Differences in aetiology and thyroid function in endemic goitre between rural and urban areas of the Darfur region of the Sudan

M. Eltom¹, M. A. M. Salih², H. Boström¹ and P.-A. Dahlberg²

Department of Medicine¹, University Hospital, Uppsala, Sweden and Department of Paediatrics², Faculty of Medicine, Khartoum, Sudan

Abstract. To investigate further the possible causes of the difference in goitre frequency between the rural and urban areas of Darfur region in the Sudan, urinary iodine excretion (UIE) and thyroid hormone concentrations were measured in 97 goitrous and 31 non-goitrous subjects from rural Darfur, 62 goitrous subjects from urban Darfur and 37 non-goitrous subjects from Khartoum. The mean UIE was equally low in goitrous subjects from rural Darfur (56.2 ± 43.1 µg/g creatinine) and urban Darfur (46.3 ± 20.7 µg/g creatinine) and both values were lower than that in the non-goitrous subjects from Khartoum (83.6 ± 41.9 µg/g creatinine). Subjects from rural Darfur also had lower mean serum thyroxine and higher triiodothyronine and thyroid stimulating hormone levels. The mean serum thiocyanate level of 3.2 mg/l in goitrous subjects from rural Darfur was significantly higher than the values of 1.8 ng/ml in goitrous subjects from urban Darfur (P < 0.001) and 1.7 mg/l in non-goitrous subjects from Khartoum (P < 0.001). It is concluded that the additional contribution of goitrogenic factors in rural Darfur induces thyroid anomalies to a greater degree than are most likely caused by the iodine deficiency alone in subjects from urban Darfur.

In a recent study the prevalence of goitre in the Darfur region of western Sudan was found to be 85.5% (Eltom et al. 1984). The main aetiological factor was considered to be iodine deficiency. A higher frequency of large goitre was observed in the rural than in the urban areas of the region, a finding which is well in accordance with earlier reports by Osman et al. (1983). They suggested that this regional variation in goitre frequency was mainly attributable to the high consumption of millet, the staple food in rural Darfur, which was found to contain a thionamide-like substance. Alternatively, they considered that other naturally occurring goitrogens in the food or water may work in concert with iodine deficiency and contribute to the higher endemicity of goitre in the rural areas. In determining the iodine intake in itself, however, no differentiation was made between the rural and urban areas in the above-mentioned studies. The aim of the present study was to investigate further the possible differences in the aetiology and pathogenesis of goitre in the rural and urban areas. Thus, urinary iodine excretion (UIE), serum and urinary thiocyanate levels and thyroid hormone concentrations were measured in subjects residing in the two areas. The results were compared with those obtained in subjects from Khartoum, where goitre is not prevalent.

Material

In rural Darfur, urine and blood samples were collected from 97 goitrous subjects (51 males and 46 females) and 31 non-goitrous subjects (19 males and 12 females), selected at random during a goitre survey carried out in
the Darfur region in November 1981 (Eltom et al. 1984). the mean age of the subjects (± SD) was 12.2 ± 6.2 years.

In El Fasher (urban Darfur), the main town of the Darfur region, urine and blood samples were collected from 62 goitrous subjects (33 males and 29 females). They were clinically euthyroid, selected from schools visited in the town of El Fasher. Their mean age was 13.3 ± 0.7 years.

In Khartoum, the capital of the Sudan, urine and blood samples were collected from 37 clinically euthyroid non-goitrous subjects (20 males and 17 females). Their mean age was 13.1 ± 0.8 years.

Separation of serum was performed in the field, whereafter the serum and urine samples were kept frozen in liquid nitrogen and flown to Sweden for analysis.

Methods

Examination and classification of thyroid glands
The thyroid glands were examined by techniques recommended by Perez et al. (1960), and the findings were classified into stages as follows: Stage 0 = no goitre; Stage I = palpable goitre; Stage II = goitre easily visible with the neck in a normal position; Stage III = very large goitre.

Urinary iodine excretion
All urine samples were assayed for their iodide content as described by Sandell & Kolthoff (1937). Iodine/creatinine ratios in single urine samples were calculated to obtain a representative index of the daily UIE (Jolin & Escobar Del Rey 1965).

Hormone assays
The serum concentrations of thyroid-stimulating hormone (TSH), serum triiodothyronine (T3) and thyroxine (T4) were measured by radioimmunoassays in use at the University Hospital, Uppsala, Sweden. A T3 resin uptake (T3U) test was performed with Sephadex®-G-25 (Pharmacia, Uppsala, Sweden) as resin. The results were expressed in per cent of the mean values of healthy controls. Free T4 index (FT4I) was calculated as the product of the result of the T3U test and the serum T4 level.

Thiocyanate levels
Thiocyanate levels in urine and serum of subjects from rural and urban Darfur and from Khartoum were determined in deproteinized samples as the ferricocomplexes according to the method described by Bowler (1944).

Statistics
Logarithmic values were used for calculating mean values, and the statistical significance of differences was evaluated by Student’s t-test.

Results
The mean values of serum TSH, thyroid hormones and UIE in goitrous and non-goitrous subjects from rural Darfur and non-goitrous subjects from Khartoum are presented in Table 1. Subjects from rural Darfur had lower mean levels of serum T4, FT4I and UIE than subjects from Khartoum. At the same time they had higher serum TSH and T3 levels.

The mean UIE and mean serum levels of thyroid hormones and TSH in subjects from rural Darfur are shown in relation to goitre size in Table 2. The mean UIE, serum T4 and FT4I were lower in subjects with large goitres (Stage II or III) than in non-goitrous subjects. The mean serum levels of TSH and T3 were higher in the former than in the latter. However, there was no significant difference in these values between subjects with small goitres (Stage I) and non-goitrous subjects.

There was a negative correlation between serum

<table>
<thead>
<tr>
<th>Subjects from</th>
<th>No. of subjects</th>
<th>TSH (mU/l)</th>
<th>T3 (nmol/l)</th>
<th>T4 (nmol/l)</th>
<th>FT4I</th>
<th>UIE (µg/g creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural Darfur</td>
<td>128</td>
<td>6.3 ± 3.9</td>
<td>2.7 ± 0.5</td>
<td>83.5 ± 27.8</td>
<td>77.3 ± 22.5</td>
<td>57.6 ± 42.2</td>
</tr>
<tr>
<td>Khartoum</td>
<td>37</td>
<td>4.5 ± 1.2</td>
<td>2.3 ± 0.4</td>
<td>90.9 ± 14.0</td>
<td>87.2 ± 9.7</td>
<td>83.6 ± 41.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Downloaded from Bioscientifica.com at 12/01/2018 06:04:09AM via free access
Table 2.
Serum TSH, serum thyroid hormones and urinary iodine excretion (UIE) in relation to goitre size in 128 subjects from rural Darfur. The results are presented as mean ± SD.

<table>
<thead>
<tr>
<th>Subjects from</th>
<th>No. of subjects</th>
<th>TSH (mU/l)</th>
<th>T3 (nmol/l)</th>
<th>T4 (nmol/l)</th>
<th>FT4I</th>
<th>UIE (µg/g creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>31</td>
<td>5.3 ± 2.3</td>
<td>2.5 ± 0.5</td>
<td>89.0 ± 19.2</td>
<td>83.1 ± 19.2</td>
<td>63.6 ± 37.9</td>
</tr>
<tr>
<td>Stage I</td>
<td>32</td>
<td>6.0 ± 2.3</td>
<td>2.7 ± 0.5</td>
<td>87.0 ± 24.1</td>
<td>79.5 ± 19.6</td>
<td>74.5 ± 59.0</td>
</tr>
<tr>
<td>Stage II</td>
<td>45</td>
<td>6.4 ± 3.0*⁻¹</td>
<td>2.7 ± 0.5*</td>
<td>81.7 ± 23.3</td>
<td>74.9 ± 19.2*</td>
<td>49.4 ± 45.7*</td>
</tr>
<tr>
<td>Stage III</td>
<td>20</td>
<td>8.8 ± 7.2*</td>
<td>2.8 ± 0.6**</td>
<td>62.9 ± 26.6***</td>
<td>58.1 ± 22.4***</td>
<td>44.8 ± 26.1*</td>
</tr>
</tbody>
</table>

¹ Level of significance of difference from Stage 0 goitre (**P < 0.001; *P < 0.01; *P < 0.05; t-test).

T4 and TSH (r = -0.433, P < 0.001) and serum T4 and T3 (r = -0.244, P < 0.01) in subjects from rural Darfur. At the same time a positive correlation was noted between serum T3 and TSH (r = 0.385, P < 0.001) in these subjects. No correlation was found between variables in non-goitrous subjects from Khartoum.

Of the 62 goitrous subjects from urban Darfur, 72.6% had Stage I goitre, 25.8% had Stage II and 1.6% had Stage III. The biochemical data of goitrous subjects from rural Darfur were further compared with those of goitrous subjects from urban Darfur (Table 3). The mean serum TSH and T3 concentrations were higher in goitrous subjects from rural Darfur than in goitrous subjects from urban Darfur (TSH, P < 0.001; T3, P < 0.001). The mean serum T4 and FT4I values were lower in the former than in the latter subjects (T4, P < 0.001; FT4I, P < 0.01). The mean UIE of 56.2 µg/g creatinine in goitrous subjects from rural Darfur did not differ significantly from that of 46.3 µg/g creatinine in goitrous subjects from urban Darfur.

Serum thiocyanate was higher in subjects from rural Darfur than in those from urban Darfur (3.2 and 1.8 mg/l, respectively, P < 0.001), while there was no significant difference in mean urinary thiocyanate concentration between these two groups (Table 3). The corresponding thiocyanate values (mean ± SD) for the 37 non-goitrous subjects from Khartoum was 1.7 ± 0.5 mg/l in serum (P < 0.001 vs rural Darfur; not significant vs urban Darfur) and 12.2 ± 3.0 mg/g creatinine in urine (not significant vs rural and urban Darfur).

Table 3.
Mean values of serum TSH, serum thyroid hormones, urinary iodine excretion (UIE) and serum (S) and urinary (U) thiocyanate in goitrous subjects from rural and urban Darfur (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Rural Darfur</th>
<th>Urban Darfur</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/l)</td>
<td>6.6 ± 4.2</td>
<td>4.4 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>T3 (nmol/l)</td>
<td>2.7 ± 0.5</td>
<td>2.3 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>T4 (nmol/l)</td>
<td>80.4 ± 27.8</td>
<td>108.0 ± 29.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>FT4I</td>
<td>72.6 ± 21.6</td>
<td>85.0 ± 23.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>UIE (µg/l)</td>
<td>40.1 ± 19.3</td>
<td>42.3 ± 15.4</td>
<td>n. s.*</td>
</tr>
<tr>
<td>U-creatinine (g/l)</td>
<td>0.92 ± 0.53</td>
<td>1.03 ± 0.40</td>
<td>n. s.*</td>
</tr>
<tr>
<td>UIE (µg/g creatinine)</td>
<td>56.2 ± 43.1</td>
<td>46.3 ± 20.7</td>
<td>n. s.*</td>
</tr>
<tr>
<td>S-thiocyanate (mg/l)</td>
<td>3.2 ± 0.8</td>
<td>1.8 ± 0.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>U-thiocyanate (mg/g creatinine)</td>
<td>16.2 ± 14.6</td>
<td>14.3 ± 4.8</td>
<td>n. s.*</td>
</tr>
</tbody>
</table>

* Not significant.
Discussion

The daily UIE is a reliable index of the quantity of iodine ingested. In this study the UIE values were well in accordance with our previous results from the Darfur region (Eltom et al. 1984), confirming that iodine deficiency is the major cause of goitre in this region. Surprisingly, the iodine intake was equally low in rural and urban Darfur, although a different pattern of thyroid hormones was observed, providing information additional to the previous observation that the frequency of large goitre was higher in the rural than in the urban area. Together, these findings strengthen the view that additional factors may contribute to the aetiology of endemic goitre in rural Darfur.

The results of thyroid hormone assays in subjects of rural Darfur were in accordance with those of other studies (Delange et al. 1971; Chopra et al. 1975), indicating that although serum T₄ may be low in individuals from endemic goitre regions, their serum TSH and T₃ levels are usually higher than those observed in subjects residing in zones free from endemic goitre.

The reciprocal correlation of serum T₄ and TSH in the rural Darfur subjects suggests that any decrease in circulating T₄ triggers an inversely proportional increase in TSH secretion. This increase, together with the increased ratio of circulating T₃ to T₄, is characteristic of adaptation to iodine depletion (Larsen 1982). It has been suggested, however, that an elevated TSH and T₃ and a low T₄ level in the serum in subjects with persistent iodine depletion indicates an incomplete compensatory mechanism (Abrams & Larsen 1973; Larsen 1982). This suggestion has been explained by the fact that the increases in plasma TSH level and T₃/T₄ ration continue until T₄ secretion has virtually ceased and most of the circulating T₃ originates from the thyroid. By that time, organs that depend mainly on plasma T₃ for intracellular T₃, such as the liver, kidney and heart, should be nearly ‘euthyroid’. On the other hand, organs that depend mainly on extracellular T₄ for a substantial fraction of their intracellular T₃, such as the anterior pituitary and the brain, should be relatively ‘hypothyroid’. The reduced pituitary intracellular concentration of T₃ caused by the reduction in serum T₄ therefore has the effect of inducing an increased production of TSH even in clinically euthyroid subjects, as was noted in this study. The eventual consequence of this prolonged thyrotrophic stimulation is the development of goitre.

In contrast to the above findings, goitrous subjects from urban Darfur had higher serum T₄ and lower T₃ and TSH levels than goitrous subjects from rural Darfur, in spite of a fairly similar iodine excretion. As the iodine intake was equally low in rural and urban Darfur, the question arises why the difference in the frequency of goitre occurred. The most likely explanation would seem to be the existence of goitrogenic factors which could accentuate the anomalies of iodine metabolism. An intriguing observation in this study was therefore the higher mean level of serum thiocyanate in subjects from rural Darfur in comparison with those from urban Darfur.

The serum levels of thiocyanate in subjects from rural Darfur were higher than those obtained in Nigerians (Monekosso & Willson 1966), but lower than were previously found in rural regions of Zaire (Bourdoux et al. 1980). In a previous study carried out in the Darfur region by Osman et al. (1983), the thiocyanate concentration was reported to be higher in goitrous than in non-goitrous school children. In addition, a negative correlation was found between the thiocyanate and thyroxine concentrations in the serum of these subjects. The results of the present study are in agreement with the concept that thiocyanate overload in conjunction with iodine deficiency induces more severe thyroid anomalies than those caused by iodine deficiency alone (Bourdoux et al. 1980). At a high concentration, thiocyanate inhibits the incorporation of iodide into thyroglobulin (Raben 1949). Halmi (1961) demonstrated that thiocyanate even in a relatively low concentration inhibited iodide transport by increasing the velocity constant of iodide efflux from the gland.

The elevated levels of serum thiocyanate may result from the catabolism of thioglucoside present in certain plants, most of which belong to the cruciferous family (Greer 1962), or from detoxification of the cyanogenic glucoside linamarin, which is contained in cassava (Bourdoux et al. 1980). In the Darfur region, neither cruciferous plants nor cassava were consumed. We have no information at present concerning the source of the high thiocyanate level. However, Osman et al. (1983) produced an evidence that millet, which is the predominant staple food in rural Darfur, contains a goitrogenic thionamide, which might be a contributory factor in endemic goitre. This food
substance was further investigated experimentally by Klopfenstein et al. (1983), who demonstrated histological change in thyroid in millet-fed rats which were similar to histopathological features in cases of human colloid goitre. Unlike our present human subjects from an area of endemic goitre, the rats used in the latter experiments were not iodine-deficient. These results suggest that millet might act as a goitrogen in itself.

The existence of antithyroid factors in drinking water from rural Darfur has been suggested (Eltom et al. 1984). However, the addition of drinking water from rural Darfur to porcine thyroid cell preparations had no apparent inhibitory effect on the organification of iodide (El Mahdi et al., in press).

In conclusion, the subjects from rural and urban areas of Darfur suffer from iodine deficiency to an almost equal extent, but the sizes of the goiters and the thyroid hormone levels differ. It is probable that multiple goitrogenic factors in the food or water in the rural areas, which need further identification, induce more thyroid anomalies than those caused mainly by iodine deficiency, as in urban Darfur. We suggest thiocyanate to be a major factor in this respect.

Acknowledgment

This work is part of the co-operation programme between the University Hospital, Uppsala, Sweden, and the Ministry of Health and the University of Khartoum, Sudan, supported by the Swedish Commission for Technical Co-operation.

References


Received on August 12th, 1984.