition of recurrence have been proposed (Hegedus *et al*., 1989, 1999; Miccoli *et al*., 1993). Although the most reliable objective method to assess goitre recurrence has been defined as the ultrasound detection of newly appeared nodular lesions (Miccoli *et al*., 1993; Rotondi *et al*., 2000), in a short-term follow-up the choice of a more sensitive marker of goitre regeneration is needed. The generation of thyroid nodules is a slow process (Studer & Derwhal, 1995) and the postoperative nodular recurrence rate increases in proportion to the length of the surveillance period (Ibis *et al*., 1991; Cooper, 1995). For these reasons, as suggested by others (Hegedus *et al*., 1989, 1999), we have considered the variation in remnant volume as a marker of response to therapy.

In iodine-deficient areas L-T4 therapy has been advocated as a useful tool to hinder the recurrence of nontoxic nodular goitre (Ibis *et al*., 1991; Miccoli *et al*., 1993; Kulacoglu *et al*., 2000). Because of the high sensitivity to TSH of the iodine-depleted thyroid gland (Bray, 1968; Brabant *et al*., 1992), suppressive L-T4 therapy is needed for the prevention of postintervention goitre recurrence (Ibis *et al*., 1991; Miccoli *et al*., 1993). However, the potential risks of such therapy prevents its extension, especially to older subjects (Biondi *et al*., 1993; Sawin *et al*., 1994; Uzzan *et al*., 1996; Parle *et al*., 2001), leading to a search for alternative therapeutic tools. In this study we have performed an L-T4 nonsuppressive treatment maintaining the TSH values in the lowest two-thirds of the normal range. By using this therapeutic regimen, we have observed a significant reduction in postsurgery thyroid remnant in about half of our patients. A previous report demonstrated that a significant decrease in thyroid remnant volume occurred 12 months after surgery for nontoxic nodular goitre both in patients treated with L-T4 and in those without this therapy (Hegedus *et al*., 1989). When our study was designed, the widespread use of L-T4 treatment for the management of thyroidectomized patients living in iodine-deficient areas prevented the possibility of a control placebo group. Thus, we cannot now confirm whether or not the variations in remnant size in our patients were dependent on L-T4 therapy. However, we have demonstrated that the thyroid remnant volume reduction occurring in the course of treatment with L-T4 alone was correlated strictly to the degree of reduction of serum TSH values, suggesting that some inhibition effect on cell proliferation is possible with TSH levels at the lowest limit of the normal range, as suggested previously (Pacini & De Groot, 2001). In these cases, the TSH measurement can be considered a reliable marker to predict the therapeutic response to L-T4. Moreover, other local growth factors, besides TSH, could be involved in the regulation of thyroid cell growth (Gartner *et al*., 1985; Derwahl *et al*., 1999). The existence of these factors could explain the fact that a significant number of our patients showed an increase in thyroid remnant size regardless of L-T4 or L-T4 + I treatment.

need to clarify what this means

In patients thyroidectomized for nontoxic goitre living in iodine-deficient areas, iodine alone has been proposed as the only therapeutic tool for preventing goitre recurrences (Feldkamp *et al*., 1997). In our experience, daily iodine supplementation for 12 months has improved the effectiveness of nonsuppressive L-T4 therapy in patients undergoing thyroid surgery for nontoxic goitre, such as was demonstrated previously in nonoperated patients with nodular goitre (Hintze *et al*., 1989; Einenkel *et al*., 1992). In our view, this is an interesting finding that could be explained by the restored sensitivity of the thyroid to TSH (Stubner *et al*., 1987) and the morphological modifications of follicular structure induced by iodine supplementation

(Einenkel *et al*., 1992). Our study design did not permit us to clarify whether the iodine alone was as effective as its combination with L-T4, as we did not consider a group of patients treated with iodine alone. However, we believe that both iodine prophylaxis and L-T4 treatment are needed for the efficient long-term prevention of goitre recurrence. After thyroidectomy for multinodular goitre, the remnant tissue maintains the physiopathological mechanisms responsible for the goitre development (Dumont *et al*., 1995). The iodine prophylaxis guarantees some reduction in remnant volume by restoring thyroglobulin turnover and modifying the follicle structure, but it is not able to completely limit the growth of those cells with higher proliferation capacity (Stubner *et al*., 1987; Einenkel *et al*., 1992). For this reason, L-T4 treatment is mandatory to minimize the effects of TSH, the major thyroid stimulator, on remnant tissue. However, our results encourage the association of the iodine prophylaxis with the L-T4 treatment for improving the therapeutic effects. In this view, whilst in patients taking L-T4 alone the effectiveness of L-T4 is closely correlated to very low serum TSH levels attained during the treatment, in patients under combined therapy (LT4 + iodine prophylaxis) a comparable efficacy could be obtained without performing a suppressive regimen.

Patients who undergo thyroid surgery for nontoxic nodular goitre are not a homogeneous category, as the degree of thyroid excision is a major determinant for the subsequent outcome (Rotondi *et al*., 2000). It has been reported previously that patients with extensive thyroid resection show a low risk of postintervention recurrence, regardless of the L-T4 therapeutic regimen (suppressive or replacement), while those with a large remnant run a high risk of goitre recurrence, especially when L-T4 treatment is performed at nonsuppressive doses (Hegedus *et al*., 1999; Rotondi *et al*., 2000). The present experience suggests that iodine can improve the effectiveness of L-T4 nonsuppressive therapy in patients with a large remnant volume, although only a longer follow-up will enable us to evaluate whether the risk of recurrence is modified.

Our short-term prospective and randomized study leads us to conclude that, in patients living in a moderate iodine-deficient area and undergoing thyroid surgery for nontoxic goitre: (1) the iodine prophylaxis improves the effects of postsurgery nonsuppressive L-T4 therapy on thyroid remnant size. (2) In patients treated with L-T4 alone the therapeutic effectiveness decreases in the presence of a large postsurgery thyroid remnant. With the addition of iodine, the L-T4 maintains a similar efficacy in patients with either a large or a small remnant. (3) During treatment with L-T4 alone the highest therapeutic effectiveness is attained by lowering the plasma TSH concentration. With the addition of iodized salt to daily diet the effects of L-T4 on remnant size are significant without the TSH suppression. Therefore, our results encourage the spread of iodized salt prophylaxis to patients undergoing thyroid surgery for nontoxic goitre, thus suggesting its association with nonsuppressive L-T4 doses as an effective alternative tool to the suppressive therapeutic regimen, especially in patients with a large thyroid remnant tissue.

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