

# JOURNAL OF ENDOCRINOLOGICAL INVESTIGATION

Official Journal of the Italian Society of Endocrinology

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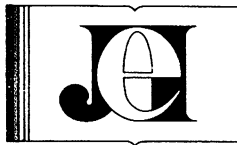
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Volume 5, 1982

Pages 1-454



**Bayerische  
Staatsbibliothek  
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# Iodine contamination as a cause of hyperthyroidism or lack of TSH response to TRH stimulation (Results based on a screening investigation)<sup>1</sup>

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**ABSTRACT.** The sera of all patients with completely suppressed TSH response to TRH obtained during one year ( $n = 668$ ), and of those with diminished TSH response ( $n = 153$ ) were screened for total serum iodine content. The ratio between serum iodine and thyroxine iodine below 1.5 indicates none or only a minor degree of iodine contamination, whereas a ratio above 1.5 is a clear index of exogenous iodine contamination. Eighty-four (21.3%) of 395 patients with overt hyperthyroidism were iodine contaminated. No prevalence of hyperthyroidism with hyperthyroxinemia could be detected as compared to  $T_3$ -hyperthyroidism in the contaminated groups. Surprisingly, the iodine contamination rate was twice as high in 273 patients with suppressed TSH response to TRH but normal thyroid hormone levels and not fully explained thyroïdal diseases. A high incidence of multifocal autonomous adenomas of the thyroid is the most probable explanation for the TSH suppression in iodine contaminated patients with normal thyroid hormone levels.

## INTRODUCTION

The increasing use of iodine containing compounds in radiographic investigations and the widespread therapy with iodine containing drugs and antiseptics have induced a variety of reports concerning the influence of these substances on thyroid hormone metabolism (1-4). At the same time, advanced diagnostic tools permit to distinguish the different forms of hyperthyroidism and focus the interest of thyroidologists on autonomous abnormalities of the thyroid gland in iodine deficiency areas (5-9). In this context, the incidence of iodine-induced hyperthyroidism in hospitalized patients as well as in outpatients is still in dispute. Therefore, we have tried to obtain some information about the frequency of iodine contamination in patients with disorders of thyroid function. Furthermore, the influence of water-soluble contrast media on thyroïdal iodine ( $^{127}\text{I}$ ) uptake in euthyroid patients was investigated.

## MATERIALS AND METHODS

To study the influence of iodine containing water-soluble contrast media, thyroid function ( $T_4$ ,  $T_3$ , thyroxine-binding-globulin (TBG), TSH, TRH test) and total iodine in serum and urine were investigated before and after coronary angiography (200 ml Meglumaminotrizoate 76% (Urografin®)  $\approx 74$  g iodine) in patients with coronary heart disease ( $n = 25$ ). Thyroïdal  $^{127}\text{I}$  content was determined by fluorescent scintigraphy and sonography (8). Iodine content in euthyroid controls was found to be between 250 and 500  $\mu\text{g/g}$  of thyroid tissue. Statistical significance was calculated by the paired Wilcoxon rank test.

To investigate the incidence of iodine-induced hyperthyroidism, all sera of patients with suppressed TSH response to TRH ( $n = 668$ ), and of those with diminished TSH response to TRH ( $n = 153$ , TSH 30 min after  $\text{TRH} < 3.0 \mu\text{U/ml}$ ) obtained during one year, as well as sixty age and sex matched in and outpatients of our hospital without thyroid disorders and normal TRH tests were screened for total serum iodine (10).

Suppression of TSH response to TRH was defined as a basal TSH below the limit of detection without measurable TSH increase after 200  $\mu\text{g}$  TRH iv. The underlying thyroïdal diseases could not yet be defined fully in most cases.

$T_4$ ,  $T_3$ , TBG and TSH were determined by radioimmunoassay, as previously described (11-13). The ratio of serum iodine over thyroxine iodine ( $\text{PBI}/T_4\text{I}$ ) was calculated. Values up to 1.5 indicate normal relationship between serum iodine content and thyroid hor-

<sup>1</sup>This work was supported by the Bundesministerium d. Inneren (AZ. St. Sch. 790c)

**Key-words:** Hyperthyroidism, TSH nonresponders to TRH, iodine contamination.

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Received August 20, 1981; accepted January 29, 1982.

Table 1 - Urinary iodine excretion, stable iodine content of thyroidal tissue and thyroid function before and after iodine load following coronary angiography in 26 euthyroid patients with coronary heart disease<sup>1</sup>.

	After coronarography			
	Basal value	1 week	2 weeks	8 weeks
iodine excretion ( $\mu\text{g/g}$ creatinine)	46 $\pm$ 37	440 $\pm$ 276	86 $\pm$ 52	52 $\pm$ 23
PBI/T <sub>4</sub> I	1.3 $\pm$ 0.3	1.7 $\pm$ 0.5	1.4 $\pm$ 0.2	1.4 $\pm$ 0.2
<sup>127</sup> I content in thyroid tissue ( $\mu\text{g/g}$ )	208 $\pm$ 104	214 $\pm$ 81	251 $\pm$ 103	235 $\pm$ 97
T <sub>4</sub> /TBG	3.8 $\pm$ 0.9	4.1 $\pm$ 0.9	4.2 $\pm$ 0.9	4.0 $\pm$ 0.5
T <sub>3</sub> /T <sub>4</sub>	25 $\pm$ 8	20 $\pm$ 6	22 $\pm$ 4	21 $\pm$ 4
TSH increase 30 min after TRH ( $\mu\text{U/ml}$ )	7.8 $\pm$ 3.2	6.8 $\pm$ 4.6	5.3 $\pm$ 3.4	6.2 $\pm$ 3.7

<sup>1</sup>All values are means  $\pm$  SD

more levels or only a minor degree of exogenous iodine contamination, whereas a ratio of 1.5 and more was undoubtedly indicative for exogenous iodine application (6).

## RESULTS

After coronary angiography in euthyroid patients, the urinary excretion of iodine was elevated above the initial value up to 14 days ( $p < 0.025$ ) whereas the PBI/T<sub>4</sub>I ratio was normalized after 2 weeks (Table 1). In these patients, the initially low iodine content of the thyroid increased only by about 20.6% after 14 days. In coincidence with this limited increase of the thyroidal iodine, the TSH response to TRH decreased ( $p < 0.015$ ), the T<sub>4</sub>/TBG ratio increased and the initially elevated T<sub>3</sub>/T<sub>4</sub> ratio decreased. All these functional changes remained within the normal range.

Among the patients with suppressed TSH response to TRH, we found four different groups:

- i) 239 patients with hyperthyroidism as defined by a T<sub>4</sub>/TBG ratio above 5.7;
- ii) 156 with T<sub>3</sub>-hyperthyroidism, which means normal T<sub>4</sub>/TBG ratio (1.8 to 5.7) but elevated total T<sub>3</sub> levels over 200 ng/dl;
- iii) 273 patients with normal thyroid hormone levels but suppressed TSH response to TRH stimulation;
- iv) 153 patients with diminished TSH response, as defined by a TSH increase below 3.0  $\mu\text{U/ml}$  30 min after 200  $\mu\text{g}$  TRH iv.

A PBI/T<sub>4</sub>I ratio above 1.5 was found in 42 (17.6%) of the patients with hyperthyroidism and again in 42 (26.9%) of the patients with T<sub>3</sub>-hyperthyroidism. This means that 84 (21.3%) of the patients with overt hyperthyroidism were iodine contaminated, whereas the iodine contamination rate was only 10% in the 60

control patients. This difference is significant on the 5% level by means of Chi-square test.

In the whole group of «nonresponders» to TRH (n = 668) we found 273 patients with normal T<sub>4</sub> and normal or decreased T<sub>3</sub> levels, who did not receive any thyroid hormone therapy (Fig. 1). A PBI/T<sub>4</sub>I ratio above 1.5 was observed in 86 patients of the latter subgroup, indicating that 39.3% were iodine contaminated. Among these patients 16 had a normal T<sub>4</sub>/TBG ratio and a suppressed TSH response to TRH stimulation but a decreased total T<sub>3</sub> level («low T<sub>3</sub> syndrome»). Fourteen of these had an elevated PBI/T<sub>4</sub>I ratio, indicating iodine contamination in 87.5% in this special subgroup.

The total incidence of increased PBI/T<sub>4</sub>I ratio in the group of TSH «nonresponders» to TRH was 29.2%.

In the group of patients with diminished TSH response to TRH 58 out of 153 had an increase in serum iodine content reflecting an incidence of 37.9% of exogenous iodine contamination.

## DISCUSSION

The increase of iodine content in the thyroid and the T<sub>4</sub>/TBG ratio in serum as well as the decrease of T<sub>3</sub>/T<sub>4</sub> ratio after coronarography indicate again (14, 15) the reversibility of a «relative T<sub>3</sub> hypersecretion» in iodine deficient states by iodine application (16).

In the group of patients with «euthyroid» function, the intrathyroidal iodine metabolism was influenced by the contrast media used, but the thyroidal uptake of stable iodine was only limited and hyperthyroidism has been induced in none of these patients (6).

Iodine contamination may have contributed to the manifestation of hyperthyroidism in patients with overt hyperthyroidism in more than 10%. Surprisingly, the

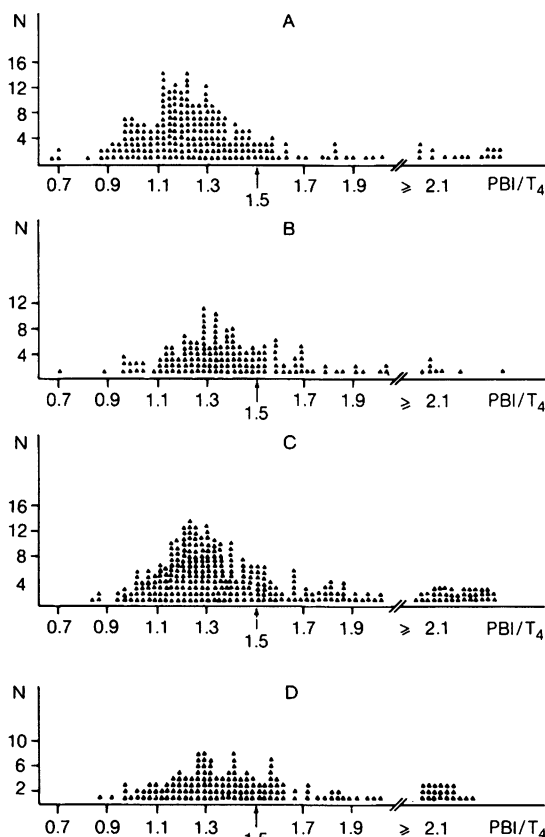


Fig. 1 - Incidence of iodine contamination in patients with hyperthyroidism ( $n = 395$ ), patients with normal thyroid hormone levels and suppressed TSH response to TRH ( $n = 273$ ) and patients with diminished TSH response to TRH ( $n = 153$ ). Hyperthyroidism (panel A) is defined as  $T_4/$ TBG ratio over 5.7 and suppressed TSH response to TRH.

$T_3$ -hyperthyroidism (panel B) means  $T_4/$ TBG ratio  $\leq 5.7$ ,  $T_3$  levels above 200 ng/dl, and suppressed TSH response.

Normal thyroid hormone levels, suppressed TSH response (panel C) means  $T_4/$ TBG ratio  $\leq 5.7$ , total  $T_3$  levels < 200 ng/dl and suppressed TSH response.

Diminished TSH response to TRH (panel D) means a TSH increase < 3.0  $\mu$ J/ml 30 min after 200  $\mu$ g TRH iv.

iodine excess did not induce preferentially hyperthyroidism with hyperthyroxinemia, since we found in the group of  $T_3$ -hyperthyroidism an equal number of  $PBI/T_4$  ratios above 1.5. These results indicate that iodine supplementation does not play a major role in the development of «  $T_4$ -hyperthyroidism ».

The contamination rate was twice as high in patients with a suppressed TSH response to TRH but normal thyroid hormone levels and not fully defined thyroidal diseases as compared to overt hyperthyroidism. With regard to this finding, the incidence of endemic goiter in the Bavarian iodine deficiency area has to be considered, which is 32% in young males (17) and nearly 55%

in an unselected group of adults (18). In long-standing goiters, the development of autonomous adenomas or multifocal autonomous areas has been shown by Miller et al. (19) and Studer et al. (20), and hyperthyroidism after iodine supplementation of those patients was observed repeatedly (3, 5, 9, 21-24). Our data indicate that the excess of exogenous iodine may result in overt hyperthyroidism, but the incidence of suppression of TSH secretion without detectable hyperthyroidism is more frequent. These screening data give no insight in the natural history of these patients and no information of subsequent hyperthyroidism can be given. The preliminary conclusion is that a follow-up of thyroid function has to be done in patients with goiter after an exogenous iodine load, since no methods are available to predict the risk of iodine induced hyperthyroidism except in those patients with a history of Graves' disease or nodular autonomy in the thyroid.

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