Endemic goiter in Greece: nutritional status, growth, and skeletal development of goitrous and nongoitrous populations


Iodine metabolism and thyroid function have been studied extensively in subjects with endemic goiter. Little attention, however, has been given to the growth pattern and general nutritional and health status of goitrous subjects with the exception of endemic cretinism, which is associated with severe iodine deficiency.

In Greece, nontoxic goiter is endemic (1), and previous work has shown that the main factor responsible is iodine deficiency (2, 3). This deficiency is of mild degree and associated with euthyroid status, absent endemic cretinism, but with a slight reduction of the mean PBI level. Any gross abnormality in the general health of persons living in endemic goiter regions of Greece would not likely escape the notice of medical field workers. More discreet and subtle defects could, however, easily escape casual clinical inspection and be revealed only by systematic comparison of goitrous and nongoitrous populations.

This study has been undertaken in spite of several inherent difficulties. Firstly, in endemic areas, nongoitrous persons share the same environment as goitrous, are iodine deficient almost to the same degree, and they also present similar metabolic abnormalities (2). It is not, therefore, appropriate to accept the nongoitrous inhabitants of endemic areas as healthy controls. Secondly, it has been shown previously (4) that subnormal iodine intake does not constitute the only deficiency in these areas, as lower concentrations of several other trace micronutrients, e.g., zinc, are present in soil and water. Furthermore, drinking water in the endemic areas is more often polluted than in the nongoitrous villages (Table 1).

These difficulties have not been underestimated nor are the findings amenable to ready interpretation. In spite of these reservations, the present work has been undertaken because of the public health problem posed. We have, therefore, compared body build, nutritional status, and skeletal development of goitrous and nongoitrous subjects from endemic areas, using comparable rural populations as controls. The present study indicates that subjects living in the goitrous regions of Greece exhibit clear evidence of calorie undernutrition, have different body build characteristics, and suffer from delayed skeletal development. The present results should, however, be considered as preliminary only. More biochemical studies are needed in order to define the problem more clearly, and, what is more important, the results indicate that more work is needed in order to decide whether the relationships observed here are causal or not.

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Study population, materials, and methods

Schoolchildren attending primary schools in seven villages were surveyed and comprised six groups: 248 male and 245 female children from three predominantly nongoitrous villages (Figs. 1–4) (the few goitrous children from these villages were not included in this study); 210 male and 185 female goitrous children from four goitrous villages (Prodromos, Kerasochorion, Pheke, and Kephalovryson); finally 176 male and 138 female children without goiter, but living in the same villages where some inhabitants were affected with endemic goiter.

Determinations included body height, weight, skin-fold thickness, and bone age. The skin-fold thickness was measured with a caliper (John Bull, British Indicators), over the triceps, half-way down the left arm between the tip of the acromion and the top of the radius. The bone age was determined by an X-ray of the left hand, obtained with a portable apparatus, according to the criteria of Greulich and Pyle (5) without prior knowledge of the chronological age of the children or the group to which they belonged. The completed chronological age was determined by obtaining the date of birth from the records of the community.

Covariance analysis (6) was used to compare the age subgroups of the six study populations. Linearity was established for height, weight, and bone age. This was not present in the case of the skin-fold thickness measurements, nor were these normally distributed, but the clear-cut difference observed in this parameter between those subjects living in the endemic and the nonendemic villages made statistical sophistication redundant.

In eight villages, two nongoitrous (Pelagia and Farkadon) and six goitrous (Prodromos, Kerasochorion, Verdikoussa, Kallipefke, Exaplatanos, and Gardikion), males aged 40 years or more were also studied. They were subdivided into three groups: 119 nongoitrous persons from the nongoitrous villages and 81 goitrous and 198 nongoitrous from the villages with endemic goiter. Goitrous males from the nongoitrous villages were again excluded, because their number was small and therefore insufficient as an independent group.

In all of these patients, the body weight and height and the skin-fold thickness were measured, and the ponderal index (7) was calculated as

$$\text{PI} = \frac{\text{BW}}{\text{IBW}}$$

where PI = ponderal index, BW = body weight and IBW = ideal body weight, calculated as

$$\text{IBW} = \text{height} - \frac{100 - \text{height} - 150}{4}.$$  

From 75 of the adult males examined in three of these villages, the nongoitrous Pelagia and the goitrous Prodromos and Verdikoussa, serum was obtained and shipped by air in Dry Ice to New York, where the serum cholesterol, tryglycerides, vitamin A, beta carotene, and folate were assayed by standard methods (8–11).

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**FIG. 1.** The body height of children in endemic and non endemic villages, according to age, separately for males and females.
Results

The results obtained in children by sex are shown in graphic form in Figs. 1–4. In all parameters, significant differences (or even suggestive trends) were not observed between children with and without goiter from the endemic areas. Therefore, these were con-
sidered together, in comparison with the non-goitrous children from the nonendemic areas.

Figure 1 reveals that the height of the children from the nonendemic areas was significantly greater than that of the children from the goitrous areas (for males \( t = 2.93, P < 0.005 \), for females \( t = 4.02, P < 0.001 \)). As seen in Fig. 2, the body weight of the children from the nonendemic areas was significantly greater compared with that of the goitrous areas (for males \( t = 5.68, P < 0.001 \), for females \( t = 6.77, P < 0.001 \)).

The skin-fold thickness (Fig. 3) of the children from the nonendemic areas was much greater than that of the children living in the goitrous areas. The difference was obvious; calculation showed that for males \( t = 9.55, P < 0.001 \) and for females \( t = 12.50, P < 0.001 \). If all the children are considered together, then the mean ± SE skin-fold thickness in the males from the control villages (10.3 ± 0.29 mm) was significantly larger than the value 7.2 ± 0.14 mm (\( P < 0.001 \)) obtained in the nongoitrous children living in the endemic areas, and from the value 6.9 ± 0.15 mm found in the goitrous children (\( P < 0.001 \)). There was no significant difference between the goitrous and the nongoitrous male children living in the same endemic goiter areas. Similarly, for the females, the mean value 12.9 ± 0.30 mm found in the control areas was significantly higher than the value 9.1 ± 0.22 mm obtained in the nongoitrous girls from the endemic areas (\( P < 0.001 \)). Again, there was no significant difference between the goitrous and nongoitrous girls living in the regions with endemic goiter.

The bone age (Fig. 4) of the children from the nonendemic areas was more advanced or less retarded compared with the American standards of Greulich and Pyle (5) than that of the children living in the endemic areas (for males \( t = 2.22, P = 0.025 \), for females \( t = 1.96, P = 0.05 \)).

Results obtained in adult males are shown in Table 2. The control subjects from the nonendemic villages were significantly shorter than either the goitrous (\( P < 0.005 \)) or the nongoitrous (\( P < 0.05 \)) inhabitants of the endemic areas. They were heavier, however, but the difference was significant only in comparison to goitrous persons. Their ponderal index was significantly greater than that of both the goitrous (\( P < 0.001 \)) and the nongoitrous (\( P < 0.02 \)) inhabitants of the endemic areas. The same was true for the skin-fold thickness (\( P < 0.001 \) for the goitrous and \( P < 0.01 \) for the nongoitrous).

The males living in the control village of Pelasgia had a significantly higher serum cholesterol level than the nongoitrous (\( P < 0.05 \)) or goitrous (\( P < 0.02 \)) men of similar age living in the endemic regions. Higher serum triglyceride

![Figure 4](https://academic.oup.com/ajcn/article-abstract/26/12/1360/4695239/4695239)

FIG. 4. The bone age, assessed by a radiograph of the hand, of children in endemic and nonendemic villages, according to age, separately for males and females.
levels were also observed, the difference approaching significance ($P < 0.05$) only from the goitrous men. A significantly higher vitamin A level from either the nongoitrous ($P < 0.02$) or the goitrous men ($P < 0.005$) was noted, and significantly higher serum carotenes ($P < 0.005$ for the nongoitrous and $P < 0.001$ for the goitrous). Serum folate was the same in the controls and the goitrous subjects but significantly higher ($P < 0.005$) in the nongoitrous men living in the endemic areas.

Within the endemic villages, there was no statistically significant difference in the height between the goitrous and the nongoitrous men, but the latter were heavier ($P < 0.05$), and had, as expected, a higher ponderal index ($P < 0.01$) and a thicker skin fold ($P < 0.001$). From the biochemical determinations, serum folate was higher in the nongoitrous compared with the goitrous men.

**Discussion**

The results presented above strongly suggest that individuals living in areas with endemic goiter present suggestive signs of suboptimal nutritional status and delayed growth compared with a control population; the possibility that the controls are actually overfed must also be considered. Although there is no difference in any of the parameters examined between goitrous and nongoitrous children living in the endemic areas, both of these groups display delayed growth and skeletal maturation compared with nongoitrous children from the control areas. Goitrous children tend to be shorter than the controls, but goitrous adult men seem to be taller and thinner.

The similarity between the goitrous and nongoitrous children living in the endemic areas may be explained by the previous observations that both goitrous and nongoitrous inhabitants of endemic areas are iodine deficient and share the same pathologic environment as defined in a previous epidemiologic study (4) and the same abnormalities of iodine metabolism (2). It seems reasonable therefore that they present also the same characteristics in body growth. The delayed bone maturation may explain why these children eventually catch up and may even become slightly taller as adults than the control population.

The observed differences in body weight, skin-fold thickness, and ponderal index between the inhabitants of the endemic and nonendemic areas can presumably be produced only by a lower intake of calories. Direct evidence for this is lacking and difficult to obtain, but Najjar and Woodruff (12) and Lobo et al. (13) have previously shown that endemic goiter especially affects rural populations and the lower socioeconomic classes. It seems probable that the more prosperous families obtain more calories and more food of animal origin, which is richer in iodine than vegetables (14), and also some food items imported from nonendemic areas.

Calorie malnutrition, however, does not exclude a contributory role of other factors, such as protein undernutrition, subclinical hypothyroidism, lack of iodine or some other element, or the other findings from the epidemiologic survey previously mentioned (4). The possible role of subclinical hypothyroidism is suggested by the finding of a lower but
not abnormal PBI in the persons living in endemic areas (2). Although the PBI values are generally normal, there is a significant mean difference or a suggestive trend in comparison to the normal controls from the nonendemic areas. Furthermore, following iodized salt prophylaxis, the serum PBI increases significantly (15). In other areas with a more severe iodine deficiency, low PBI values may be found (16–20). Although a low PBI may not necessarily mean hypothyroidism, if the decrease in circulating thyroxine is compensated by an increase in its turnover or in the triiodothyronine secretion rate (14, 21), all the evidence available points to a mild degree of subclinical hypothyroidism. In areas with a severe deficiency, the raised serum TSH values (20) are confirmatory.

The possibility that iodine deficiency per se has a deleterious effect cannot be lightly dismissed. That endemic cretinism is due to a prenatal deficiency of iodine acting on the fetus after conception has been recently suggested (22). It is therefore conceivable that a milder deficiency of this halogen may somehow hinder normal development, though not to a degree comparable to cretinism.

A deficiency of some other elements, such as sodium, potassium, calcium, magnesium, zinc, and others (4) may exist and may play a role in the delayed growth of children living in endemic areas. A syndrome characterized by short stature and sexual retardation has been described and attributed to zinc deficiency (23–25). In the endemic areas of Greece, serum zinc has not been measured, but it may be low because the concentration of this element in the drinking water is low. Furthermore, bacterial pollution of the drinking water, which is frequent in the endemic areas, cannot be absorbed without further studies. The increased growth of germfree animals is well-known.

A survey of the literature is not helpful in assessing the relative importance of the potential factors discussed. Fierro-Benitez et al. (26) studied two goitrous towns in Ecuador and found a lower mean body weight in the inhabitants of one compared with the other. The same team (27) found decreased body height and weight in the goitrous children, but in a preliminary study, they could not detect any effect of iodized oil on the growth pattern. Furthermore, after iodized oil, they found (28) an increase in the mass of compact bone without a greater linear growth than expected or an amelioration in the rate of ossification. The same team also tried to estimate the effect of iodized oil on intelligence but could not arrive at conclusive results (29). Generalized malnutrition was mentioned in endemic goiter in Mexico (30), but the data reported did not allow an elucidation of the various factors involved.

Furthermore, the possibility that a generalized protein–calorie undernutrition plays a potentiating effect in the pathogenesis of endemic goiter should also be investigated by obtaining more biochemical parameters of nutrition and by supplementing total calories, proteins, and trace metals excluding iodine. It is perhaps relevant that the thyroid gland of rats fed a low protein diet shows histological signs of hypoactivity, which is probably secondary to insufficient secretion of TSH, as their pituitary contains only minute amounts of TSH (31). On the other hand, male rats receiving a low protein, low iodine diet had a high 6-hr $^{131}$I thyroidal uptake with gradual discharge of $^{131}$I in the following hours and high plasma inorganic $^{131}$I and BE $^{131}$I 51 hr after the administration of the tracer (31). It was assumed that these changes could be attributed to the concomitant decrease in renal clearance of $^{131}$I (32). On the other hand, Aschkenasy (33) found that a protein-free diet induced a relatively greater hypertrophy of the thyroid gland in response to iodine deficiency associated with propyl-thiouracil treatment. Recently, children with protein–calorie malnutrition were found to have low plasma TSH levels, which rose after a well-equilibrated diet (34).

From all this evidence it should be clear that the present results are preliminary only, and that further work is required in order to find out which of the possible factors mentioned is actually operating. A prospective controlled study of the effects of iodine prophylaxis is urgently required. This may solve the problem whether iodine deficiency plays a direct role on the retardation of goitrous children and the anthropometric characteristics of the adults, or whether these are due solely to some other associated nutritional deficiency.

In any case, the results of the present study, although preliminary, are in agreement with other findings (2) and allow the conclusion that
it is no longer legitimate to compare the inhabitants of the endemic areas with those living in the nonendemic as if the only difference were the iodine intake. Persons with endemic goiter live in a well-defined geological environment which presents many deficiencies, such as drinking water with less iodine and smaller concentrations of several other elements, whereas bacterial pollution is more frequent. Also, these persons are considerably thinner than persons living in control areas and display some other minor differences. Their deviations should not be ascribed to iodine deficiency alone without consideration of the other factors outlined.

Summary

The height, weight, skin-fold thickness, and bone age were measured in 395 goitrous and 314 nongoitrous children living in four villages with endemic goiter comparatively with 493 nongoitrous children living in three goiter-free villages. There was no significant difference between the goitrous and nongoitrous children living in the endemic areas, but all these children as a group presented a lower body height, a smaller body weight, a thinner skin fold, and delayed bone maturation, comparatively, than the children living in the goiter-free villages. Similarly, 81 goitrous and 198 nongoitrous men more than 40 years old and living in six villages with endemic goiter were compared with 119 nongoitrous men from two goiter-free villages. The control subjects were shorter but heavier and with a larger skin fold than the men living in the endemic areas and had a higher level of serum cholesterol, triglyceride, vitamin A, and carotene. There was no significant difference in the serum folate, except for the higher values in the nongoitrous men from the endemic areas. We concluded that 1) endemic goiter is associated with evidence of generalized malnutrition, 2) nongoitrous persons living in the endemic areas cannot be considered as metabolically normal controls, and 3) more research is required to define the role, if any, of generalized undernutrition in the pathogenesis of iodine deficiency goiter.

References

16. SCRIMSHAW, N. S., A. CABEZAS, F. CASTILLO AND J. MENDEZ. Effect of potassium iodate on endemic goiter and protein-bound...