

The Effect of Voluntary Iodine Prophylaxis in a Small Rural Community: The Pescopagano Survey 15 Years Later

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Context: Iodine deficiency disorders are a major public health problem, and programs have been implemented to improve iodine nutrition.

Objective: The objective of the study was to verify the effects of voluntary iodine prophylaxis in a small rural community (Pescopagano, Italy).

Design: The design of the study was the evaluation of the prevalence of thyroid disorders 15 years after a previous survey conducted before iodine prophylaxis.

Setting: The setting for this study was a general community survey.

Participants: One thousand one hundred forty-eight residents were examined in 2010 and 1411 in 1995.

Results: In 2010, 757 of 1148 subjects (65.9%) routinely used iodized salt, urinary iodine excretion being significantly higher than in 1995 (median 98.0 $\mu\text{g/L}$, vs 55.0 $\mu\text{g/L}$, $P < .0001$). The prevalence of goiter was lower in 2010 than in 1995 (25.8% vs 46.1%, $P < .0001$), mainly due to the reduction of diffuse goiter (10.3% vs 34.0%, $P < .0001$). In 2010 vs 1995, thyroid autonomy in subjects younger than 45 years old (3 of 579, 0.5% vs 25 of 1010, 2.5% $P = .004$) and nonautoimmune hyperthyroidism in subjects older than 45 years old (8 of 569, 1.4% vs 18 of 401, 4.5%, $P = .03$) were less frequent. The prevalence of hypothyroidism was higher in 2010 vs 1995 (5.0% vs 2.8%, $P = .005$), mainly because of an increased frequency of subclinical hypothyroidism in subjects younger than 15 years old (7 of 83, 8.4% vs 0 of 419, 0.0%, $P < .0001$). Accordingly, serum thyroid autoantibodies (19.5% vs 12.6%; $P < .0001$) and Hashimoto's thyroiditis (14.5% vs 3.5%; $P < .0001$) were more frequent in 2010 than in 1995.

Conclusions: In the present work, the role of voluntary iodine prophylaxis was assessed in a small rural community relatively segregated, in which genetic and other environmental factors have not substantially changed between the 2 surveys. Iodine intake strongly affected the pattern of thyroid diseases, but the benefits of correcting iodine deficiency (decreased prevalence of goiter and thyroid autonomy in younger subjects and reduced frequency of nonautoimmune hyperthyroidism in older subjects) far outweighs the risk of development of thyroid autoimmunity and mild hypothyroidism in youngsters. (*J Clin Endocrinol Metab* 98: 1031–1039, 2013)

Iodine is an essential component of thyroid hormones and is obtained primarily through the diet. The spectrum and the prevalence of thyroid disorders are influenced by iodine intake (1–3), and iodine deficiency disorders

are a major public health problem because approximately 29% of the world's population is estimated to live in areas of iodine deficiency. Public health strategies have been implemented to improve iodine nu-

trition, including voluntary or mandatory fortification of food. Iodized salt is considered the most appropriate measure for iodine fortification (4) and has been proved to be effective in decreasing the prevalence of iodine deficiency induced disorders (5, 6).

Iodine intake has been shown to modulate the pattern of thyroid diseases in cross-sectional studies comparing populations living in areas characterized by different iodine intake (7). In iodine-deficient countries, nonautoimmune hyperthyroidism is more frequent, the natural evolution of goiter being the development of thyroid autonomy and eventually of thyrotoxicosis. On the other hand, studies in populations living in areas with different iodine intakes in Great Britain (8) in Denmark and Iceland (9) have shown that the frequency of thyroid autoimmunity and hypothyroidism is higher in iodine-replete than in iodine-deficient populations. Longitudinal studies conducted in Denmark have shown an increased incidence of overt hypothyroidism (10) and thyroid autoantibodies (11) after the beginning of a cautious iodization program. However, it is important to underline that iodine-induced adverse effects can be almost entirely avoided by adequate and sustained quality control and monitoring of iodine supplementation. Available evidence clearly confirms that the benefits of correcting iodine deficiency far outweigh the risks of iodine supplementation (12, 13).

In 1995 we investigated the prevalence of thyroid disorders in subjects living in Pescopagano (14), a southern Italian village with mild to moderate iodine deficiency. In this survey an age-dependent increased prevalence of goiter, thyroid nodularity, and functional autonomy was observed. Overt hyperthyroidism was twice as high as that reported in iodine-sufficient areas, mainly due to an increased frequency of toxic nodular goiter, and although low titer serum thyroid antibodies were relatively frequent, the prevalence of both overt and subclinical autoimmune hypothyroidism was not different from those observed in iodine-sufficient areas. After the survey of 1995, the population living in Pescopagano was made aware of the consequences of iodine deficiency, and local authorities strongly supported the use of iodized salt on voluntary basis. This process has been reinforced in 2005, when the Italian Parliament has passed a law for iodine prophylaxis, which prescribes that both iodized and noniodized salt must be available at each point of sale, but noniodized salt is provided and sold only on specific request by the consumer. According to Italian law, salt is iodized at 30 ppm (30 mg of potassium iodate per kilogram), which is typical of many European programs. The aim of this work was to evaluate the prevalence of thyroid disorders in the community of Pescopagano 15 years after the first survey. We intended to verify whether iodine supplementation has

affected the spectrum of thyroid disorders in this population living in a relatively isolate village, in which genetic and other environmental factors have not substantially changed between the 2 surveys.

Subjects and Methods

Subjects

The survey was conducted in Pescopagano, a southern Italian village located in the Lucan Apennines at 954 meters above sea level. Of the 2045 residents registered in Pescopagano in 2010, 897 subjects (43.9%) failed to respond to 2 consecutive calls to participate in the survey. Only a few pregnant and lactating women were living in the village at the time of the survey. Their number was too small for any statistical evaluation, and these women were not included in the study. Thus, 1148 residents (56.1%) were actually examined: 83 (39 males and 44 females) 1- to 14-year-old subjects, representing 40.6% of this age group, and 1065 (429 males and 636 females) aged 15 years or more representing 57.8% of this age group (15–25 years, $n = 156$; 26–35 years, $n = 157$; 36–45 years, $n = 183$; 46–55 years, $n = 185$; 56–65 years, $n = 186$; 66–75 years, $n = 112$; older than 75 years, $n = 86$). 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 history of thyroid disease and treatment with levothyroxine (L-T₄) or other drugs affecting thyroid function. Alimentary habits and use of iodized salt were also evaluated.

Results were compared with data of the previous survey conducted in same village in 1995 (14). At that time, 1411 residents were examined: 419 (215 males and 204 females) 1- to 14-year-old children, representing 94.1% of this age group, and 992 (573 females and 419 males) of the 1368 subjects aged 15 years or older, representing 72.5% of this age group (15–25 years, $n = 193$; 26–35 years, $n = 194$; 36–45 years, $n = 204$; 46–55 years, $n = 140$; 56–65 years, $n = 130$; 66–75 years, $n = 79$; older than 75 years $n = 52$). Five hundred five subjects were evaluated in both surveys.

Thyroid ultrasound

Thyroid ultrasound examination was performed by a portable real-time instrument (Esaote; Biomedica, Firenze, Italy) using a 7.5- to 10-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 \times length \times thickness \times 0.52 for each lobe). Thyroid ultrasound examinations were performed by 2 examiners (R.T. and A.L.). The interobserver variability of the thyroid volume measured at the thyroid ultrasound was estimated to be lower than 10%, as already reported in a previous work (15).

Thyroid function tests

In 2010, serum TSH was measured by a chemoluminescent assay (Immulite 2000; Siemens, Llanberis, United Kingdom). The normal range for this assay, determined in 127 normal subjects aged 15–75 years, was 0.4–3.4 μ U/mL. In the first survey,

serum TSH was measured by a sensitive immunoradiometric assay (Gamma Coat 125I; Incstar Corp, Stillwater, MN), as previously described (14).

In 2010 serum free T_4 (FT4) and free T_3 (FT3) were measured by a chemoluminescent assay (Vitros Ortho-Clinical Diagnostics, Rochester, New York; normal range for FT4 7–17 pg/mL and for FT3 2.7–5.7 pg/mL). The normal range was determined using serum samples from 329 subjects as reported in a previous paper (16). In 1995 serum FT4 and FT3 were measured by RIA (FT4 Liso-Phase kit and FT3 Liso-Phase kit; Technogenetics, Milan, Italy; normal range for FT4 6.5–18 pg/mL and for FT3 2.9–5.5 pg/mL).

In 2010, serum thyroid autoantibodies (TAb), antithyroglobulin (TgAb) and antithyroperoxidase (TPOAb) were measured by an automated immunoassay system (AIA-Pack TgAb, and TPOAb; Tosoh, Tokyo, Japan) and expressed as units per milliliter. Normal values were less than 30 U/mL for TgAb and less than 10 U/mL for TPOAb. In 1995 TgAb and TPOAb were measured by agglutination (Serodia-ATG and Serodia-AMC; Fujirebio, Inc, Tokyo, Japan).

Diagnostic criteria of thyroid disease

The clinical diagnosis of thyroid disease was performed according to the same criteria in the surveys of both 1995 and 2010. In particular, the criteria used were the following:

Hashimoto's thyroiditis (HT)

HT included the following: 1) hypothyroidism and positive TAb; 2) euthyroidism and high titers of TAb (>100 U/mL of both TgAb and TPOAb); and 3) euthyroidism, undetectable or low titers of TAb and a hypoechoic thyroiditis pattern at thyroid ultrasound.

Euthyroid subjects with positive TgAb and/or TPOAb and normal pattern at thyroid ultrasound were not included in the HT group.

Graves' disease

Hyperthyroidism (untreated or under treatment with methimazole) included hyperthyroidism with or without ophthalmopathy, positive TAb, and/or serum anti-TSH receptor antibodies and a hypoechoic thyroiditis pattern at thyroid ultrasound. Patients with a previous diagnosis of Graves' disease treated with thyroidectomy or radiometabolic therapy with ^{131}I were also included in this group.

Goiter (diffuse or nodular)

Goiter included thyroid volume (assessed by thyroid ultrasound) higher than 2 SD above the mean thyroid volume of age- and sex-matched controls in children. In adults, thyroid volumes greater than 18 mL in males and 13 mL in females were considered indicative of goiter. Size and echographic pattern of nodules were evaluated. Subjects with goiter, normal pattern at thyroid ultrasound, and positive TgAb and/or TPOAb (not included in the HT group) were included in this group.

Thyroid functional autonomy

Thyroid functional autonomy included normal serum concentrations of FT4 and FT3 and subnormal serum TSH concentrations (<0.4 mU/L), excluding subjects under L-T4 treatment.

Nonautoimmune hyperthyroidism

This disorder included hyperthyroid subjects with hyperfunctioning thyroid nodule at a thyroid scan and hyperthyroid subjects with a nodular goiter who did not meet the diagnostic criteria of Graves' disease. A thyroid scan was performed only in patients with low serum TSH.

Normal subjects

These included a normal value of TSH and thyroid hormones, negative or low titer TAb, and normal thyroid ultrasound.

Urinary iodine secretion (UIE)

We collected morning urinary samples from all the subjects examined. A number was assigned to each urine sample, and UIE was measured in 453 urine samples randomly selected of the 1148 subjects included in the survey. The number of random samples to analyze was determined, taking into account that about 500 samples represent the optimal sample size to estimate population iodine excretion, with a confidence interval of 95% and a precision range of $\pm 5\%$ (17). Urinary iodine concentration was measured by a colorimetric method using an autoanalyzer apparatus (Technicon, Rome, Italy), as already described (18). The results were calculated as micrograms of iodine per liter of urine and are expressed as median and interquartile range (IR).

Statistics

Parametric and nonparametric tests (χ^2 tests, Fischer's exact tests, or Mann-Whitney U tests) were used as appropriate and considered statistically significant when $P < .05$.

Results

Questionnaire data

In the first survey of 1995, no subject reported the use of iodized salt, whereas in 2010, of the 1148 subjects examined, 757 (65.9%) declared to routinely use iodized salt, 304 (26.4%) to never use iodized, and 86 (7.6%) failed to answer this question or anamnestic data were not congruent within the same family.

Of 1148 subjects, 80 (7.0%) were under L-T4 treatment (43 with nodular goiter, 32 with hypothyroid HT and 5 with toxic nodular goiter or Graves' disease after thyroidectomy or ^{131}I treatment), and 4 were hyperthyroid (3 with Graves' disease and 1 with toxic nodular goiter) under treatment with methimazole.

Urinary iodine excretion

UIE in 2010 and in 1995 is shown in Figure 1. UEI (Figure 1) was significantly higher in 2010 (median 98.0 $\mu\text{g/L}$, IR 58.0–159.5 $\mu\text{g/L}$) than in 1995 (median 55.0 $\mu\text{g/L}$, IR 35.9–99.1 $\mu\text{g/L}$; $P < .0001$).

Goiter

The prevalence of goiter (diffuse and nodular) was significantly lower in 2010 (266 of 1148, 23.2%) than in 1995

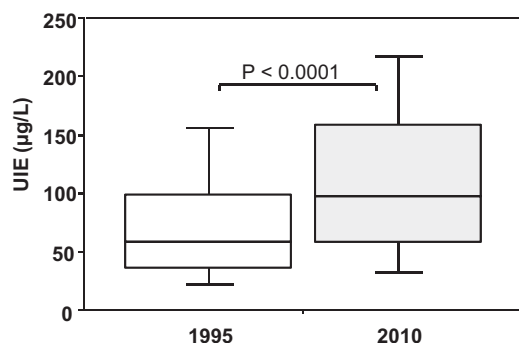


Figure 1. Box-whisker plot of UIE measured in 1995 ($n = 1186$) and in 2010 ($n = 453$). Results are reported as median values (black lines), interquartile (25 to 75 percentiles) range (boxes), and 10th to 90th percentiles (whiskers). UIE was significantly higher in 2010 than in 1995 (Mann-Whitney U test: $P < .0001$).

(650 of 1411, 46.1%, $P < .0001$). The lower prevalence of goiter was mainly due to the reduction of diffuse goiter, found in 118 of 1148 (10.3%) subjects in 2010 and in 480 of 1411 (34.0%, $P < .0001$) in the previous survey. In 2010 no diffuse goiter was found in the 83 children examined, whereas in 1995, the prevalence of diffuse goiter in the same class of age was 65 of 419 (15.5%). The prevalence of diffuse goiter progressively increased with age both in 1995 and 2010 (Figure 2A), but in each class of age, the frequency of goiter was significantly lower in 2010 compared with 1995, with the exception of subjects older than 75 years.

The overall frequency of nodular goiter was not significantly different in 2010 (148 of 1148, 12.9%) and in 1995 (172 of 1411, 12.2%, $P = .59$). When age was taken into account, the frequency of nodular goiter was low both in 2010 and in 1995 in subjects younger than 25 years old, was significantly lower in 2010 than in 1995 in patients aged 26–35 years (6 of 157, 3.8% vs 22 of 194, 11.3%;

$P = .001$), whereas no difference was observed in subjects older than 35 years old (Figure 2B).

Thyroid functional autonomy

The overall frequency of thyroid functional autonomy was not significantly different in 2010 (54 of 1148, 4.7%) and in 1995 (67 of 1411, 4.7%, $P = .95$). However, in 2010 thyroid functional autonomy was significantly lower than in 1995 in subjects younger than 45 years (3 of 579, 0.5% vs 25 of 1010, 2.5%, Fischer test $P = .004$), whereas in older subjects, the frequency of thyroid functional autonomy was not significantly different in the 2 surveys (Figure 3A).

Hyperthyroidism

As shown in Table 1, the overall frequency of overt hyperthyroidism was not significantly different in 2010 (18 of 1148, 1.6%) and in 1995 (29 of 1411, 2.1%, $P = .36$). Graves' disease was diagnosed in 9 of 1148 (0.8%) subjects (5 untreated, 3 under methimazole, and 1 previously treated with radioiodine therapy with ^{131}I) in 2010 and in 9 of 1411 (0.6%) subjects (all untreated) in 1995. The overall frequency of nonautoimmune hyperthyroidism was not significantly different in 2010 (9 of 1148, 0.8%) and in 1995 (20 of 1411, 1.4%, $P = .13$). However, when patients were grouped according to age (Figure 3B), the frequency of toxic nodular goiter/toxic adenoma was significantly lower in 2010 than in 1995 in subjects older than 45 years (8 of 569, 1.4% vs 18 of 401, 4.5%, $P = .03$), whereas it was not different in younger subjects (1 of 579, 0.2% vs 2 of 1010, 0.2%; $P = .91$).

Hypothyroidism

In 2010 overt hypothyroidism (Table 2) was newly diagnosed in 2 subjects and subclinical hypothyroidism in

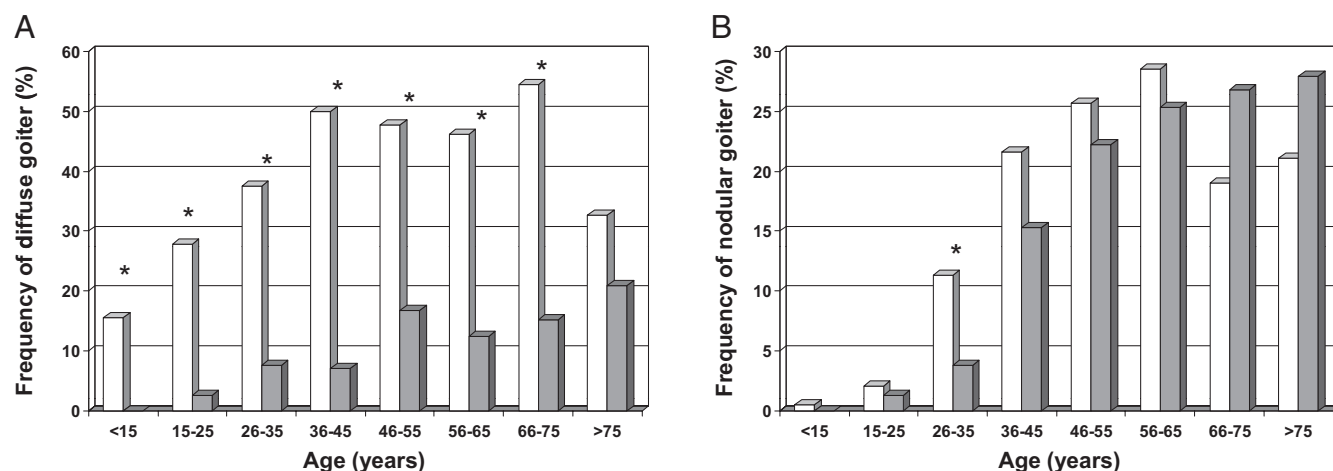


Figure 2. Frequency of diffuse goiter (panel A) and nodular goiter (panel B) in subjects resident in Pescopagano in 1995 (white columns) and in 2010 (gray columns). The prevalence of diffuse goiter progressively increased with age both in 1995 and 2010 and in each class of age was significantly lower in 2010 compared with 1995, with the exception of subjects older than 75 years. The frequency of nodular goiter was significantly lower in 2010 than in 1995 in patients aged 26–35 years, whereas no difference was observed in older classes of age. $^*\chi^2 P < .05$. The number of subjects included in each class of age is reported in *Subjects and Methods*.

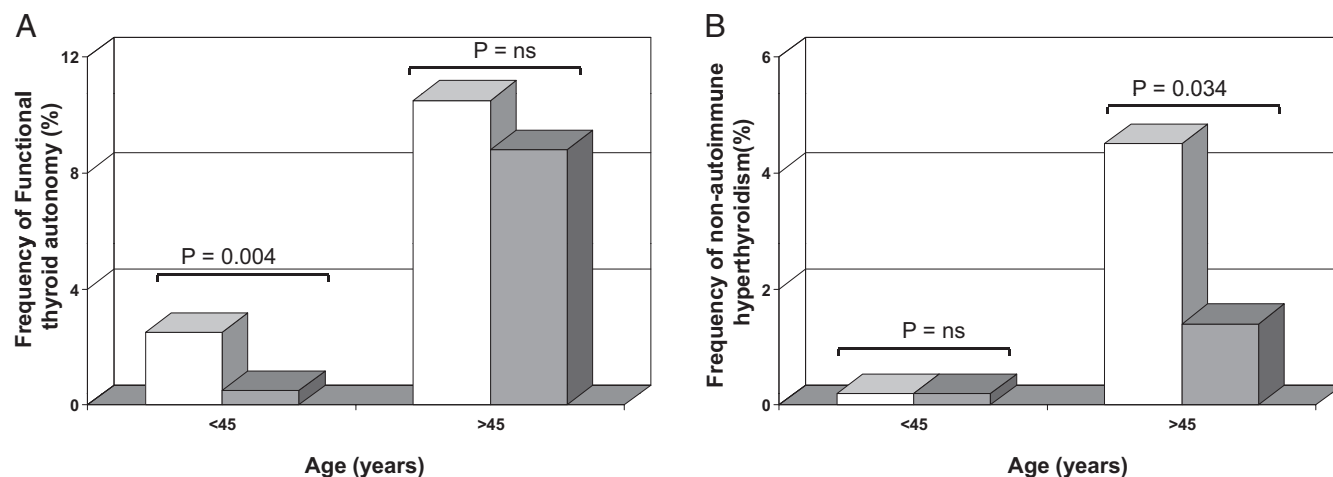


Figure 3. Frequency of functional thyroid autonomy (panel A) and nonautoimmune hyperthyroidism (panel B) in subjects resident in Pescopagano in 1995 (white columns) and in 2010 (gray columns). The frequency of functional thyroid autonomy was significantly lower in 2010 than in 1995 in subjects younger than 45 years (Fischer test $P = .004$) and was not different in older subjects. The frequency of nonautoimmune hyperthyroidism was significantly lower in 2010 than in 1995 in subjects older than 45 years ($\chi^2 P = .03$), whereas it was low and not different in younger subjects. The number of subjects younger or older than 45 years was 1010 and 401, respectively, in 1995 that number was 579 and 569, respectively, in 2010.

23 subjects. Furthermore, 32 patients with HT were under treatment with L-T4. Probably most of these subjects were hypothyroid before starting L-T4 therapy, but unfortunately, we were not able to recover their clinical records. Of these 32 patients, 6 were still mildly hypothyroid under L-T4 treatment. Considering hypothyroid also, in the other 26 subjects under L-T4 treatment, the overall frequency of hypothyroidism in 2010 was 57 of 1148 (5.0%), significantly higher than the frequency of hypothyroidism found in 1995 (40 of 1411, 2.8%, $P = .005$). In 1995 of the 40 hypothyroid patients, none was under L-T4 treatment, 38 (95.0%) presented a subclinical hypothyroidism, and 2 (5.0%) had an overt hypothyroidism.

When age was taken into account, in subjects older than 15 years, no difference was found in hypothyroidism in 2010 with respect to 1995 (50 of 1065, 4.7% vs 40 of 992, 4%; $P = .46$), whereas in subjects younger than 15 years, the frequency of untreated subclinical hypothyroidism was significantly higher in 2010 than in 1995 (7 of 83, 8.4% vs 0 of 419, 0.0%, $P < .0001$). Of the 7 hypothyroid young subjects in 2010, 3 had HT and 4 presented with a mild increase of TSH, with negative serum TAb and normal pattern at thyroid ultrasound.

No significant difference was observed in untreated patients with overt hypothyroidism (2 of 1148, 0.17% vs 2 of 1411, 0.14% in 2010 and 1995, respectively).

Thyroid autoimmunity

The frequency of positive TAb (Figure 4) was significantly higher in 2010 (224 of 1148, 19.5%) than in 1995 (178 of 1411, 12.6%; $P < .0001$), both in females (174 of 680, 25.6% vs 134 of 777, 17.2%; $P = .0001$) and in males (50 of 468, 10.7% vs 37 of 634, 5.8%; $P = .003$).

HT, diagnosed according to the criteria defined in the *Subjects* section, was also significantly more frequent in 2010 (167 of 1148, 14.5%) than in 1995 (50 of 1411, 3.5%; $P < .0001$), both in females (125 of 680, 18.4% vs 38 of 777, 4.9%; $P < .0001$) and in males (42 of 468, 9.0% vs 12 of 634, 1.9%; $P < .0001$) (Figure 5A). In 2010 the prevalence of HT progressively increased with age and in each class of age was significantly higher in 2010 compared with 1995, with the exception of subjects older than 75 years (Figure 5B).

Discussion

The aim of this study was to evaluate the prevalence of thyroid disorders in the community of Pescopagano, a

Table 1. Hyperthyroidism

	1995		2010		P
	Patients, n	%	Patients, n	%	
Graves' disease	9	0.6	9	0.8	NS
Nonautoimmune hyperthyroidism	20	1.4	9	0.8	0.13
Total	29	2.1	18	1.6	0.37

Abbreviation: NS, not significant.

Table 2. Hypothyroidism

Age, y	1995		2010		P
	Subjects, n	%	Subjects, n	%	
<15	0/419	0.0	7/83	8.4	<.0001
≥15	40/992	4.0	50/1065	4.7	NS
All	40/1411	2.8	57/1148	5.0	.005

Abbreviation: NS, not significant.

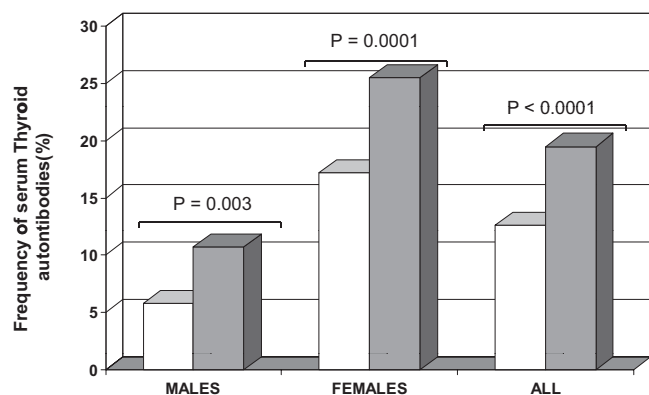


Figure 4. Frequency of TABs in resident subjects in Pescopagano in 1995 (white columns) and in 2010 (gray columns). The frequency of positive TAb was significantly higher in 2010 than in 1995 in both females and males (χ^2 P value reported in figure). The number of males and females was 634 and 777, respectively, in 1995 and 468 and 680, respectively, in 2010.

southern Italian village located in an area of iodine deficiency, 15 years after a previous survey conducted in the same community (14). After the survey of 1995, the population living in Pescopagano was made aware of thyroid diseases due to iodine deficiency, and local authorities strongly supported the use of iodized salt. This process has been reinforced in 2005, when Italian Parliament has passed a law for iodine prophylaxis. In 2010 about 65% of residents in Pescopagano used iodized salt, and UEI was significantly higher than in 1995 (median 98.0 vs 55.0 $\mu\text{g/L}$).

In this work we have studied the frequency and the distribution of thyroid disease after the beginning of iodine supplementation in this population living in a relatively isolated village, in which genetic and other environmental factors have not substantially changed between the 2 surveys. Furthermore, 505 of 1148 subjects (44.0%) were evaluated in both surveys.

Our results show that the prevalence of goiter was significantly lower in 2010 than in 1995 (25.8% vs 46.1%), mainly due to the reduction of diffuse goiter (10.3% vs 34.0%). In 2010 no case of diffuse goiter was found in the 83 subjects younger than 15 years old, whereas in 1995 it was diagnosed in 65 of 419 of the subjects of the same class of age (15.5%). The prevalence of diffuse goiter progressively increased with age both in 1995 and 2010 but in each class of age was significantly lower in 2010 compared with 1995, with the exception of subjects older than 75 years, conceivably due to the small size of the sample of this class of age. The overall prevalence of nodular goiter was not significantly different in the 2 surveys, but when age was taken into account, its frequency was low in both 2010 and 1995 in subjects younger than 25 years old, significantly lower in 2010 than in 1995 in subjects aged 26–35 years (3.8% vs 11.3%), whereas no difference was

observed in subjects older than 35 years old. The absence of a significant difference of the frequency of nodular goiter in subjects older than 35 years may be explained by the fact that in most the subjects of this class of age, the process of goiter development was initiated already before the increase of iodine intake.

On the whole, these data indicate that the iodine prophylaxis in this community has dramatically reduced the prevalence of goiter, which has been totally eradicated in the younger subjects. These results confirm our previous work (19) showing that the use of iodized salt is able to prevent the development of goiter in children born after the implementation of a program of iodine prophylaxis and to further control thyroid enlargement in older subjects.

In iodine-deficient countries, nonautoimmune hyperthyroidism is relatively frequent. Thyroid autonomy and eventually thyrotoxicosis are the natural evolution of nodular goiter (20, 21) and represent an important cause of atrial fibrillation and mortality in older people (22, 23). Our results show that in 2010 thyroid autonomy was significantly lower than in 1995 in subjects younger than 45 years (0.5% vs 2.5%). The decreased frequency of thyroid functional autonomy in a younger age was associated with a significant reduction of the frequency of hyperthyroidism due to toxic nodular goiter/toxic adenoma in older age. We did not observe the increased frequency of hyperthyroidism after the beginning of iodine prophylaxis that has been reported in other studies (24, 25), conceivably due to the lower level of iodine supplementation in our population. However, an increased frequency of toxic nodular goiter has been reported, even after a small raise of iodine content of salt in Switzerland in 1980 (26). In this respect, it is important to underscore that the increased frequency of hyperthyroidism in Switzerland was transient, and thus, it is possible that in the community of Pescopagano, which we studied 15 years after the first survey, we have missed this phenomenon.

Taken as a whole, these data indicate that iodine prophylaxis is associated with a reduced frequency of thyroid autonomy in younger subjects and toxic nodular goiter in older patients. This observation may have a relevant impact on the health of this population, thyrotoxicosis being associated with arrhythmias and mortality in older people. It is also important to underline that in our population the frequency of autoimmune hyperthyroidism was the same in the 2 surveys. Bulow Pedersen and coworkers (27) have shown that in Danish populations, even a cautious iodization of salt results in an increased incidence rate of hyperthyroidism, mainly in young subjects and most probably of autoimmune origin. In this study the authors used a computer-based register of all new cases of hyperthyroid-

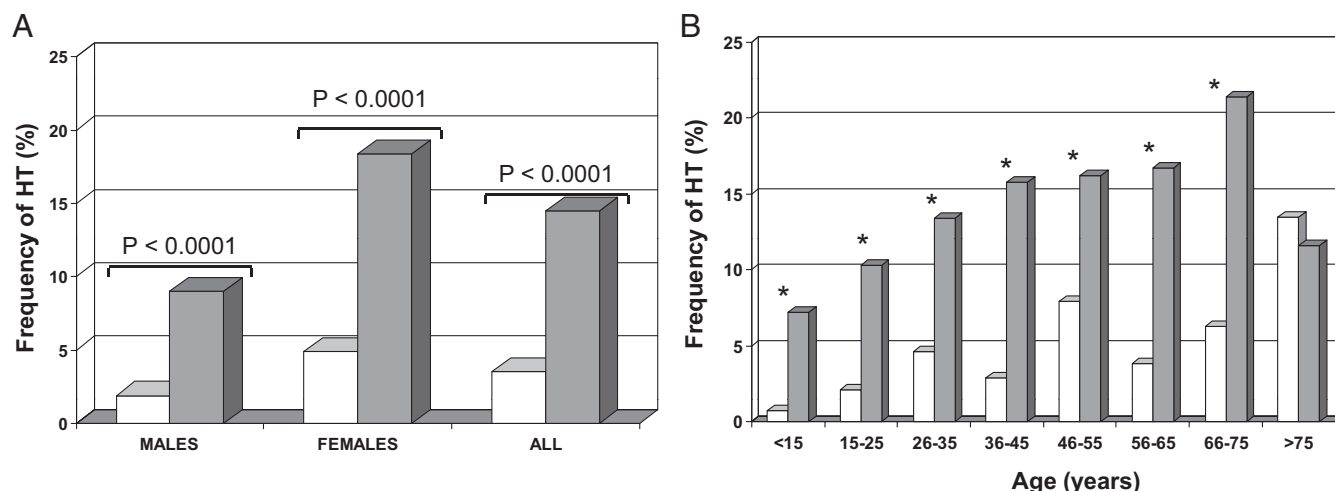


Figure 5. A, Frequency of HT in subjects resident in Pescopagano in 1995 (white columns) and in 2010 (gray columns) according to sex. HT was significantly more frequent in 2010 than in 1995 in all subjects considered together and in both females and males taken separately (χ^2 P value reported in figure). The number of males and females was 634 and 777, respectively, in 1995 and 468 and 680, respectively, in 2010. B, Frequency of HT in subjects resident in Pescopagano in 1995 (white columns) and in 2010 (gray columns) according to age. The frequency of HT increased with age in both 1995 and 2010 and in each class of age was significantly higher in 2010 compared with 1995, with the exception of subjects older than 75 years. * χ^2 $P < .05$. The number of subjects included in each class of age is reported in *Subjects and Methods*.

ism in a population of about half a million subjects living in a moderate iodine-deficient (Aalborg) or in mild iodine-deficient (Copenhagen) area. It is possible that the relatively small size of our study group may not allow us to detect a small increase of autoimmune hyperthyroidism.

Another potential complication of iodine supplementation is the worsening or the induction of autoimmune thyroiditis. Cross-sectional studies of populations with different iodine intakes in Great Britain (8), Denmark, and Iceland (9) showed that the frequency of thyroid autoantibodies and hypothyroidism is higher in iodine-replete than in iodine-deficient populations. Boukis et al (28) showed that in goitrous patients from a mildly iodine-deficient area in Greece treated with iodized oil, thyroid autoantibodies, undetectable before treatment, became positive in 42.8% of the subjects 3 and 6 months later. Recently Pedersen et al (11) found an increased prevalence of thyroid autoantibodies after the beginning of a cautious iodization program, supporting the view that even a small increase of iodine supplementation may be associated with an increased thyroid autoimmunity.

The results of our survey are in keeping with data reported in the literature. We have found a significant increased frequency of positive TAb in 2010 compared with 1995 (19.5% vs 12.6%), both in females (25.6% vs 17.2%) and in males (10.7% vs 5.8%). One limit of our work is that 2 different assays were used to measure serum TAb in the 2 surveys: hemagglutination in 1995 and immunofluorometry in 2010. However, it has been shown that even if immunometric assay are more sensitive than those based on passive hemagglutination, a highly significant positive correlation is present between the 2 methods

(29). Furthermore, in the community that we have studied, we have also found an increased frequency of HT (14.5% vs 3.5% in 2010 and 1995, respectively), diagnosed according to the criteria defined in the *Subjects* section. In 2010 vs 1995, the frequency of HT was significantly higher in both females (18.4% vs 4.9%) and males (9.0% vs 1.9%) and progressively increased with age, being significantly higher in each class of age. These data are in keeping with results reported after iodine supplementation in Greece (30, 31), showing an increase in the prevalence of thyroid autoimmunity, mainly in young subjects.

An increased frequency of hypothyroidism has been reported after the careful introduction of iodized salt in Denmark (10) using a computer-based register to identify all new cases of overt hypothyroidism in 2 different geographical areas with previous moderate or mild iodine deficiency. The frequency of hypothyroidism increased only in the area with previous moderate iodine deficiency. In Pescopagano, the increased frequency of HT was associated with an overall increased prevalence of hypothyroidism detected in 5.0% and 2.8% of population in 2010 and 1995, respectively. However, it is important to underscore that in 2010 only 25 new cases of hypothyroidism (2 overt and 23 subclinical) were diagnosed. Other 32 subjects had a clinical diagnosis of HT and were under treatment with L-T₄. Of these 32 patients, 6 were still mildly hypothyroid under L-T₄ treatment. The remaining 26 HT patients were euthyroid under L-T₄ treatment, and unfortunately, we were not able to ascertain their thyroid function before treatment. We assumed that all these patients under L-T₄ treatment were hypothyroid, and we are aware that this is a limit of our work. However, the fre-

quency of subclinical hypothyroidism was clearly increased in subjects younger than 15 years (8.4% vs 0% in 2010 and 1995, respectively), none of whom was treated. Of the 7 hypothyroid young subjects in 2010, 3 had HT and 4 presented a mild increase of TSH, with negative serum TAb and normal pattern at thyroid ultrasound. It is conceivable that even these 4 children may be affected by thyroid autoimmunity. Indeed, it has already been described that young subjects with initially negative serum TAb may later develop positive tests (32, 33). These data indicate that overall the prevalence of hypothyroidism is increased, mainly in young subjects, and this observation should be taken into account when planning the monitoring of the effects of iodine prophylaxis.

In summary, in the community of Pescopagano, about two thirds of subjects routinely used iodized salt, mainly because the population awareness of the importance of iodine prophylaxis increased after a first survey conducted 15 years before. Voluntary iodine prophylaxis has led to a significant improvement of iodine nutrition of the population close to iodine sufficiency. A change in the spectrum of thyroid diseases has been observed in this community. In this respect, the role of iodine intake has already been shown in cross-sectional studies and in a few longitudinal computer-based population studies. In the present work, the role of iodine nutrition was assessed in a small rural community relatively segregated, in which genetic and other environmental factors have not substantially changed between the 2 surveys. Iodine intake strongly affects the pattern of thyroid diseases, but the benefits of correcting iodine deficiency (decreased prevalence of goiter and thyroid autonomy, mainly in younger subjects and reduced frequency of nonautoimmune hyperthyroidism in older subjects) far outweigh the risk of development of thyroid autoimmunity and mild hypothyroidism in youngsters.

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