Thyroid Hormones in Generalized Scleroderma
A Controlled Study

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Parameters of thyroid metabolism were analysed in 42 patients with generalized scleroderma and healthy individuals matched with respect to sex and age for comparison. Decreased free thyroxine (p<0.01), decreased free triiodothyronine (p<0.001), and increased thyroid-stimulating hormone (p<0.001) evidenced an associated state of myxedema in scleroderma. Total thyroxine was normal, and total triiodothyronine was increased (p<0.01) probably reflecting binding to abnormal serum proteins in scleroderma. Normal concentrations of reverse triiodothyronine indicated a normal peripheral metabolism of thyroid hormones. Thyroid-stimulating immunoglobulins also analysed were within normal range. Changes in free thyroxine, free triiodothyronine, and thyroid-stimulating hormone were quantitatively small with mean values within normal ranges.

In conclusion, this study evidenced a mild associating myxedema state in generalized scleroderma. Probably, this reflected slight and subclinical affection of the thyroid. Key words: Thyroxine; Triiodothyronine; Thyroid-stimulating hormone; Thyroid-stimulating immunoglobulin. (Received June 24, 1985.)

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In the early fifties, in histological experiments, Asboe-Hansen showed that thyroid hormone and thyrotrophic hormone influence the mucopolysaccharides of connective tissue of skin (1, 2, 3). These findings correlated well with known alterations in myxedema and malignant exophthalmos.

In scleroderma skin, histological, ultrastructural and biochemical studies accordingly show that acid mucopolysaccharides (later named glycosaminoglycans) are altered, in particular in the hypertrophic and oedematous state of the disease (4, 5, 6, 7). In generalized scleroderma the excretion of glycosaminoglycans in the urine is also increased (8). As a result of these observations, treatment of scleroderma with dextro-thyroxine was tried (9).

It was recently briefly stated that patients with Raynaud's disease have levels of thyroid-stimulating hormone approximtely ten times that of controls (10). Schwarz, Schell & Hornstein in a study of 14 patients with generalized scleroderma could not confirm these findings (11). However, some of their patients presented elevated thyroid-stimulating hormone.

In the present study of a larger material of patients suffering from generalized scleroderma, and healthy controls matched with respect to sex and age, a more detailed evaluation of the thyroid physiology including the peripheral metabolism of thyroid hormones was undertaken.

MATERIAL AND METHOD
The study included 42 patients (37 females, 5 males) with a definite diagnosis of generalized scleroderma according to the American Rheumatism Association criteria (12). Their mean age was
Table I. Analyses of parameters of thyroid metabolism in 42 patients with generalized scleroderma in comparison with matched controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Generalized scleroderma</th>
<th>Matched controls</th>
<th>Conclusion</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_4$ Mean</td>
<td>105.6</td>
<td>103.6</td>
<td>Normal</td>
<td>57-124 nmol/l</td>
</tr>
<tr>
<td>$T_4$ SD</td>
<td>28.0</td>
<td>22.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_3$ Mean</td>
<td>1.696</td>
<td>1.532</td>
<td>Increased**</td>
<td>1.10-2.38 nmol/l</td>
</tr>
<tr>
<td>$T_3$ SD</td>
<td>0.343</td>
<td>0.216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$FT_4$ Mean</td>
<td>16.5</td>
<td>19.5</td>
<td>Decreased**</td>
<td>12.6-21.6 pico/mol/l</td>
</tr>
<tr>
<td>$FT_4$ SD</td>
<td>4.91</td>
<td>3.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$FT_3$ Mean</td>
<td>5.73</td>
<td>6.60</td>
<td>Decreased***</td>
<td>4.8-8.3 pico/mol/l</td>
</tr>
<tr>
<td>$FT_3$ SD</td>
<td>1.09</td>
<td>1.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$rT_3$ Mean</td>
<td>0.357</td>
<td>0.374</td>
<td>Normal</td>
<td>0.24-0.57 nmol/l</td>
</tr>
<tr>
<td>$rT_3$ SD</td>
<td>0.140</td>
<td>0.087</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH Mean</td>
<td>1.303</td>
<td>0.498</td>
<td>Increased**</td>
<td>&lt;35 milliunits/l</td>
</tr>
<tr>
<td>TSH SD</td>
<td>1.276</td>
<td>0.943</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** $p<0.01$, *** $p<0.001$. 

51.3 years (range 18–71). The mean duration of scleroderma was 7.9 years (range 1–22). Thirty-eight patients had Raynaud's phenomenon, 29 had radiological affection of the esophagus, and 15 and 5 had pulmonary affection according to lung function test and radiography of the chest respectively. None of the patients had verified renal affection or uaeuria. The patients had been treated with inhibitors of collagen synthesis as described by Asboe-Hansen (13). Thirty-six received penicillamine in combination with glutamine, three glutamine only, one hydralazine, and two chlorpromazine. The mean duration of therapy was 3.8 years (range 0.5–20).

Forty-two healthy individuals matched with respect to sex and age (mean age 50.2 years, range 22–61) were studied for comparison.

Blood samples were taken in the morning for analysis of total thyroxine ($T_4$), free thyroxine ($FT_4$), total triiodothyronine ($T_3$) free triiodothyronine ($FT_3$), reverse triiodothyronine ($rT_3$) as well as thyroid-stimulating hormone (TSH). $T_4$, $FT_4$, $T_3$, $FT_3$, and TSH were analysed by the Department of Nuclear Medicine, Rigshospitalet, Copenhagen according to radioimmunological routine techniques, and $rT_3$ was analysed at Medicinsk Laboratorium, Copenhagen, by similar principle. This laboratory also determined thyroid-stimulating immunoglobulins (TSI) of the scleroderma patients by a radioreceptor assay (14).

Statistical analysis was carried out by Student's $t$-test.

RESULTS

Table I shows results of analyses of thyroid hormones in scleroderma patients in comparison with matched controls. $T_4$ was not changed, but $T_3$ was significantly increased ($p<0.01$). $FT_4$ and $FT_3$ were both decreased ($p<0.01$ and $p<0.001$) while TSH was increased ($p<0.01$). The $rT_3$ was not changed. Normal ranges as given by the laboratories are also included in the table.

TSI of scleroderma patients (mean 1.148 arbitrary units, SD 0.204 was within normal range (0.41–1.24 arbitrary units), however, in the upper third of this.

DISCUSSION

Thyroxine and to a lesser extent triiodothyronine are produced in the thyroid. In peripheral tissues thyroxine is mainly deiodinated to triiodothyronine, which is the metabolically more active hormone (Fig. 1). In numerous conditions with affection of the general condition the peripheral deionidation follows the foetal pattern with increased formation of
Peripheral Thyroid Metabolism

**Fig. 1.** Peripheral metabolism of thyroid hormones in adult and foetal life. During diseases affecting the general condition the deiodination changes in the direction of a foetal metabolism with increased formation of reverse triiodothyronine.

rT₃, which is metabolically inactive, leading to decreased concentration of FT₃ in the blood (15, 16). In severe affection of the general condition the hypophyseal stimulation of the thyroid as represented by TSH may be depressed resulting in decreased concentration of FT₄ in addition to decreased FT₃ (17, 18, 19, 20).

The main findings of the present study were decreased free thyroid hormones including FT₄ and FT₃ in combination with increased TSH. This pattern is well known and characteristic for a myxoedema state. The increase in T₃ but not in T₄ was probably attributable to binding to abnormal serum proteins in scleroderma known frequently to influence concentrations of total thyroid hormones. TSI was normal as this immunoglobulin is in true myxoedema in contrast to elevated concentrations in hyperthyroidism (21).

Normal concentration of rT₃ indicated a normal peripheral metabolism of thyroid hormones in scleroderma. As mentioned, increased concentration of TSH is not typical in severely affected general condition despite decreased concentrations of thyroid hormones in the blood. The slight myxoedema state of scleroderma was, probably, secondary to minor glandular affection with slight insufficiency and compensatory increase in hypophyseal incretion of TSH.

Decreases of FT₄ and FT₃, and the increase in TSH were quantitatively small with mean values within normal ranges in accordance with the study of Schwarz, Schell & Hornstein (11). Thus, it is questionable whether the mild but definite myxoedematous state of scleroderma patients is of any clinical consequence. The characteristic myxoedematous alteration of skin afflicted with scleroderma mentioned initially seems mainly to have a local causation linked to the pathological process of connective tissue formation.

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**REFERENCES**

1. Asboe-Hansen G. The variability in the hyaluronic acid content of the dermal connective tissue under the influence of thyroid hormone. Acta Derm Venereol (Stockh) 1950; 30: 221-230.