

TREATMENT OF GOITER AND NODULES IS SUCCESSFUL WITH NON-TSH-SUPPRESSING DOSES OF THYROXINE PLUS IODINE

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SUMMARY ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ●

INTRODUCTION

Thyroid nodules and multinodular or diffuse goiters are frequent clinical findings, particularly since ultrasound examinations have become routine. In some European countries with moderate iodine deficiency, goiters and or thyroid nodules can be found in one third of the elderly adult population. For many decades the standard nonsurgical treatment for both conditions was to administer thyroxine at doses high enough to suppress serum thyrotropin (TSH) to <0.2 or <0.1 mU/L. With this approach, volume reduction of nodules was not only unpredictable and highly variable, but side effects were frequent, in particular atrial fibrillation and a tendency toward osteopenia in postmenopausal women. With progress in ultrasound examination, more precise studies could be undertaken, and some studies have indicated that even a partial inhibition of thyroid function, with serum TSH levels remaining above 0.2 mU/L, was still able to reduce thyroid or nodule volume to some extent, but only in some patients. Therefore, there was never any agreement as to whether this method deserved widespread clinical application. Some authors have recommended the addition of iodide for reduction of thyroid volume. In the present German multicenter study, carried out in a modestly iodine-deficient population, three treatment groups were compared and evaluated against placebo. One group of patients received thyroxine only (approximately 75 µg per day), another 150 µg of iodide only, and the third thyroxine plus 150 µg of iodide.

METHODS AND RESULTS

In more than 60 centers, a total of 1013 patients were investigated. The observation period was 12 months. Warm nodules and pretreated patients

were excluded. Since the quality and precision of the ultrasound evaluation was crucial for the study, two test phantoms with six different nodules had to be evaluated by each center. The coefficient of variation of the different estimations was quite high, 10% to 11%. For TSH suppression, the target was 0.2 to 0.8 mU/L. This was obtained with an average dose of 75 µg of thyroxine per day. There was no difference in the decrease of serum TSH if thyroxine alone or thyroxine plus iodide was given. In the first 3 months, the serum TSH decreased to 0.2 mU/L and increased thereafter to 0.6 mU/L, possibly because of minor adjustments of treatment. As expected in Germany, iodide excretion before treatment was rather low, approximately 60 µg/L in all groups (World Health Organization recommendation, >100 µg/L).

Reduction of the total thyroid volume was significant as compared with the placebo group, but even in the best-responding group (the one treated with thyroxine plus iodide) it did not exceed 10%. For thyroid nodules, the results of volume changes were more interesting. All treated groups showed significant reductions in volume. The highest success rate—a 17% reduction of nodular volume—was obtained with the combined treatment of thyroxine plus iodide. With thyroxine alone or with iodide alone, the nodular volume reductions were not significant (−7% and −4%). The volume of the nodules in patients treated with thyroxine plus iodide seemed to decrease continuously over the 12 months, whereas for the other two groups, the volume reduction was seen only in the first 3 months. Yet, even though the thyroid nodules treated with thyroxine plus iodide decreased in volume, the response of the individual cases was quite variable. Surprisingly, in 26% of these cases the volume increased even under treatment.

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CONCLUSIONS

In a moderately iodine-deficient area, 12 months of treatment with thyroxine plus iodide significantly reduced thyroid nodule size. The decrease in volume seemed to be a continuous process until the end of the observation period. However, 26% of the cases were not only nonresponders, but the size of the nodule increased with thyroxine plus iodide treatment.

These results were obtained with only partial TSH suppression. Indeed, serum TSH levels in the second half of the treatment period were 0.6 mU/L, a level certainly not associated with any side effects. The volume reduction of the nodules with thyroxine treatment alone or iodide alone did achieve a small but nonsignificant volume reduction. The effects on total thyroid volume have to be considered marginal.

COMMENTARY ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ●

This is a large multicenter study performed in a country with moderate iodine deficiency. Under these circumstances, the treatment with a moderate dose of thyroxine combined with 150 µg of iodide for thyroid nodules is clearly superior to a treatment with thyroxine or iodide alone. The effect of the combined treatment was surprising, because the results were obtained with an average serum TSH of 0.6 mU/L, which is likely to be well tolerated. The volume decrease was 17%, as compared with the placebo group. This reduction is significant but not remarkable. There was, in addition, a large variability of individual responses. In some cases, the volume reduction exceeded 50%, while in 26% of cases the volume of the nodule even increased. This is not unexpected, since in benign nodules growth is not necessarily dependent on TSH-mediated mechanisms. For instance, a recent study showed that benign nodules bearing RET/PTC rearrangements and mutations were particularly prone to rapid growth (1); 15% of all investigated nodules were positive for

these gene alterations. This number is about the same order of magnitude as that seen in the study under discussion for nodules increasing under treatment.

An important question remains unanswered. In areas of sufficient iodine supply, is this combined treatment of thyroxine plus iodide superior to thyroxine alone? In these areas, most endocrinologists do not advise suppressive treatment with thyroxine and rely on the growth rate of the nodule for choosing clinical follow-up alone or surgery. Still, since the effect of the combined treatment with thyroxine plus iodide was possibly not simply an additive effect of the two components, it is possible that this treatment could show some beneficial results in a subgroup of thyroid nodules, even in the presence of adequate iodine intake. The heterogeneity of clinically relevant responses favors the hypothesis that a successful treatment would be limited to possible subgroups of thyroid nodules. Therefore, careful ultrasound follow-up under treatment is certainly indicated.

— Albert G. Burger, MD

REFERENCE

1. Sapiro MR, Guerra A, Marotta V, Campanile E, Formisano R, Deandrea M, Motta M, Limone PP, Fenzi G, Rossi G, Vitale M. High growth rate of benign thyroid nodules bearing ret/ptc rearrangements. *J Clin Endocrinol Metab* 2011;96:E916-9. Epub March 16, 2011.