NON-TOXIC GOITRE

The role of iodine deficiency in goitre formation in a non-endemic area

By

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ABSTRACT

Among 29 patients operated on for non-toxic goitre 17 had a plasma-iodine concentration and thyroid clearance within the normal range for the region while 12 patients were iodine deficient in comparison to the former group. Extensive investigations of the 29 patients were performed including chromatography of the serum, urine and thyroid-gland digest and measurement of the iodine concentration and content of the goitrous tissue.

No qualitative differences were found between the groups, on the contrary, a continuum existed, findings being related to the degree of iodine deficiency. Thus, the group with a low plasma inorganic iodine (PII) showed the largest goitres, lowest thyroid tissue iodine concentration and highest \([^{125}\text{I}]\) MIT/DIT and \([^{123}\text{I}]\) T\(_3\)/T\(_4\) thyroid-tissue ratio. In the group with a "normal" PII concentration, iodoamino acid distribution in the para-adenomatous tissue was similar to that of "normal" thyroid glands in the present region, whereas nodular tissue compared with the goitrous tissue of the most iodine deficient group. Thus, only quantitative differences were found between the groups, and it is concluded that the goitres of both groups were due to iodine deficiency.

In a region where non-toxic goitre is not endemic, we previously evaluated the dynamic pattern of iodine in 129 patients with non-toxic goitre and 27 normal controls and found that the group of non-goitrous persons had a mean
plasma inorganic iodine (PII) concentration a little higher than the group of goitrous patients (114 ng/100 ml against 89 ng/100 ml) and the thyroid clearance of iodide was lower (29 ml/min against 61 ml/min). But in fact most of the goitrous patients had a PII, thyroid clearance (thyr.cl.) and absolute iodine uptake (AIU) within normal limits for this area (Agerbæk & Jensen 1974).

The present investigation was undertaken to elucidate any possible metabolic differences between non-toxic goitrous patients with low and with high PII values in order to determine whether it is justified to classify all simple goitres as being mainly caused by iodine deficiency.

MATERIALS AND METHODS

In 29 patients with simple non-toxic goitre submitted for operation, 12 had PII values of 14-77 ng/100 ml mean 59 ng/100 ml, and 17 had PII values of 83-246 ng/ml, mean 128 ng/100 ml. These two artificially separated groups of patients, one with a low PII (group A) and the other (group B) with a PII a little higher than the mean for our normal controls were compared. Group A was composed of 11 women and 1 man, and group B of 15 women and 2 men; all the patients were clinically euthyroid and had normal values of BMR, PBI, Ts-Sephadex uptake, and serum cholesterol. The two groups were comparable regarding body weight (group A 58 kg ± 7.5 and group B 59 kg ± 10.3) (mean ± so), serum creatinine (group A 0.8 mg/100 ml ± 0.11 and group B 0.8 mg/100 ml ± 0.12), renal clearance of iodide (group A 34 ml/min ± 5.0 and group B 33 ± 7.0), BMR (group A + 1.3% ± 6.7 and group B + 1.1% ± 8.6), PBI (group A 5.0 µg/100 ml ± 0.94 and group B 5.3 µg/100 ml ± 0.88), Ts-Sephadex uptake (group A 5.7% ± 0.68 and group B 5.8% ± 0.54) (in calculations of PBI and Ts-Sephadex uptake values from 3 patients who got P-pills were excluded), and serum cholesterol (group A 250 mg/100 ml ± 39 and group B 223 mg/100 ml ± 46). Mean age in group A was 39 years ± 9 (so) and in group B 32 ± 9, a significant difference (P < 0.025). The patients were studied as previously described (Agerbæk 1972, 1973) investigations including 24 hour urinary excretion of stable iodine measured for 2-3 days, measurements of [125I] PBI, [125I] NBEI (non-butanol-extractable iodine) and total plasma radioactivity daily for seven days after a tracer dose, chromatography of serum for radioactive labelled compounds, and digestion and chromatography of thyroid gland tissue (nodular and para-nodular tissue separately) for 125I-labelled amino acids. Goitre weight was estimated at operation, and the concentration of stable iodine in the thyroid gland measured after homogenization of representative pieces of tissue and dilution with water; the final estimation was done with an autoanalyser technique set up for PBI estimations. The ability to deiodinate [125I] MIT was tested in vivo. Autoantibodies against thyroglobulin and complement-fixing serum antibodies were evaluated.

Statistics

A conventional t-test was used in all statistical calculations.
RESULTS

$^{125}$I excretion and thyroid clearance

Iodine deficiency is conventionally evaluated by measuring urinary iodine excretion: Excretion in group A (low PII) was 47 μg/24 h ± 28 (mean ± sd) and in group B 66 μg/24 h ± 25. The difference is significant with a $P < 0.05$. In group A + B a positive correlation between PII and iodine excretion was found ($r = 0.53$ and $P < 0.0025$).

In group A the mean thyroid clearance was 107 ml/min, in group B 38 ml/min ($P < 0.0125$).

Goitre size

All but two of the goitres were nodular; the two diffusely enlarged thyroids were in group A.

In group A with most severe iodine deficiency, goitre weight was 127 g ± 78 (mean ± sd) which was significantly higher than for group B, 75 g ± 38 ($P < 0.01$). The estimated mean weight of paranodular tissue in group A was 28 g and in group B 39 g.

Iodine content and concentration

No significant difference was found between the two groups as regards total iodine content of the goitres – in group A 16 mg ± 11 and in group B 14 mg ± 8 (mean ± sd) were found.

Iodine concentration in the tissues was as follows:

<table>
<thead>
<tr>
<th></th>
<th>group A</th>
<th>group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>para-adenomatous tissue</td>
<td>251 μg/g ± 177</td>
<td>395 μg/g ± 266 (mean ± sd)</td>
</tr>
<tr>
<td>adenomatous tissue</td>
<td>114 μg/g ± 79</td>
<td>125 μg/g ± 120 (mean ± sd)</td>
</tr>
</tbody>
</table>

Significantly less iodine was found in adenomatous tissue than in para-adenomatous tissue in both groups ($P < 0.05$ in group A and $P < 0.0005$ in group B). Iodine concentration in para-adenomatous tissue was greater in group B than in group A ($P < 0.05$) but no significant difference was found on comparison of adenomatous tissue in the two groups ($P < 0.35$).

A negative correlation between iodine concentration and the estimated weight of the para-adenomatous tissue could not be demonstrated.
**Chromatography of the in vivo ¹²⁵I-labelled, digested thyroid tissue**

No difference in the distribution of labelled iodoamino acids was found between the adenomatous or para-adenomatous tissue in group A and group B, but in group B a more undigested material was found at the origin of the chromatograms of para-adenomatous tissue.

The number of tissues investigated in group A was 19 because 2 goitres were diffuse and accounted as "para-adenomatous"; in 3 cases no para-adenomatous tissue was found between the nodules. In one case in group B radioactivity of adenoma was so low that only Or., DIT and MIT could be measured on chromatogram with reasonable precision; thus n = 33 in group B for I⁻, T₄ and T₃.

On comparing adenomatous and para-adenomatous tissue within each of the two groups (Table 1), the only difference seen in group A with severe iodine deficiency was a higher [¹²⁵I] DIT concentration in the para-adenomatous tissue. In group B more [¹²⁵I] origin material and [¹²⁵I] DIT and less [¹²⁵I] MIT and [¹²⁵I] T₃ were found in the para-adenomatous tissue. In Fig. 1 the

**Table 1.**
The relative concentration (mean ± sd) of [¹²⁵I]-labelled thyroid metabolites of adenomatous and para-adenomatous tissue in groups A and B. Figures for single specimens are in % of total radioactivity on chromatogram - mean of duplicate estimations. The only significant difference between group A and B was more material at the origin on chromatography of para-adenomatous tissue of group B (P < 0.05). Significant differences between adenomatous and para-adenomatous tissue within each group are indicated by their P-values.

<table>
<thead>
<tr>
<th></th>
<th>Adenomatous Tissue</th>
<th>Para-adenomatous tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Origin</td>
<td>11.3 ± 4.2</td>
<td>12.0 ± 3.7</td>
</tr>
<tr>
<td>DIT</td>
<td>21.1 ± 6.6</td>
<td>28.1 ± 6.9</td>
</tr>
<tr>
<td>MIT</td>
<td>53.8 ± 6.6</td>
<td>49.6 ± 10.2</td>
</tr>
<tr>
<td>I⁻</td>
<td>7.2 ± 2.5</td>
<td>6.0 ± 1.1</td>
</tr>
<tr>
<td>T₄</td>
<td>3.8 ± 2.3</td>
<td>2.7 ± 1.9</td>
</tr>
<tr>
<td>T₃</td>
<td>1.7 ± 1.6</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Origin</td>
<td>12.1 ± 2.8</td>
<td>15.5 ± 4.1</td>
</tr>
<tr>
<td>DIT</td>
<td>21.2 ± 6.0</td>
<td>28.5 ± 5.1</td>
</tr>
<tr>
<td>MIT</td>
<td>51.2 ± 7.5</td>
<td>44.1 ± 6.1</td>
</tr>
<tr>
<td>I⁻</td>
<td>6.9 ± 2.0</td>
<td>6.8 ± 2.0</td>
</tr>
<tr>
<td>T₄</td>
<td>4.2 ± 1.8</td>
<td>3.5 ± 1.8</td>
</tr>
<tr>
<td>T₃</td>
<td>2.1 ± 1.8</td>
<td>1.1 ± 0.6</td>
</tr>
</tbody>
</table>
[\(^{125}\)I] MIT/DIT ratios for both groups are plotted against the logarithmic transformation of iodine concentration in the tissues, and a highly significantly negative correlation is obtained \((P < 0.0005 \text{ and } r = -0.69)\). This correlation is statistically significant not only for para-adenomatous tissue, \(P < 0.0005 \text{ and } r = -0.66\) but also for adenomatous tissue, \(P < 0.0025 \text{ and } r = -0.59\). It deserves notice that in only one case was the MIT/DIT ratio less than one, indicating a relative iodine deficiency of nearly all the goitrous tissues investigated.

The ratio \([^{125}\)I] T\(_3\)/T\(_4\) was significantly negatively correlated to the logarithmic transformation of stable iodine concentration in the tissue \((P < 0.005, r = -0.37 \text{ and } n = 52)\).

**Dehalogenase ability**

In group A \([^{125}\)I] MIT excretion in the urine was \(0.9 \pm 0.5\% \text{ dose/6 h} \) and in group B \(1.4 \pm 1.2\% \text{ dose/6 h} \); the difference is not significant. According to McGirr et al. (1959) a MIT excretion less than \(6\% \text{ dose/6 h} \) is normal, and thus all our patients had normal dehalogenase ability.

![Fig. 1](image-url)  
A highly significantly negative correlation between the iodine concentration of wet thyroid tissue (● adenomatous and ○ para-adenomatous) and ratio of radioactive MIT/DIT in the tissue was found \((P < 0.005 \text{ and } r = -0.69)\). In all specimens but one the \([^{125}\)I] MIT/DIT ratio was > 1. The results from one adenoma are excluded from the Fig. 1 because iodine concentration was zero (MIT/DIT ratio was 5.47).
Excretion of total $^{125}\text{I}$ 6 hours after the $[^{125}\text{I}]$ MIT dose was 23% of the dose in group A and 34% in group B, a statistically significant difference ($P < 0.025$) probably caused by a higher uptake of $^{125}\text{I}$ by the thyroids of the patients in group A. In both groups the most radioactive component excreted was by far iodide.

$^{125}\text{I}$-labelled components of the plasma

After the Na$^{125}\text{I}$-tracer dose was given $[^{125}\text{I}]$ PBI, $[^{125}\text{I}]$ NBEI and total $^{125}\text{I}$ concentrations were measured daily in the serum for 6–7 days. No difference between group A and B was found as regard $[^{125}\text{I}]$ PBI and $[^{125}\text{I}]$ NBEI concentration, i.e. in group A the 24 h values of $[^{125}\text{I}]$ PBI was $0.035 \pm 0.018 \%\text{dose/l}$ and in group B $0.044 \pm 0.038 \%\text{dose/l}$ (mean ± sd). $[^{125}\text{I}]$ NBEI in group A was $0.025 \pm 0.016$ and in group B $0.034 \pm 0.018 \%\text{dose/l}$. The total plasma radioactivity at 24 h was significantly higher in group B $0.176 \pm 0.91$ (mean ± sd) as compared to group A $0.069 \pm 0.033 \%\text{dose/l}$ plasma. $P < 0.0005$, indicating a faster elimination of iodide from the blood in group A patients where iodine deficiency was most pronounced.

Chromatography of the serum seven days after the Na$^{125}\text{I}$ dose was given was effectuated in 22 cases. In 11 cases the chromatography solvent used was n-butanol:ethanol:$\text{NH}_3$ 0.4 N (15:3:6) which separated $\text{T}_4$, $\text{T}_3$, MIT, and DIT very well. In nine cases only $[^{125}\text{I}]$ $\text{T}_4$ was found. One chromatogram was inconclusive because of low radioactivity, but small peaks corresponding to $\text{I}^-$, $\text{T}_4$ and $\text{T}_3$ were found. In the last chromatogram distribution percentages were $60\% \text{T}_4$, $11\% \text{T}_3$, MIT + DIT $7\%$ and an unidentified peak of $8\%$. The thyroid of that patient was multinodular with cysts and in the paranonodular tissue scarce interstitial fibrosis was found; no antibodies against thyroglobulin or complement-fixing antibodies were detected in the blood. In another 11 cases chromatography of the serum was performed in n-butanol:acetic acid:water (12:3:5). This solvent does not separate $\text{T}_4$ and $\text{T}_3$. In ten cases only a $^{125}\text{I}$-peak was found corresponding to the area of $\text{T}_4 + \text{T}_3$, which averaged about $83\%$ of the radioactivity of the chromatogram. On the last chromatogram $64\%$ was found on the $\text{T}_3 + \text{T}_4$ area and a unidentified peak of $22\%$ between the $\text{I}^-$ and MIT-bands.

Thus, no obvious difference in the distribution of $^{125}\text{I}$-labelled amino acids were found in the blood of group A and group B. In only two cases (one from each group) were iodinated components other than thyronines found.

Thyroid antibodies

In only one case was antibody against thyroglobulin found (titer 5). No patient had serum complement-fixing antibodies. Signs of thyroiditis were not found on microscopy of the goitrous tissue.
In endemic goitre regions it has been shown that persons with and without goitre have the same or nearly the same urinary iodine excretion. PII and radioactive iodine uptake in the thyroid gland (Roche et al. 1957; Lamberg et al. 1958; Malamos et al. 1966). Recently we have found that this is also the case in an area where goitre is sporadic (Agerbæk & Jensen 1974).

In the present investigation goitrous patients with a low PII (group A) were compared to goitrous patients with a mean PII a little higher than the mean for non-goitrous persons from the same region (group B).

PII is a suitable parameter for iodine intake. In group A with a low PII, urinary excretion was significantly lower and the thyroid clearance significantly higher than in group B. Patients in group A were thus iodine deficient at the time of investigation.

The weight of the goitres in group A was significantly greater than in group B. All goitres but two were nodular and iodine concentration in parano-dular tissue was significantly lower in the group with the largest goitres, a finding similar to Ermans et al. (1968). Mean iodine concentration of parano-dular tissue in group B (395 μg/g wet thyroid tissue) was very close to the mean concentration of "normal" thyroid glands in Jutland - preliminary results from 100 medico-legal autopsies show a mean iodine concentration of 404 μg/g and a mean thyroid weight of 24 g (Agerbæk, to be published). Iodine concentration in the nodular tissue was low in both groups, and no differences were found between the groups.

The relative concentrations of the various $^{125}$I-iodoamino acids in the thyroid tissue were not significantly different in group A and B, but comparing tissues with the largest differences in iodine concentration (adenomatous and para-adenomatous tissue of group B) more $^{125}$I DIT and less $^{125}$I MIT were found where iodine concentration was highest and significantly more $^{125}$I T₃ where iodine concentration in the tissue was lowest.

These findings can probably be explained by differences in iodine concentrations in the various tissues since a reduction in iodine concentration increases the MIT/DIT ratio (Ermans et al. 1963) and, at least in animal experiments, results in a preferential synthesis of T₃ (Lachiver & Leloup 1955; Postmes 1966).

Ermans et al. (1963, 1968) have found a highly significant correlation between iodine concentration in thyroid tissue and the iodination of thyroglobulin and a negative correlation between $^{131}$I MIT/DIT and iodine concentration in parano-dular tissue. We found a significantly negative correlation between $^{125}$I MIT/DIT and the log iodine concentration in adenomatous and para-adenomatous tissue (Fig. 1), when calculated both separated and together.
The relative concentration of $^{125}\text{I}$ amino acids in normal thyroids from the Aarhus region (Agerbæk 1973) is not different from the findings in para-adenomatous tissue in group B. In both cases a $[^{125}\text{I}]$ MIT/DIT ratio > 1 was found suggesting iodine deficiency of all the tissues investigated, “normal” thyroid tissue included.

The relative concentration of $[^{125}\text{I}]$ T$_3$ was significantly higher in the adenomatous tissue where stable iodine concentration was low. Furthermore, a significantly negative correlation was found between the ratio of radioactive T$_3$/T$_4$ and the logaritmic transformation of the stable iodine concentration of the tissues. Results indicating preferential synthesis of T$_3$ in iodine deficient animals have been published (Leloup & Lachiver 1955; Postmes 1966), but it has not been shown in man.

A defective deiodinase ability could bring about a secondary iodine deficiency (Wayne et al. 1964). In all our patients a normal in vivo deiodinase ability was found, and there was no difference between group A and B.

The $[^{125}\text{I}]$ PBI measured daily for a week was not different in the two groups suggesting no or only small differences in the exchangeable iodine pools of the thyroid. The $[^{125}\text{I}]$ NBEI was elevated in all the patients investigated. Similar results have been obtained in patients from an endemic goitrous area (Malamos et al. 1966). On chromatography of the serum unidentified iodinated components were found in two of 22 patients, in the rest only $^{125}\text{I}$ thyronines were detected.

We found no qualitative differences between non-toxic goitrous patients with iodine deficiency and patients without such deficiency. Stable iodine concentrations in paranodular tissue from the least iodine deficient group were the same as iodine concentrations in normal gland from the same region. The distribution of iodinated amino acids is not different.

It is likely that the Danish population as a whole is iodine deficient (Munkner 1969) and that permanent goitre develops in persons who have iodine deficiency for a period of time sufficient for the development of irreversible, nodular changes in the thyroid gland (Wahner et al. 1966).

At present a large-scaled, goitre survey among all Danish school children is in progress. If goitre frequency is found to be significantly great, iodine prophylaxis should be provided.

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