Insulin-like growth factor-1 and zinc status of goitrous primary-school children in Arak, Islamic Republic of Iran

M.R. Rezvanfar,1 H. Farahany,2 M. Rafiee3 and B. Eshratee3

ABSTRACT Despite a successful national salt iodination programme, endemic goitre still persists in Iranian children. In a cross-sectional study in Arak the prevalence of goitre was 5.2% in a sample of 6520 primary-school children. Subsamples of 193 children with goitre and 151 healthy children were assessed for urinary iodine excretion, thyroid hormone profile, insulin-like growth factor-1 (IGF-1) and serum zinc. The mean urinary iodine levels of goitrous children and healthy children were 17.4 µg/dL and 15.3 µg/dL respectively, suggesting that iodine consumption was adequate. No significant differences were found between goitrous and healthy schoolchildren in mean levels of urinary iodine, serum IGF-1 or serum zinc. Other factors need be evaluated to explain the residual prevalence of goitre.

1Division of Endocrinology, Department of Internal Medicine; 2Division of Hormones, Department of Biochemistry; 3Division of Statistics, Department of Social Medicine, Arak University of Medical Sciences, Arak, Islamic Republic of Iran (Correspondence to M.R. Rezvanfar: rezvanfar@gmail.com).

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Iodine deficiency used to be common in the Islamic Republic of Iran and, after a national programme of salt iodization was set up in 1994, considerable success has been achieved in reducing endemic goitre. Nevertheless, endemic goitre still persists in Iranian schoolchildren.

Introduction

The present study was a cross-sectional descriptive study, conducted during the school year 2005–06 in 16 urban government primary schools (8 boys’ and 8 girls’ schools) in Arak, the capital of Markazi province in the Islamic Republic of Iran.

Methods

The schools were chosen using a 1-stage clustered random sampling technique from 2 different educational divisions in Arak educational organization. The sites were selected to include areas with different environmental and socioeconomic characteristics.

All students in the chosen schools were included in the study and 6520 schoolchildren aged 6–11 years were screened for thyroid gland volume. Goitre was assessed clinically and assigned to 1 of 3 stages according to the World Health Organization/International Council for the Control of Iodine Deficiency Disorders/United Nations Children’s Fund (WHO/ICCIDD/UNICEF) criteria: stage 0 (no palpable or visible goitre); stage 1 (goitre detectable only by palpation and not visible when the neck is in the normal position, and including nodular glands even if not goitrous); stage 2 (goitre visible with the neck in normal position, and is consistent with an enlarged thyroid when the neck is palpated) [13].

Of 6520 children screened, 400 students aged 6–11 years (200 goitrous and 200 healthy) and their parents were selected using random number tables and invited to participate in the laboratory investigations. The exclusion criteria were the presence of any systemic chronic disease or having received prior thyroid medication. The biochemical evaluations included measurements of urinary iodine, total serum T₄, total serum T₃, serum thyroid-stimulating hormone (TSH), serum IGF-1 and serum zinc level.

Data collection

Casual urine samples were obtained from children in the morning hours and were frozen until analysis. Urinary iodine concentrations were measured at the University of Arak by alkaline washing followed by iodide extraction from ash residue and spectrophotometry using the Sandell–Kolthoff reaction [14].

The normal level of urinary iodine was defined as ≥ 10.0 µg/dL, mild iodine deficiency 5.0–9.9 µg/dL, moderate iodine deficiency 2.0–4.9 µg/dL and severe iodine deficiency < 2.0 µg/dL.

Blood samples were obtained from the children and serum was prepared and frozen until analysis. Total T₄ and total T₃ were measured by radioimmunoassay (Radim ELA kit, Italy). The detection limits of the T₄ and T₃ assays were 4.0 ng/mL and 0.15 ng/mL, and normal ranges were 45–120 ng/mL and 0.5–1.6 ng/mL respectively. Serum TSH concentration was measured by immunoenzymometric assay technique (Radim IEMA kit, Italy). The detection limit of the TSH assay was 0.1 mU/L, and the normal reference range was 0.32–4.00 mU/L.

Serum IGF-1 was assayed by a competitive binding radioimmunoassay (Nichols Institute Diagnostics, California). The intra-assay coefficient of variation (CV) was less than 3%, and the interassay CV was less than 8.4%.

The children’s serum zinc status was evaluated by an improved version of the method of Lampugnani et al. [15]. The serum zinc concentration was determined by spectrophotometric methods after deproteinization of samples. The chromogen used was 4-(2-pyridylazo)resorcinol sodium salt. The interference of iron and copper ions was eliminated by masking agents. The absorbance of the obtained colour solution was recorded at λ = 490 nm. The absorption was proportional to the zinc concentration. Zinc deficiency was defined as a zinc level ≤ 65 mg/dL [8].
The ethics committee of Arak University of Medical Sciences approved the study, which was carried out in accordance with the ethical standards of the Helsinki Declaration, 1975 (revised 1983). Written permission for the study was obtained from the Education Organization of Arak city and the headteachers and chiefs of the schools involved. Parents also signed consent forms.

Statistical analysis

The differences between groups of subjects were assessed by the chi-squared and Mann–Whitney tests for comparisons between frequencies. Statistical significance was set at \( P < 0.05 \).

Results

The clinical examinations showed that the prevalence of goitre (stage 1 and 2) among the whole schoolchild population in Arak was 5.2%, ranging from 3.6% to 6.4% in different schools. Of the 340 children with goitre, 43.5% were classified as stage 2 according to the WHO/ICCIDD/UNICEF criteria. The prevalence of goitre increased with age, from 3.0% in children aged 6–7 years to 6.3% in children aged 11 years (\( P < 0.001 \)). The prevalence of goitre was not significantly different from that of healthy children [89.0 (SD 17.0) mg/dL] (\( P = 0.16 \)) (Table 2).

The mean serum total \( T_3 \) and \( T_4 \) levels in zinc-deficient children were similar to those without deficiency, whereas serum TSH was significantly lower in zinc-deficient children (\( P = 0.04 \)) (Table 3). Of the zinc-deficient children, 62.5% had goitre compared with only 45.1% of those without zinc deficiency, although this was not a statistically significant difference (\( P > 0.46 \)).

Discussion

Because goitre represents maladaptation of the thyroid to iodine deficiency, a reduction of the goitre rate to < 5% in school-age children is thought to indicate the disappearance of iodine deficiency disorder as a significant public health problem [13]. In our study, the prevalence of goitre in the sample of schoolchildren in Arak was 5.2%, which is slightly higher than this criterion but is dramatically lower than the goitre rate of 20% reported in a previous study in Arak in 1997 [16].

Our results showing that the total mean urinary iodine concentrations of the goitrous and healthy children were above the cut-off for abnormal levels indicate that the iodine supply in children’s diets in Arak is adequate. It supports the suggestion that iodine deficiency was not the cause of the persistence of goitre after a decade of successful nationwide salt iodination and that other goitreogenic factors may be responsible for the continuing prevalence of goitre in this area of Islamic Republic of Iran.

Growth factors are well-documented factors regulating the proliferation of follicle cells of the thyroid in many in vitro experiments [17]. It has been demonstrated that IGF-1 stimulates cellular mitogenesis of tyreoocytes, whereas TGF-β1 inhibits the proliferation of follicle cells of the thyroid in experimental conditions [4]. In our study we did not find any significant difference in serum IGF-1 levels between goitrous and healthy children. These results were similar to Aydin et al.’s study in Turkey [6]. This might be due to the negative impact of thyroid dysfunction on IGF-1 levels. There are some other reports of a negative impact

### Table 1 Demographic characteristics of schoolchildren with and without goitre

<table>
<thead>
<tr>
<th>Variable</th>
<th>With goitre (n = 193)</th>
<th>Without goitre (n = 151)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean (SD)] (years)</td>
<td>9.33 (1.36)</td>
<td>8.90 (1.35)</td>
<td>0.33*</td>
</tr>
<tr>
<td>Males [No. (%)]</td>
<td>106 (55)</td>
<td>92 (61)</td>
<td>0.26*</td>
</tr>
<tr>
<td>Females [No. (%)]</td>
<td>87 (45)</td>
<td>59 (39)</td>
<td>0.38*</td>
</tr>
<tr>
<td>Weight [mean (SD)] (kg)</td>
<td>29 (6.2)</td>
<td>28 (5.9)</td>
<td>0.12*</td>
</tr>
<tr>
<td>Height [mean (SD)] (cm)</td>
<td>136 (9.0)</td>
<td>134 (8.5)</td>
<td>0.16*</td>
</tr>
<tr>
<td>BMI [mean (SD)] (kg/m²)</td>
<td>15.7 (1.8)</td>
<td>15.7 (1.9)</td>
<td>0.81*</td>
</tr>
<tr>
<td>Educational sampling area 1 [No (%)]</td>
<td>77 (40)</td>
<td>67 (45)</td>
<td>0.53*</td>
</tr>
<tr>
<td>Educational sampling area 2 [No (%)]</td>
<td>116 (60)</td>
<td>84 (55)</td>
<td>0.99*</td>
</tr>
</tbody>
</table>

*\( \chi^2 \)-test; **Mann–Whitney test.

\( SD = \) standard deviation; \( BMI = \) body mass index.
of thyroid dysfunction or iodine deficiency on IGF-1 levels [18,19].

Mild-to-moderate zinc deficiency is common in developing countries because of a low dietary intake of zinc-rich animal-source foods, in which zinc is more bioavailable, and a high consumption of legumes and cereal grains, which contain inhibitors of zinc absorption [20–22]. No children had serum zinc concentration < 55 mg/dL, below the cut-off for moderate deficiency, but serum zinc ≤ 65 mg/dL, indicating mild zinc deficiency, was found in 10.8% of the goitrous children and 7.2% of the healthy children. This rate is lower than that found in other developing countries (30%–55%) [23,24], but still higher than in industrialized nations [25].

In our study, the plasma TSH level was significantly lower in zinc-deficient children, but serum total T3 and T4 concentrations were not affected by zinc status. T4 to T3 conversion and feedback to the hypophysis may be affected by zinc deficiency. In animal studies, severe zinc-deficient rats had flattened epithelial cells, colloid accumulation and lower T3 concentration [26,27]. However, the thyroid glands of zinc-deficient animals were smaller in size and pale or whitish pale in colour. Histopathologically, these glands showed atrophy and degeneration in the follicles [11]. Olivieri et al. did not find any relation between human zinc status and thyroid function [28], whereas Onishchenko et al. found that in regions exposed to some toxic metals and organic compounds zinc deficiency was a goitrogenic factor that aggravated the severity of goitre prevalence in the presence of iodine deficiency [10].

In a zinc depletion–repletion study carried out in humans, TSH, total T4 and free T4 tended to decrease during the depletion phase and returned to control levels after zinc repletion [29]. Those results suggested that zinc may play an important role in thyroid hormone metabolism, although the exact mechanism by which zinc affects thyroid hormone function is far from clear.

Some of the selected children did not complete the survey and this was a limitation of the present study. Furthermore, as our study was limited to data from 16 urban schools in Arak it may not be possible to generalize the results to the whole schoolchild population of Islamic Republic of Iran.

To summarize, normal levels of urine iodine were found in both goitrous and healthy children. We found no significant differences in thyroid hormone, zinc, iodine or IGF-1 levels between goitrous and healthy schoolchildren. There was no significant difference in the prevalence of goitre between children with low and normal zinc levels. Further studies are needed to explain the residual prevalence of goitre the Islamic Republic of Iran.

Acknowledgements

The authors are indebted the General Office of Education and Training in Arak city and the head teachers and chiefs of the schools for their kind cooperation. We are extremely indebted to the authorities of the Research Deputy of Arak University of Medical Sciences for their financial and logistic support. We are most grateful to the laboratory centres of Vali-Asr hospital and the biochemistry department.

<table>
<thead>
<tr>
<th>Variable</th>
<th>With goitre (n = 193)</th>
<th>Without goitre (n = 151)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine iodine (μg/mL)</td>
<td>Mean 17.4 (95% CI 13.7–21.1)</td>
<td>Mean 15.3 (95% CI 12.1–18.5)</td>
<td>0.75*</td>
</tr>
<tr>
<td>Serum T3 (ng/mL)</td>
<td>Mean 85.6 (95% CI 82.9–88.3)</td>
<td>Mean 85.6 (95% CI 82.6–88.6)</td>
<td>0.88*</td>
</tr>
<tr>
<td>Serum T4 (ng/mL)</td>
<td>Mean 1.36 (95% CI 1.30–1.42)</td>
<td>Mean 1.28 (95% CI 1.22–1.33)</td>
<td>0.06*</td>
</tr>
<tr>
<td>Serum TSH (μg/mL)</td>
<td>Mean 2.46 (95% CI 2.04–2.88)</td>
<td>Mean 2.52 (95% CI 2.06–2.44)</td>
<td>0.25*</td>
</tr>
<tr>
<td>Serum IGF-1 (ng/mL)</td>
<td>Mean 101.0 (95% CI 76.8–125.2)</td>
<td>Mean 84.0 (95% CI 62.6–105.4)</td>
<td>0.22*</td>
</tr>
<tr>
<td>Serum zinc (μg/dL)</td>
<td>Mean 84.3 (95% CI 79.9–88.7)</td>
<td>Mean 89.0 (95% CI 84.0–93.9)</td>
<td>0.11b</td>
</tr>
</tbody>
</table>

*Mean–Whitney test; Student t-test.

T3 = tri-iodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; IGF-1 = insulinlike growth factor.
CI = confidence interval.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum zinc level</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum T3 (ng/mL)</td>
<td>Mean (SD) 90 (18.2)</td>
<td>Mean (SD) 82 (21.8)</td>
</tr>
<tr>
<td>Serum T4 (ng/mL)</td>
<td>Mean (SD) 1.35 (0.30)</td>
<td>Mean (SD) 1.30 (0.05)</td>
</tr>
<tr>
<td>Serum TSH (μg/mL)</td>
<td>Mean (SD) 1.50 (1.05)</td>
<td>Mean (SD) 2.78 (0.30)</td>
</tr>
</tbody>
</table>

*Mean–Whitney test.

T3 = tri-iodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; SD = standard deviation.
References


