Endemic goiter with iodine sufficiency: a possible role for the consumption of pearl millet in the etiology of endemic goiter\textsuperscript{1–3}

Abdelsalam Elnour, Leif Hambraeus, Mohammed Eltom, Michèle Dramaix, and Pierre Bourdoux

ABSTRACT

Background: Deficiencies of iodine, iron, and vitamin A are the 3 most common micronutrient deficiencies in developing countries, although control programs, when properly implemented, can be effective.

Objective: We investigated these deficiencies and their possible interaction in preschool children in the southern Blue Nile area of Sudan.

Design: Goiter, signs of vitamin A deficiency, and biochemical markers of thyroid, vitamin A, and iron status were assessed in 984 children aged 1–6 y.

Results: The goiter rate was 22.3%. The median urinary iodine concentration was 0.79 \( \mu \text{mol/L} \) and 19.3% of the children had a concentration > 1.57 \( \mu \text{mol/L} \). Although serum thyroxine and triiodothyronine concentrations were within reference ranges, the median thyrotropin concentration was 3.78 mIU/L and 44% of the children had thyrotropin concentrations above normal. The mean urinary thiocyanate concentration was high (259 ± 121 \( \mu \text{mol/L} \)). The prevalences of Bitot spots and night blindness were 2.94% and 2.64%, respectively, and 32% of the subjects had serum retinol binding protein concentrations < 15 mg/L. A significant positive correlation was observed between thyrotropin and retinol binding protein. Whereas 88% of the children had hemoglobin concentrations < 12 g/L, only 13.5% had serum ferritin concentrations below the cutoff of 12 \( \mu \text{g/L} \) and 95% had serum transferrin concentrations above the cutoff of 2.50 g/L.

Conclusions: Our results indicate that goiter is endemic in this region of Sudan despite iodine sufficiency and that both anemia and vitamin A deficiency are health problems in the area. Moreover, consumption of millet, vitamin A deficiency, and protein-energy malnutrition are possible etiologic factors in this endemic area. *Am J Clin Nutr* 2000;71:59–66.

KEY WORDS Iodine, goiter, vitamin A, iron, anemia, southern Blue Nile area, Sudan, pearl millet, micronutrient deficiency, children

INTRODUCTION

Deficiencies of iodine, iron, and vitamin A are the 3 most important nutritional problems in most developing countries (1). More than 1 billion persons are at risk of iodine deficiency worldwide and 200 million have goiter. In Africa, goiter is endemic in many countries, notably Congo, Uganda, Kenya, and Sudan; the prevalence of goiter is as high as 81% in some parts of these countries (2). Although iodine deficiency is the main factor in the etiology of endemic goiter (3), the additional role of goitrogens has been shown or suspected in areas such as Congo (4) and Sudan (5), in which goiter is endemic. As a whole, however, the role of goitrogens is often disregarded.

In Sudan, endemic goiter and iodine deficiency disorders are serious health problems in many areas. The prevalence of goiter among schoolchildren was estimated to be 85% in the Darfur region in western Sudan, 74% in the Kosti area in the center of Sudan, 13.5% in Port Sudan in eastern Sudan, and 17% in the capital, Khartoum (6). Little is known about the prevalence of goiter in other areas of Sudan. In the areas studied so far, iodine deficiency was identified as the principal etiologic factor. However, consumption of pearl millet, vitamin A deficiency, and protein-energy malnutrition were also suggested as instrumental factors in the etiology of endemic goiter in western Sudan (5, 7).

Vitamin A deficiency affects ~250 million children worldwide and has been implicated in the etiology of endemic goiter (8). Although vitamin A deficiency is estimated to be endemic in many developing countries, few data on vitamin A are available for many parts of Sudan and to our knowledge no biochemical data on vitamin A status have been collected in this country. Similarly, although ~15% of the world population suffers from significant iron deficiency anemia (9), a condition with adverse effects on physical capacities that has been shown to disturb thyroid hormone economy (10), no biochemical data are available to support the presence of anemia in Sudan.

\textsuperscript{1}From the Department of Medical Sciences, Nutrition, Uppsala University, Sweden; the Department of Physiology, Faculty of Medicine, University of Khartoum, Sudan; the Omdurman Nutrition and Endocrinology Research Center, Khartoum, Sudan; and the Laboratory of Medical Statistics, School of Public Health, and the Laboratory of Pediatrics, Free University of Brussels (ULB).

\textsuperscript{2}Supported by the Fonds de la Recherche Scientifique Médicale Belge (convention 3.4505.97 to PB). Additionally, UNICEF (Khartoum Office) supported the field work and the International Science Programs at Uppsala University, Sweden, provided financial support for the laboratory analysis.

\textsuperscript{3}Address reprint requests to P Bourdoux, ULB-Laboratoire de Pédiatrie, Hôpital Universitaire des Enfants, Avenue JJ Crocq 15, B-1020 Brussels, Belgium. E-mail: pbourdou@ulb.ac.be.

\textsuperscript{4}Accepted August 19, 1998.

\textsuperscript{5}Accepted for publication May 12, 1999.

Because surveys showed that goiter is endemic in the west, east, and center of Sudan, additional surveys were needed to cover other areas of the country to help in the planning of goiter control programs. The purpose of the present study was to survey the Blue Nile area in southeast Sudan to assess endemic goiter, iron status, and vitamin A status.

SUBJECTS AND METHODS

The study was conducted in 1994 in the southern Blue Nile area of Sudan, which lies on the border with Ethiopia, a country in which goiter is also endemic (11). The southern Blue Nile area is 350–600 km southeast of Khartoum, the capital of Sudan. It extends from the Ethiopian border southeast through the southern Sudanese states and southwest on both sides of the Blue Nile River up to the central Sudanese state in the west and north. Difficult socioeconomic and political conditions have prevailed in this part of the country for several years. The Southern Blue Nile area is divided geographically into 4 provinces, each of which is divided into many urban and rural councils. Urban councils comprise many quarters in towns whereas rural councils comprise several villages.

We studied preschool children because they are the most vulnerable to deficiencies of vitamin A, iron, and iodine (12, 13). To meet epidemiologic criteria, we used a multistage cluster sampling procedure with 30 clusters. The total number of clusters was stratified between the 4 provinces according to their respective population sizes. The primary sampling unit was a quarter in urban councils or a village in rural councils. The required number of clusters was sampled in each of the 4 provinces from the list of the primary sampling unit. In each of the selected clusters, the appropriate number of children was sampled randomly.

Goiter was diagnosed and graded according to World Health Organization criteria (14). Mothers of the children included in the study were questioned carefully about night blindness and signs of vitamin A deficiency (15). A total of 984 children were examined (ratio of boys to girls: 1.03). Their mean (±SD) age was 4.7 ± 1.6 y. Anthropometric indicators (height and weight) were recorded during the survey. Blood (n = 177) and casual urine (n = 191) samples were collected from every fifth child. Two kinds of blood samples were collected in evacuated tubes. One small sample was collected in a tube containing anticoagulant (EDTA) for hemoglobin estimation and the other sample was collected in a plain evacuated tube (with no additive) for further serum separation. The 2 blood samples were placed immediately on ice in a sealed thermostatic device. Hemoglobin was measured within 12 h of blood collection with a colorimeter and Drabkins reagent [ferric cyanide and potassium cyanide, prepared according to Dacie and Lewis (16)]. Within 12 h, serum samples were separated and kept in liquid nitrogen in a cylinder protected from light. Urine and serum samples were then packed on dry ice and flown to Belgium.

Urinary thiocyanate and iodine concentrations were analyzed in casual urine samples by methods described previously (4, 17). Serum thyroxine (T₄), triiodothyronine (T₃), and thyrotropin were also analyzed by methods described previously (18). Serum ferritin was evaluated with an immunoradiometric assay (Ferritin MAb; Becton Dickinson, Orangeburg, NY). Serum transferrin and retinol binding protein (RBP) were analyzed by immunonephelometry (19) with an automated Behring nephelometer (Behringwerke, Marburg, Germany) with specific nephelometry antisera to human transferrin and to human RBP.

Data are expressed as means ± SDs for normally distributed variables (hemoglobin; serum T₄, T₃, and transferrin; and urinary thiocyanate) or as medians and 95% CIs for data that were not normally distributed (serum thyrotropin, RBP, and ferritin and urinary iodine). Student’s t test, the Mann-Whitney test, or the chi-square test was used to test for possible differences between groups. Correlation analysis was performed between different variables by using Spearman’s test. Possible effects between the study variables were tested by multifactor analysis of variance, multiple linear regression, or logistic regression. Analyses were performed with SPSS (version 8.0; SPSS Inc, Chicago).

The present study was approved by and conducted in close collaboration with the head of the Department of Nutrition Division of the Sudan’s National Ministry of Health. Moreover, it was discussed and approved by the head of the nutrition division of the central Sudanese state where the study was conducted. We also discussed the study with the regional health directors of each province and council. Finally, the study design was discussed with a consultant on vitamin A from the World Health Organization. Verbal consent was obtained from the mothers and the procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

RESULTS

Nutritional status

For all subjects, the median height-for-age was below the 5th percentile, whereas the median weight-for-height was between the 75th and 90th percentiles. The median weight-for-height was slightly but not significantly lower in children with high serum thyrotropin concentrations (n = 72) than in those with normal thyrotropin concentrations (n = 89). Staples of the diet in the area studied are millet and sorghum.

Prevalence of goiter, thyroid function, and concentrations of urinary iodine and thiocyanate

The overall prevalence of goiter in the study population was 22.3%; there were no significant differences between boys and girls or between rural and urban children (Table 1). Only 12 (1.2%) of 984 children examined had grade 2 goiter and no children had grade 3 goiter. Univariate analysis of the whole cohort showed no significant predictors of the presence or absence of goiter. In subjects for whom biochemical data were available, univariate analysis showed 2 significant associations between biochemical data and goiter: for RBP (considering values ≤ or > 15 mg/L) and serum transferrin after log transformation. The logistic regression that included RBP and log transferrin, however, showed no significant effect of these variables on the presence of goiter.

The median urinary iodine concentration of the study group was 0.79 μmol/L, with significant differences between boys and girls (Table 1). A fairly high percentage of subjects had urinary iodine concentrations > 1.57 μmol/L (19.3% of all subjects, 24.0% of boys, and 17.4% of girls; P > 0.05).

Serum total T₄ and T₃ concentrations were within their respective reference ranges. In contrast, serum thyrotropin concentrations were greater than the upper limit of the reference range.
TABLE 1

Prevalence of goiter and concentrations of serum thyroxine (T₄), triiodothyronine (T₃), and thyrotropin and urinary iodine and thiocyanate (SCN) in the study population.

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence of goiter</th>
<th>Serum T₄</th>
<th>Serum T₃</th>
<th>Serum thyrotropin</th>
<th>Urinary iodine</th>
<th>Urinary SCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>22.3</td>
<td>121 ± 27</td>
<td>2.26 ± 0.55</td>
<td>3.78 (3.27, 4.23)</td>
<td>0.79 (0.69, 0.98)</td>
<td>257 ± 124</td>
</tr>
<tr>
<td>Boys</td>
<td>[984]</td>
<td>[159]</td>
<td>[159]</td>
<td>[159]</td>
<td>[191]</td>
<td>[180]</td>
</tr>
<tr>
<td></td>
<td>21.2</td>
<td>120 ± 26</td>
<td>2.23 ± 0.57</td>
<td>4.05</td>
<td>0.94</td>
<td>269 ± 114</td>
</tr>
<tr>
<td></td>
<td>[496]</td>
<td>[78]</td>
<td>[78]</td>
<td>[78]</td>
<td>[96]</td>
<td>[89]</td>
</tr>
<tr>
<td></td>
<td>23.4</td>
<td>122 ± 28</td>
<td>2.30 ± 0.55</td>
<td>3.42</td>
<td>0.72</td>
<td>245 ± 134</td>
</tr>
<tr>
<td></td>
<td>[488]</td>
<td>[81]</td>
<td>[81]</td>
<td>[81]</td>
<td>[95]</td>
<td>[91]</td>
</tr>
<tr>
<td>Girls</td>
<td>23.0</td>
<td>120 ± 23</td>
<td>2.27 ± 0.45</td>
<td>3.42</td>
<td>0.88</td>
<td>243 ± 103</td>
</tr>
<tr>
<td></td>
<td>[222]</td>
<td>[43]</td>
<td>[43]</td>
<td>[43]</td>
<td>[51]</td>
<td>[50]</td>
</tr>
<tr>
<td>Urban</td>
<td>21.5</td>
<td>121 ± 28</td>
<td>2.26 ± 0.60</td>
<td>3.78</td>
<td>0.79</td>
<td>262 ± 131</td>
</tr>
<tr>
<td></td>
<td>[762]</td>
<td>[116]</td>
<td>[116]</td>
<td>[116]</td>
<td>[140]</td>
<td>[130]</td>
</tr>
<tr>
<td></td>
<td>21.9</td>
<td>121 ± 24</td>
<td>2.33 ± 0.51</td>
<td>3.74</td>
<td>0.76</td>
<td>252 ± 128</td>
</tr>
<tr>
<td></td>
<td>[562]</td>
<td>[91]</td>
<td>[91]</td>
<td>[91]</td>
<td>[112]</td>
<td>[101]</td>
</tr>
<tr>
<td>Beside Nile</td>
<td>22.8</td>
<td>121 ± 30</td>
<td>2.18 ± 0.61</td>
<td>3.80</td>
<td>0.94</td>
<td>264 ± 121</td>
</tr>
<tr>
<td></td>
<td>[422]</td>
<td>[68]</td>
<td>[68]</td>
<td>[68]</td>
<td>[79]</td>
<td>[79]</td>
</tr>
<tr>
<td>Away from Nile</td>
<td>20.0</td>
<td>121 ± 31</td>
<td>2.23 ± 0.58</td>
<td>3.36</td>
<td>0.79</td>
<td>257 ± 124</td>
</tr>
<tr>
<td></td>
<td>[460]</td>
<td>[76]</td>
<td>[76]</td>
<td>[76]</td>
<td>[93]</td>
<td>[83]</td>
</tr>
<tr>
<td>East of Nile</td>
<td>24.2</td>
<td>121 ± 22</td>
<td>2.30 ± 0.54</td>
<td>4.33 (3.8, 4.77)</td>
<td>0.86</td>
<td>262 ± 134</td>
</tr>
<tr>
<td></td>
<td>[524]</td>
<td>[83]</td>
<td>[83]</td>
<td>[83]</td>
<td>[98]</td>
<td>[97]</td>
</tr>
</tbody>
</table>

1. n in brackets.
2. r ± SD.
3. Median; 95% CI in parentheses.
4. Significantly different from boys, P < 0.0049.
5. Significantly different from east of Nile, P < 0.0013.

(4.0 mIU/L) in 44% of the children (n = 70). The median serum thyrotropin values were 3.78, 3.42, and 4.05 mIU/L for all subjects, girls, and boys, respectively (Table 1). There were no significant differences in mean serum T₄ or serum T₃, the ratio of T₃ to T₄, or median serum thyrotropin between goitrous (thyrotropin: 3.64 mIU/L; n = 26) and nongoitrous (thyrotropin: 3.78 mIU/L; n = 133) children. No cases of biochemical hypothyroidism (low serum T₄ and T₃ with high thyrotropin concentrations) or hyperthyroidism (high serum T₄ and T₃ with undetectable thyrotropin concentrations) were observed.

 Serum thyrotropin values correlated positively with urinary iodine concentrations (r = 0.17, P = 0.0377), with a more marked correlation in boys (r = 0.30, P = 0.0064) than in girls (r < 0.1, NS). Stratification of normal (≤4.0 mIU/L; n = 89) and elevated (>4.0 mIU/L; n = 72) thyrotropin concentration was associated with a significantly different (P < 0.05) median urinary iodine concentration (0.79 compared with 0.96 μmol/L) and with a significantly higher (P < 0.05) number of children with a urinary iodine concentration >1.57 μmol/L (16% compared with 29%). Serum T₃ and T₄ concentrations and the ratio of T₃ to T₄ were not significantly correlated with urinary iodine or serum thyrotropin concentrations. Serum T₃ was positively correlated with serum T₄ (r = 0.56, P < 0.0001).

The overall mean urinary thiocyanate concentration was 257 ± 124 μmol/L. There were no significant differences in mean urinary thiocyanate between groups.

Vitamin A status

The prevalence of Bitot spots in the study population was 2.95% and that of night blindness was 2.54% (Table 2). The prevalence of Bitot spots and history of night blindness were significantly lower in girls than in boys. Also, rural children had a significantly higher prevalence of Bitot spots than did urban children. The pattern of prevalence of night blindness was similar to that of Bitot spots. A logistic regression indicated 2 significant predictors of Bitot spots: sex and weight-for-age (considering z scores < -2 compared with ≥-2; the former was observed in 30% of our study children). A similar analysis for night blindness indicated a significant association only with sex.

Of 157 preschool children, 50 (32%) had serum RBP concentrations below the cutoff corresponding to the lower limit of the reference range for this age (15–30 mg/L). Among the different groups of children, there were no significant differences in the proportions of children having serum RBP values below the cutoff.
The mean hemoglobin concentration of the study population was 1.58 ± 0.26 mmol/L (Table 2); 88% and 68% of children had hemoglobin concentrations < 1.86 and < 1.71 mmol/L, respectively. There were no significant differences in hemoglobin concentrations among the different groups. As expected, serum ferritin was not normally distributed; the median value was 56 μg/L. We found that 13.5% of children had serum ferritin concentrations below the cutoff of 12 μg/L and that 22% had values < 20 μg/L. Additionally, 11.6% of children had both hemoglobin and serum ferritin values below the cutoff (1.71 mmol/L and <12 μg/L, respectively). On the other hand, serum transferrin was approximately normally distributed, with a mean of 3.68 g/L.

Anemia and iron status

The mean hemoglobin concentration of the study population was 59% in girls, there was a significant negative correlation between serum ferritin and serum transferrin concentrations. In girls, there was a significant negative correlation between serum ferritin and serum transferrin concentrations. However, such associations were not specific to the rural population.

Relation between iodine, vitamin A, and iron

A significant, positive correlation was observed between serum T4 and RBP (r = 0.41, P = 0.0059) but not between serum T4 and RBP. In boys, serum T4 also correlated positively with serum ferritin (r = 0.27, P = 0.018). In girls, serum T4 correlated negatively with serum ferritin (r = -0.24, P = 0.0434). No significant modification in serum T4 (120 ± 22 compared with 121 ± 27 mmol/L), serum RBP (22 ± 5 compared with 24 ± 14 mg/L), or serum transferrin (4.02 ± 1.37 compared with 3.60 ± 0.93 g/L) was observed in children with Bitot spots (n = 29) compared with children without Bitot spots.

No specific association was observed between the different variables indicating deficiencies in vitamin A (low RBP concentration), iron (low ferritin concentration), or iodine (low urinary iodine or high thyrotropin concentration) (Table 3). Some variables were associated with low hemoglobin and high transferrin concentrations. However, such associations were not specific to the rural population.
TABLE 3
Percentages of subjects exhibiting an association between the different biochemical indexes investigated in the study

<table>
<thead>
<tr>
<th>Selection criteria</th>
<th>Low RBP (&lt;15 mg/L)</th>
<th>Normal RBP (&gt;15 mg/L)</th>
<th>High thyrotropin (&gt;4 mIU/L)</th>
<th>Normal thyrotropin (&lt;4 mIU/L)</th>
<th>Low ferritin (&lt;20 μg/L)</th>
<th>Normal ferritin (&gt;20 μg/L)</th>
<th>Low Hb (&lt;1.7 mmol/L)</th>
<th>Normal Hb (&gt;1.7 mmol/L)</th>
<th>Low urinary iodine (&lt;0.79 μmol/L)</th>
<th>Normal urinary iodine (&gt;0.79 μmol/L)</th>
<th>Low serum ferritin (&lt;20 μg/L)</th>
<th>Normal serum ferritin (&gt;20 μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ferritin (&lt;20 μg/L)</td>
<td>17.6</td>
<td>24.5</td>
<td>26.8</td>
<td>19.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.0</td>
<td>7.6</td>
<td>8.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Normal ferritin (&gt;20 μg/L)</td>
<td>82.4</td>
<td>75.5</td>
<td>73.2</td>
<td>80.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>17.6</td>
<td>24.5</td>
<td>26.8</td>
<td>19.5</td>
</tr>
<tr>
<td>Low Hb (&lt;1.7 mmol/L)</td>
<td>72.5</td>
<td>66.0</td>
<td>70.8</td>
<td>66.7</td>
<td>77.8</td>
<td>39.3</td>
<td>—</td>
<td>—</td>
<td>45.8</td>
<td>50.5</td>
<td>42.4</td>
<td>53.0</td>
</tr>
<tr>
<td>Normal Hb (&gt;1.7 mmol/L)</td>
<td>27.5</td>
<td>34.0</td>
<td>29.2</td>
<td>33.3</td>
<td>22.2</td>
<td>60.7</td>
<td>—</td>
<td>—</td>
<td>58.8</td>
<td>53.8</td>
<td>—</td>
<td>47.2</td>
</tr>
<tr>
<td>Low urinary iodine (&lt;0.79 μmol/L)</td>
<td>45.8</td>
<td>50.5</td>
<td>42.4</td>
<td>53.0</td>
<td>46.9</td>
<td>49.1</td>
<td>50.5</td>
<td>43.1</td>
<td>54.2</td>
<td>49.5</td>
<td>57.6</td>
<td>53.1</td>
</tr>
<tr>
<td>Normal urinary iodine (&gt;0.79 μmol/L)</td>
<td>54.2</td>
<td>49.5</td>
<td>57.6</td>
<td>47.0</td>
<td>53.1</td>
<td>50.9</td>
<td>49.5</td>
<td>56.9</td>
<td>58.8</td>
<td>53.8</td>
<td>—</td>
<td>52.8</td>
</tr>
<tr>
<td>Normal thyrotropin (&lt;4 mIU/L)</td>
<td>58.8</td>
<td>53.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>47.2</td>
<td>57.4</td>
<td>53.2</td>
<td>41.2</td>
<td>46.2</td>
<td>—</td>
<td>52.8</td>
</tr>
<tr>
<td>High thyrotropin (&gt;4 mIU/L)</td>
<td>41.2</td>
<td>46.2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>52.8</td>
<td>42.6</td>
<td>42.0</td>
<td>2.0</td>
<td>7.6</td>
<td>8.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Normal transferrin (&lt;2.5 g/L)</td>
<td>2.0</td>
<td>7.6</td>
<td>8.6</td>
<td>3.5</td>
<td>0.0</td>
<td>7.5</td>
<td>5.7</td>
<td>6.1</td>
<td>98.0</td>
<td>92.4</td>
<td>91.4</td>
<td>96.5</td>
</tr>
<tr>
<td>High transferrin (&gt;2.5 g/L)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Low RBP (&lt;15 mg/L)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Normal RBP (&gt;15 mg/L)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

1 For the number of subjects in each subgroup, refer to Tables 1 and 2. RBP, retinol binding protein; Hb, hemoglobin.

Because low hemoglobin and high transferrin concentrations were present in most of the study children (68% and 95%, respectively). The multifactor analysis of variance run on the different biochemical indexes explored in the study indicated only one possible association between these different variables. The statistical model showed that when hemoglobin concentration, serum ferritin, and serum RBP were used as independent variables, children with low serum ferritin had a significantly higher ratio of T₃ to T₄ than did children with normal serum ferritin values (Figure 1).

DISCUSSION

We reported data on the iodine status (as assessed by the prevalence of goiter, urinary iodine concentrations, and biochemical indexes of thyroid function), iron status (as assessed by serum ferritin and transferrin concentrations), and vitamin A status (as assessed by the prevalences of Bitot spots and nightblindness and concentrations of serum RBP) of preschool children from the southern Blue Nile area in Sudan. The prevalence of goiter in this population (22.5%) lies in the range of moderate iodine deficiency disorders (20), a finding in contrast with the observation of a high (3.78 mIU/L) median serum thyrotropin concentration in the study population. Whereas the concentrations of circulating T₃ and T₄ suggested complete thyroid compensation for the production of thyroid hormones, the high median thyrotropin value indicates that this compensation was not optimal. A possible effect linked to high iodine intake (19.3% of subjects had urinary iodine concentrations >1.57 μmol/L) is suggested by the positive correlation observed between serum thyrotropin and urinary iodine as well as the association of high thyrotropin values with high urinary iodine concentrations (19 subjects had both urinary iodine concentrations >1.57 μmol/L and thyrotropin concentrations >4 mIU/L). On the contrary, the normal or even elevated urinary iodine concentrations were accompanied by normal

Also contrasting with the fairly high prevalence of goiter, mean and individual serum T₃ and T₄ concentrations were within their respective reference ranges. A second unexpected finding was the observation of a high (3.78 mIU/L) median serum thyrotropin concentration in the study population. Whereas the concentrations of circulating T₃ and T₄ suggested complete thyroid compensation for the production of thyroid hormones, the high median thyrotropin value indicates that this compensation was not optimal. A possible effect linked to high iodine intake (19.3% of subjects had urinary iodine concentrations >1.57 μmol/L) is suggested by the positive correlation observed between serum thyrotropin and urinary iodine as well as the association of high thyrotropin values with high urinary iodine concentrations (19 subjects had both urinary iodine concentrations >1.57 μmol/L and thyrotropin concentrations >4 mIU/L). On the contrary, the normal or even elevated urinary iodine concentrations were accompanied by normal

![FIGURE 1. Mean (±SD) ratio of serum triiodothyronine (T₃) to thyroxine (T₄) in 122 children with normal serum ferritin concentrations (>20 μg/L) and 36 children with low serum ferritin concentrations (<20 μg/L). The difference between groups was significant (P = 0.0362).](https://academic.oup.com/ajcn/article-abstract/71/1/59/4729192)
serum thyroid hormone concentrations, suggesting an intrathyroidal effect on the metabolism of iodine. Such an effect is further supported by the absence of a significant relation between \( T_3 \) and urinary iodine or between \( T_4 \) and thyrotropin.

The pattern of alterations in iodine metabolism observed in our study children is markedly similar to that we reported recently in rats fed a fermented millet diet (7). Notwithstanding an appropriate iodine intake, rats developed an enlargement of the thyroid gland concomitant with a rise in serum thyrotropin, despite normal or even slightly elevated serum \( T_3 \) and \( T_4 \) concentrations. Although a direct causal relation is difficult to establish because biochemical markers of the presence of flavonoids are not available, one can reasonably assume that these are the first data collected in humans that clearly suggest that flavonoids from millet play a role in the development of goiter in the study area. In contrast with thiocyanate, flavonoids (polyhydroxyphenols) do not act on the active transport of iodide but instead inhibit the processes of organification of iodide and the coupling of iodotyrosines (moniodotyrosine and diiodotyrosine), exactly as synthetic antithyroid compounds do. The effect of flavonoids that cannot be balanced by an increase in iodine intake could be mediated either through an action on the deiodinase at the pituitary level or through an inhibition of the binding of \( T_3 \) to transthyretin (26). This of course does not exclude other possibilities because the mechanism of action of phenolic compounds is not yet fully elucidated.

The mean urinary thiocyanate concentration in the population studied was high (257 \( \mu \text{mol/L} \)) and is similar to values observed in subjects in Central Africa who ate cassava (27). Millet has been shown to contain little if any precursors of thiocyanate (28; A. Elnour, unpublished observations, 1998). One can thus reasonably assume that sorghum, the other staple food in the area, was the major source of thiocyanate in our subjects because beside flavonoids (29), sorghum contains dhurrin, a cyanogenic glucoside. The fairly high thiocyanate concentration may not have been a major factor in the development of goiter, however, because the mean ratio of iodine to thiocyanate (0.0053 \( \mu \text{mol} / \mu \text{mol} \), or 11.6 \( \mu \text{g/mg} \)) was well above the critical level of 0.0014 \( \mu \text{mol} / \mu \text{mol} \) (3 \( \mu \text{g/mg} \)) below which goiter develops (30).

Most likely other factors accounted for the presence of endemic goiter (31). These include protein-energy malnutrition, vitamin A deficiency, and possibly other goitrogens. The study population was deficient in vitamin A, as evidenced by the prevalence of night blindness (2.64%) and Bitot spots (2.94%), which by far exceeded the criteria used for defining a public health problem (15). Similar prevalences were reported in other parts of the country (32, 33). The striking difference between children living in urban and rural areas was probably related to better nutrition and sanitary conditions in the urban environment. Low concentrations of serum RBP in 32% of the study population corroborated the clinical indicators of vitamin A deficiency. The cause of the higher prevalence of vitamin A deficiency in boys than in girls is not known but similar sex differences were reported previously (1, 32–34). Other studies have also implicated vitamin A deficiency in the etiology of endemic goiter (1, 8, 35).

The low serum RBP concentrations observed in 32% of the study population may indicate the existence of protein-energy malnutrition. The role of protein-energy malnutrition in the etiology of endemic goiter has been suggested repeatedly (36, 37). RBP circulates in the blood complexed to transthyretin (38), an indicator of subclinical malnutrition (39, 40) that has been shown to correlate negatively with the grade of goiter (8). Noteworthy in our study was the observation that serum RBP correlated positively with serum \( T_4 \). The low median height-for-age of the study population indicated chronic malnutrition, whereas the high median weight-for-height indicated that the study population was not suffering from an acute energy deficit (41). Furthermore, the observation of high transferrin concentrations in 95% of our study children precludes the existence of protein deficiency (42).

The subjects’ hemoglobin, serum ferritin, and serum transferrin concentrations—which are regarded as the most suitable biochemical indexes for determining iron status (43)—indicated that anemia was a major problem in the study area. The mean hemoglobin value in our population was 1.58 mmol/L and 68% of the children had concentrations <1.71 mmol/L, the cutoff indicative of anemia according to criteria recommended by the World Health Organization (44). Serum ferritin measurements, an indicator of the status of body iron stores, showed that only 11.6% of the study children had some sort of iron deficiency (hemoglobin <1.71 mmol/L and serum ferritin <12 \( \mu \text{g/L} \)). However, it has been suggested that in the presence of anemia the cutoff for serum ferritin be raised to 20 \( \mu \text{g/L} \) (45). With use of this criterion, 22% of the study children would have been classified as having some sort of iron deficiency. On the other hand, if a rise in serum transferrin was used as indicator of iron depletion, 72% of the children would have been classified as having iron depletion. However, concentrations of both serum ferritin and serum transferrin are known to be elevated in chronic infection, which was common in the study population. Moreover, anemia from causes other than iron deficiency (eg, sideroachrestic anemia) was also shown to raise serum ferritin concentrations (46). This condition, however, is exceptional. Malaria, which is highly endemic in the study area, is another known cause of anemia and may consequently raise serum ferritin and serum transferrin concentrations, thereby reducing the specificity of these indexes of iron status (47). These results indicate that the exact contribution of iron deficiency to the anemia observed in the studied group is difficult to evaluate. Of special interest here was the vitamin A deficiency observed because it was shown that hypovitaminosis A affects iron metabolism (48–51).

In conclusion, our data failed to yield direct evidence of iodine deficiency in preschool children in the southern Blue Nile area but did suggest for the first time the instrumental role of goitrogenic substances from millet in the etiology of endemic goiter. Our observations confirm that assessing endemic goiter simply by the prevalence of goiter and the measurement of urinary iodine is not sufficient; assessment should also include at least the measurement of serum \( T_4 \) and thyrotropin (52). In contrast with our findings for iodine status, vitamin A deficiency and iron deficiency anemia were found to be serious problems for the preschool children living in this area. Although we did not collect data for other age groups, it is highly probable that the whole population is affected by these disorders. Such a situation requires intervention in this target group or possibly even in the entire population.

We thank E Fadul, the ophthalmology registrar, for his great help in conducting the clinical examinations. We are also grateful to Adil Balal, technician at the Department of Physiology, University of Khartoum, Sudan, for technical assistance.
REFERENCES


