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The Spectrum of Thyroid Disorders in an Iodine-Deficient Community: The Pescopagano Survey*

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ABSTRACT

We carefully assessed thyroid status and goiter by ultrasound in 1411 subjects virtually representing the entire resident population of Pescopagano, an iodine-deficient village of Southern Italy. Median urinary iodine excretion was 55 μg/L. The prevalence of goiter was 16.0% in children and 59.8% in adults. Thyroid nodularity was 0.5% in children and progressively increased with age to 28.5% in the 56- to 65-yr-old group. The prevalence of present or past hyperthyroidism was 2.9%, including 9 cases with toxic diffuse goiter and 20 with toxic nodular goiter. Functional autonomy was rare in children, progressively increased with age up to 15.4% in the elderly, and was related to nodular goiter. The prevalences of overt and subclinical hypothyroidism in the adults were 0.2% and 3.8%, respectively. Serum autoantibodies to thyroglobulin and thyroperoxidase were detected in 12.6% of the entire population. The prevalence of diffuse autoimmune thyroiditis was 3.5%, being very low in children. Thyroid cancer was found in only 1 case. In conclusion, in the present survey of an iodine-deficient community, a progressive increase with age of goiter prevalence, thyroid nodularity, and functional autonomy was observed. Hyperthyroidism was twice as high as that reported in iodine-sufficient areas, mainly due to an increased frequency of toxic nodular goiter. Although low titer serum thyroid antibodies were relatively frequent, the prevalences of both overt and subclinical autoimmune hypothyroidism were not different from those observed in iodine-sufficient areas. (*J Clin Endocrinol Metab* **84:** 561–566, 1999)

THE SPECTRUM and the natural history of thyroid disorders occurring in the adult population living in an iodine-sufficient environment were well documented in the classic Whickham survey carried out by Tunbridge *et al.* in a mixed urban and rural region in Northeastern England (1). Studies of other iodine-sufficient areas confirmed the findings of this survey (2, 3). The spectrum and the prevalence of thyroid disorders are known to be influenced by environmental factors, especially by iodine intake (4). Indeed, iodine deficiency is regarded as the most common cause of thyroid disorders worldwide (4–6). Epidemiological studies in iodine-deficient areas have mainly focused on the prevalence of goiter and cretinism (6–9). To our knowledge there are no recent cross-sectional studies using modern technologies on the spectrum of thyroid disorders occurring in communities with mild or moderate iodine deficiency.

In the present study, the prevalence of thyroid disorders has been investigated in virtually the entire child population and in a high and representative proportion of the adult population living in Pescopagano, a southern Italian village with mild to moderate iodine deficiency.

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Subjects and Methods

Study population

The survey was conducted in Pescopagano, a southern Italian village located in the Lucan Apennines at 954 meters above the sea level. The nearest town is 70 km away. Pescopagano was selected for its long term exposure to iodine deficiency with no previous iodine prophylaxis. The economy of this area is progressively converting from agriculture to service activities. The usual diet consists mainly of local products. At the time of the survey, the registered population of Pescopagano was 2348 people. Daily commuters with neighboring towns accounted for 620 people. They were excluded from the survey because of their exposure to higher iodine dietary intake. A total of 317 people of the 1728 permanently residing in the village failed to respond to 2 consecutive calls to participate in the survey. Thus, 1411 residents were actually examined: 419 (215 males and 204 females) 1- to 14-yr-old children, representing 94.1% of this age group, and 992 (573 females and 419 males) of the 1368 subjects aged 15 yr or more, representing 72.5% of this age group and referred to as the adult population. General practitioners of the village actively took part in each step of the survey. Civil and health authorities strongly supported the project, and informed consent was obtained from parents of the minors and from adult subjects. A questionnaire sheet was completed for each subject and included personal and family histories of thyroid disease with details of treatment and special attention being paid to L-T_4 and any other medication affecting thyroid function. Alimentary habits and coexistent autoimmune disorders were also taken into account. In the schoolchildren, population height and weight were measured.

A randomized sample of 75 adult subjects, drawn from the group of 317 subjects who failed to respond to the first and second calls, was personally approached by family physicians and invited to participate

in the survey again. In 64 subjects complying with such personalized invitation, urinary iodine excretion (UIE) measurements and goiter assessments were performed. The data were compared with those obtained in the general survey.

UIE

Casual urinary samples were collected for measurement of iodine concentration by a colorimetric method using an autoanalyzer apparatus (Technicon, Rome, Italy) (10). The results were calculated as micrograms of iodine per L urine and are expressed as a median.

Thyroid ultrasound

Thyroid ultrasound examination was performed by a portable real-time instrument (Esaote, Biomedica, Firenze, Italy) using a 7.5-MHz linear transducer. Subjects were examined in the supine position with the neck hyperextended. Thyroid volume was calculated according to the formula of the ellipsoid model: width × length × thickness × 0.52 for each lobe (11). As previously described, goiter as assessed by ultrasound was defined when the thyroid volume was more than 2 SD above the mean thyroid volume of age-matched controls in children and of sex-matched controls in adults. The normal thyroid volume in children was obtained from 2709 children residing in urban nonendemic areas (12). The normal thyroid volume in adults residing in nonendemic areas and with no clinical or laboratory evidence of thyroid disease was 11.3 ± 6.8 mL (mean ± 2 SD) in males (n = 125) and 8.6 ± 4.4 mL in females (n = 132). Thus, in adults, thyroid volumes greater than 18.1 mL in males and 13 mL in females were considered to indicate goiter. The reproducibility of thyroid volume measurement by ultrasound was assessed by determining the interobserver error among 4 examiners in 30 children and 30 adults.

Thyroid function tests

Serum free T_4 (FT_4) and serum free T_3 (FT_3) were measured by RIA (FT_4 Liso-Phase kit and FT_3 Liso-Phase kit, Technogenetics, Milan, Italy). Serum TSH was measured by a sensitive immunoradiometric assay (Gamma Coat ^{125}I, Incstar Corp., Stillwater, MN). The functional sensitivity of the TSH assay was 0.03 mU/L. The normal range, determined in 123 15- to 75-yr-old subjects, was 0.4–3.7 mU/L. Serum autoantibodies to thyroglobulin (TgAb) and thyroperoxidase (TPOAb) were measured by agglutination (Serodia-ATG and Serodia-AMC, Fujirebio, Inc., Tokyo, Japan).

Fine needle aspiration

Fine needle aspiration (FNA) was advised in all subjects with nodular goiter and was performed in 132 of 171 (77.2%) subjects who gave their consents. FNA was performed in 119 solid and mixed nodules larger than 1.5 cm. Smaller nodules were examined by FNA (n = 13) only when clinical findings or the echographic pattern suggested the opportunity of excluding malignancy.

Statistics

Statistical evaluation was performed by the χ^2 test and *t* test using the Statxact Program of Cytel Software Corp. (Cambridge, MA).

Results

Questionnaire data

At the time of the survey, no subject was receiving treatment. Previous treatment with methimazole was documented in 9 patients with a past history of toxic nodular goiter. Six of 10 patients who were previously subjected to partial thyroidectomy and 11 subjects with nontoxic nodular goiter were receiving replacement therapy with L-T_4. They all had normal serum concentrations of FT_4, FT_3, and TSH. No subject reported the use of iodized salt or iodine-containing drugs.

UIE

The median UIE was 55 μg/L (mean ± SD, 76 ± 53). Values lower than 100 μg/L were found in 81% of subjects, and values greater than 200 μg/L were documented in less than 1.0% of subjects (Fig. 1).

Prevalence of goiter

As reported in Table 1, the overall prevalence of goiter progressively increased with age. Thyroid enlargement was found in 67 of 419 children (16.0%). The prevalence of goiter progressively increased from 10.1% in 6- to 8-yr-old children to 17.0% and 37.6% in 9- to 11-yr-old and 12- to 14-yr-old groups, respectively. No thyroid abnormality was documented in children under 6 yr of age. All goitrous children had a diffuse goiter less than twice the thyroid volume of age-matched controls, with the exception of one 14-yr-old girl and one 13-yr-old boy who had nodular goiter. No significant difference was found in the prevalence of goiter between females and males [39 of 204 (19.1%) and 28 of 215 (13.0%), respectively].

In the adult population (≥15 yr-old), goiter, regardless of thyroid function, was observed in 583 of 992 subjects (58.8%). Ten patients were previously subjected to partial thyroidectomy for nontoxic goiter. Thus, the overall prevalence of goiter in the adult population was 59.8%. The prevalence of nodular goiter was negligible in the 15–25 yr age class, increased up to 28.5% in the 56–65 yr age class, and declined in older subjects. The prevalence of goiter was not different between females (59.5%) and males (58.0%). Among subjects with enlarged thyroid (excluding patients previously subjected to thyroidectomy), moderate goiter (≤30 mL) was found in 62.3% of subjects, large goiter (30–60 mL) was found in 30.2% of subjects, and very large goiter (≥60 mL) was found in 7.5% of subjects. Symptoms and/or signs indicating a compression of adjacent structures of the neck were present in 142 goitrous subjects (14.3% of the adults).

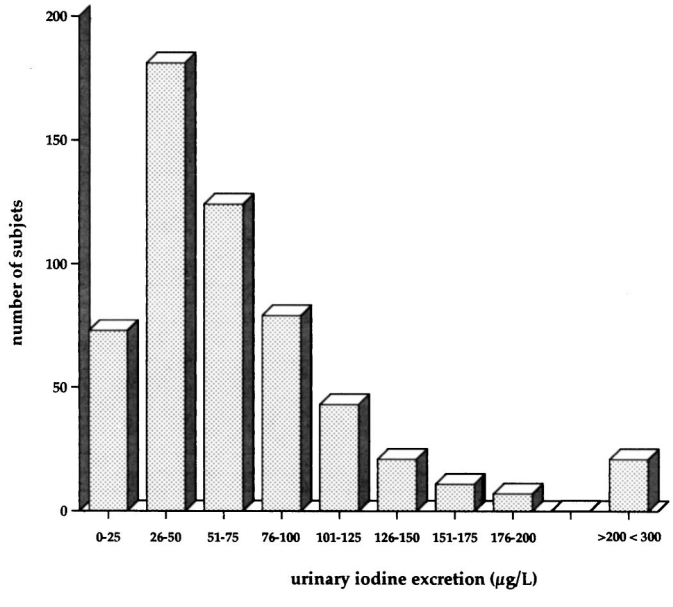

FIG. 1. Frequency of distribution of median values of UIE (micrograms per L) in the study population.

TABLE 1. Prevalence and age distribution of diffuse and nodular goiter regardless of thyroid function

Age (yr)	Subjects [n (m, f)]	Goiter (%)	Diffuse goiter (%)	Nodular goiter (%)
1–5	135 (66, 69)			
6–8	79 (43, 36)	10.1	10.1	
9–11	88 (46, 42)	17.0	17.0	
12–14	117 (60, 57)	37.6	35.9	1.7
Children (1–14)	419 (215, 204)	16.0	15.5	0.5
15–25	193 (88, 105)	30.0	27.9	2.1
26–35	194 (78, 116)	48.9	37.6	11.3
36–45	204 (94, 110)	71.6	50.0	21.6
46–55	140 (65, 75)	73.5	47.8	25.7
56–65	130 (50, 80)	74.6	46.1	28.5
66–75	79 (22, 57)	73.4	54.4	19.0
>75	52 (22, 30)	53.8	32.7	21.1
Adults (≥15)	992 (419, 573)	58.8	41.8	17.0

m, males; f, females.

TABLE 2. Prevalence and age distribution of thyroid functional autonomy

Age (yr)	Subjects (n)	Cases		Diffuse goiter (n)	Nodular goiter (n)
		n	%		
1–14	419	3	0.7	3	
15–25	193	4	2.1	1	3
26–35	194	6	3.1	4	2
36–45	204	12	5.9	8	4
46–55	140	12	8.6	6	6
56–65	130	14	10.8	6	8
66–75	79	8	10.1	2	6
>75	52	8	15.4	1	7
Subtotal (≥15)	992	64	6.4	28	36
Total	1411	67	4.7	31	36

The frequency of symptoms was related to thyroid size, being present in 5.2% of subjects with moderate goiter, in 46.6% of subjects with large goiter, and in 93.2% of subjects with very large goiter. Seventy-three subjects were considered possible candidates for surgery. Surgical removal of the goiter because of severe pressure symptoms was advised in 27 and has been performed in 6 subjects to date.

Nontoxic goiter accounted for virtually all cases of goiter in children (64 of 67) and for the large majority of adults (490 of 593, 82.6%). Thyroid disorders associated with thyroid enlargement in the remaining subjects are described below.

Functional autonomy

For the purpose of the present study, thyroid functional autonomy was defined by the finding of normal serum concentrations of FT_4 and FT_3 and subnormal serum TSH concentrations (<0.4 mU/L). Thyroid hormone medication and other conditions leading to TSH suppression were excluded. As reported in Table 2, thyroid functional autonomy was found in 67 of 1411 (4.7%) subjects, with no difference between females (5.2%) and males (4.1%). Its frequency progressively increased with age from 0.7% in children to 15.4% in elderly subjects (>75 yr old); the overall prevalence in the adult population was 6.4%. Thyroid functional autonomy was unrelated to goiter size and occurred in both nodular (n = 36) and diffuse goiter (n = 31), but its relative frequency was significantly greater in the former group (21.2% *vs.* 6.4%; $P < 0.0001$).

TABLE 3. Prevalence and age distribution of toxic diffuse goiter and toxic nodular goiter in the adult population

Age (yr)	Subjects (n)	Toxic diffuse goiter cases		Toxic nodular goiter cases	
		n	%	n	%
15–25	193				
26–35	194	2	1.0	2	1.0
36–45	204	1	0.5		
46–55	140	2	1.4	2 + 1[a]	2.1
56–65	130	2	1.5	3 + 7[a]	7.7
66–75	79	1	1.3	4 + 1[a]	6.3
>75	52	1	1.9		
Total	992	9	0.9	11 + 9[a]	2.0

[a] Patients with past history of hyperthyroidism.

Overt hyperthyroidism

Nine patients had a history of toxic nodular goiter. Active hyperthyroidism was documented in 20 adults and in none of the 419 children. The overall prevalence of hyperthyroidism was 29 of 992 (2.9%) adults (Table 3), with no difference between females (17 of 573, 2.96%) and males (12 of 419, 2.86%). Nine patients (0.9%) had toxic diffuse goiter, and 20 (2.0%) had toxic nodular goiter, including 1 male with active toxic adenoma in whom the diagnosis was confirmed by scintiscan and all 9 patients with a past history of hyperthyroidism. Thus, the nonautoimmune/autoimmune hyperthyroidism ratio was 2.2:1. Toxic diffuse goiter was equally distributed in each class of adult age, whereas toxic nodular goiter increased from 1.0% in 26–35 yr age class to 7.7% in the 56–65 yr age class. No cases of toxic nodular goiter were found beyond the age of 75 yr.

Overt and subclinical hypothyroidism

No subject had previously been diagnosed and treated for hypothyroidism. Spontaneous overt hypothyroidism was newly diagnosed in 2 of 992 (0.2%) adults and in none of the 419 children. Both hypothyroid subjects were females (2 of 573, 0.34%) and had high serum TgAb and TPOAb titers. One of them had a reduced thyroid volume and diffuse hypoechogenicity at ultrasound, indicative of atrophic autoimmune thyroiditis, whereas the other had a diffuse goiter.

Subclinical hypothyroidism, as defined by serum TSH greater than 3.7 mU/L with serum levels of free thyroid hormones within the normal range, was found in 38 of 992 (3.8%) adults with no difference between females (25 of 573, 4.4%) and males (13 of 419, 3.1%). Ten of 38 subjects had humoral evidence (TPOAb and/or TgAb, ≥1:100) of thyroid autoimmunity.

Serum thyroid antibodies and diffuse autoimmune thyroiditis

Figure 2 shows the prevalence of thyroid autoantibody-positive tests (≥1:100 for both TPOAb and TgAb) in each age class regardless of other thyroid abnormalities. The overall prevalence was 12.6% (females, 17.3%; males, 7.0%) and progressively increased from 2.4% in children to 21.9% in the 46–55 yr age class, with little change in older subjects. Thy-

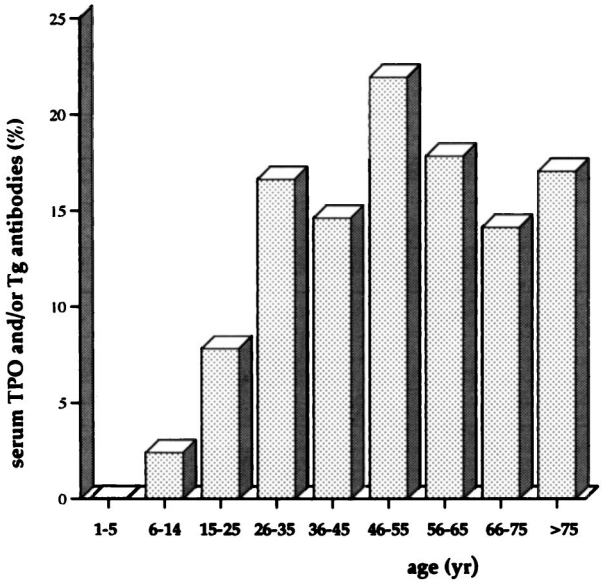

FIG. 2. Prevalence of thyroid autoantibody-positive tests (TPOAb and TgAb, ≥1:100) in each age class regardless of other thyroid abnormalities.

TABLE 4. Prevalence, age and sex distribution of diffuse autoimmune thyroiditis

Age (yr)	Subjects (n)	Cases (n)	Prevalence (%)		
			Total	m	f
1–14	419	3	0.7	0.5	1
15–25	193	4	2.1	1.1	2.8
26–35	194	9	4.6	2.6	6.0
36–45	204	6	2.9	2.1	3.6
46–55	140	11	7.8	6.1	9.3
56–65	130	5	3.8		6.2
66–75	79	5	6.3		10.5
>75	52	7	13.5	9.0	23.3
Total	1411	50	3.5	1.9	4.9

m, Males; f, females.

roid autoantibodies were more frequently found in goitrous (95 of 651, 14.6%) than in nongoitrous (45 of 760, 5.9%) subjects ($P < 0.0001$).

Circulating TgAb and TPOAb (≥1:400) and thyroid echographic pattern of diffuse hypoechogenicity indicative of diffuse autoimmune thyroiditis (13) were found in 50 of 1411 (3.5%) subjects (Table 4): 44 were euthyroid, 5 were subclinically hypothyroid, and 1 had overt hypothyroidism. Goiter was present in 26 of these 50 subjects.

Serum TSH distribution

As shown in Fig. 3, median TSH values progressively decreased from 2.2 mU/L in children to 0.9 mU/L in 56- to 65-yr-old subjects, with no further changes in the older age classes. No significant difference between males and females was found in any age class. The mean serum TSH concentration in the adult population was significantly lower ($P < 0.0001$) in goitrous (1.4 ± 1.1 mU/L) than in nongoitrous (2.0 ± 2.4 mU/L) subjects.

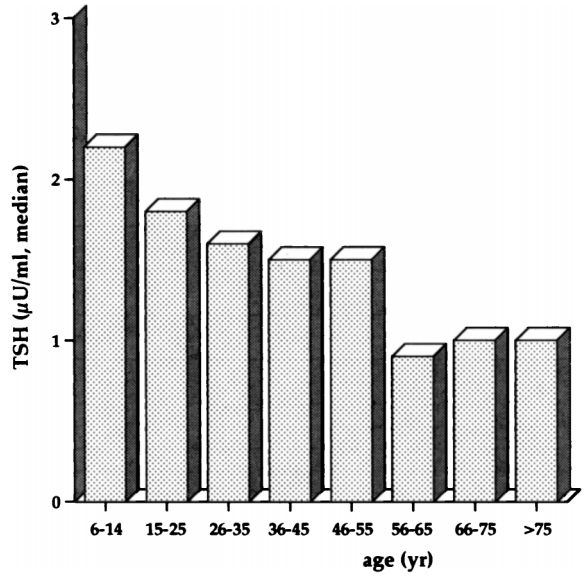

FIG. 3. Median TSH (milliunits per L) values in each age class.

Thyroid cancer

No subject with a past history of thyroid cancer was found. Of the 132 patients submitted to FNA, 1 had papillary thyroid cancer confirmed by histology. Thus, the prevalence of ascertained thyroid cancer in the study population was 1 of 1411. A follicular adenoma was documented by histology in an additional subject with a microfollicular pattern with nuclear atypias by cytology. Benign thyroid lesions at cytology were found in 116 (87.9%) subjects, whereas the FNA specimens were nondiagnostic in 14 (10.6%) subjects.

Other thyroid disorders

In a 53-yr-old male, clinical features of panhypopituitarism associated with low serum FT_4, FT_3, and TSH concentrations were documented, indicating the diagnosis of central hypothyroidism. Two cases of thyroid hemiagenesis with normal thyroid function were also identified.

Validation study

In the randomized sample, the median UIE was 51 μg/L, and the overall frequency of goiter was 54.7%, with no significant difference with respect to the study population.

Discussion

The prevalence and the spectrum of thyroid disorders in an iodine-deficient community were assessed in the present survey. The study was conducted in Pescopagano, a southern Italian village located in an area of iodine deficiency that has never been submitted to any iodine prophylaxis program. Virtually all the children and the large majority of the adults were examined. The results obtained by examining a randomized sample of the adult residents who failed to respond to the initial recruitment showed that the data are representative of the entire population.

The prevalence of goiter progressively increased with age, being 16.0% in children and 59.8% in adults. Age and sex

goiter distributions were similar to those observed in other iodine-deficient areas (5–9, 14–16), but differed from those observed in iodine-sufficient areas in which the goiter prevalence is higher in young adults than in middle-aged and elderly people and is much more frequent in females than in males (2). Thus, it would appear that iodine deficiency not only overcomes the increased female susceptibility to develop goiter, but also influences the natural history of goiter by counteracting its declining prevalence with age. Rather than an increase, we observed a fall in goiter prevalence in very old subjects (>75 yr old), as reported in other iodine-deficient areas (5–9). The question of whether and to what extent this decline is due to the selection of people reaching such an advanced age remains to be established. On the basis of the UIE of 55 μg/L, Pescopagano could be classified as an area with mild to moderate iodine deficiency. Compared with areas with similar degrees of iodine deficiency, the prevalence of goiter observed in the present study appears to be much higher than expected, especially in the adults. This may be related to a prolonged exposure of this area to a more severe iodine deficiency in the past. As previously reported from other areas of Italy, silent prophylaxis due to improved socioeconomic and nutritional conditions most likely occurred in recent years, resulting in an improved iodine intake. This prevented the development of new goiters in younger subjects, but was not accompanied by a parallel reduction in the prevalence of established goiter (17).

In the present survey, thyroid nodularity was exceptional in children and was rare in 15- to 25-yr-old subjects, progressively increased with age up to 65 yr and tended to decline thereafter. Clinically significant pressure symptoms were not rare in the adults; 73 patients required medical attention for pressure symptoms, and surgery was advised in 27 subjects. These findings underscore the role of prolonged exposure to iodine deficiency in the growth of goiter and the progression of nodularity. The prevalence of thyroid nodularity in the adults living in Pescopagano was apparently lower than that recently reported from some iodine-sufficient areas using thyroid ultrasound (18, 19). The use of different criteria for the definition of nodularity largely accounts for this discrepancy. Although only lesions greater than 10 mm were considered in the present survey, lesions as small as 3–10 mm were included in the above reports.

The overall prevalence of overt hyperthyroidism was twice as high as that found in the Whickham survey (1, 3). At variance with iodine-sufficient areas, in which hyperthyroidism is mainly due to toxic diffuse goiter (4, 20–24), toxic nodular goiter accounted for the majority of thyrotoxic subjects living in Pescopagano, being twice as frequent as toxic diffuse goiter. Toxic nodular goiter occurred in older subjects and was more prevalent in males than in females. On the contrary, toxic diffuse goiter was equally distributed in different age classes of adults, with a pronounced preponderance of female subjects. The prevalence of thyroid functional autonomy progressively increased from 0.7% in children to 15.4% in subjects more than 75 yr old and was more frequent in subjects with nodular goiter. The prevalence of functional autonomy observed in the adults (6.4%) was much higher than that reported in iodine-sufficient areas, where this condition is rare (25–28). When data from the survey carried out in the iodine-sufficient Whickham community were recalculated (3) using the same criteria adopted in this study, a frequency of 0.6% for functional autonomy was found.

Overt hypothyroidism was only found in two adult females and in none of the males, with a prevalence of 0.2% of the adult population. Subclinical hypothyroidism was found in 3.8% of the adults. Thus, the overall prevalence of both overt and subclinical hypothyroidism was slightly, but not significantly, lower than that recalculated from the Whickham survey (0.5% and 5.3%, respectively) (1–3).

Humoral and echographic evidence of diffuse autoimmune thyroiditis was found in 3.5% of the entire population; women over the age of 45 yr were more frequently affected. Most of these subjects were clinically and biochemically euthyroid, and about half of them had an enlarged thyroid gland. To our knowledge, no epidemiological study using thyroid antibody tests combined with ultrasound for the assessment of thyroid autoimmunity has been performed as yet. In agreement with previous studies performed in iodine-deficient areas (29, 30), the detection of serum thyroid antibodies was relatively frequent, especially in goitrous females. Antibody titers were low in most cases and were not associated with thyroid functional alterations or with diffuse autoimmune thyroiditis, as assessed by ultrasound. This finding is in keeping with the concept that the development of goiter due to iodine deficiency may overexpose the immune system to thyroid antigens, leading to humoral and cell-mediated immune reactions (29–32).

The question of whether iodine intake influences the development of thyroid cancer remains controversial (33). In the present survey only a single case of papillary thyroid carcinoma was found. Although a number of surgical and autopic (34–37) data on the relationship between iodine intake and thyroid cancer are available, to our knowledge no comparable epidemiological studies have been performed in iodine-deficient areas. The size of the iodine-deficient community examined by us is not sufficient to draw any conclusion. Clearly, more extensive studies are required to address this problem.

In conclusion, the present survey performed in virtually the entire population of a village with mild to moderate iodine deficiency shows a cross-sectional picture of the spectrum of thyroid disorders occurring in iodine deficiency and provides relevant information on the natural history of iodine-deficient goiter. In the present survey of an iodine-deficient community, a progressive increase with age in goiter prevalence, thyroid nodularity, and functional autonomy was observed. Hyperthyroidism was twice as high as that reported in iodine-sufficient areas, mainly due to an increased frequency of toxic nodular goiter. Although low titer serum thyroid antibodies were relatively frequent, the prevalence of both overt and subclinical autoimmune hypothyroidism was not different from that observed in iodine-sufficient areas.

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