Non-palpable thyroid nodules in a borderline iodine-sufficient area: Detection by ultrasonography and follow-up

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ABSTRACT. Thyroid ultrasonography was performed in 482 subjects, free of known thyroid disease and living in a borderline iodine-sufficient urban area, to assess the prevalence of non-palpable thyroid nodules and evaluation their evolute during a 3-yr follow-up. The mean (±SD) thyroid volume in the whole study group was 10.9±3.7 ml and was higher in males (12.9±3.6 ml) than in females (9.2±2.9 ml) ($p<0.0001$). Thyroid volume was correlated with body surface, height and weight, while no correlation was present with lean and fat body mass. Goiter was found in 5/256 females and in 13/226 males. Thyroid nodules were found in 27/482 subjects (18 females, 9 males). Single nodules were found in 17/464 subjects (3.66%) with a thyroid gland of normal volume and in 4/18 subjects (22.2%) with goiter ($\chi^2=10.21$; $p=0.001$). Multiple nodules were found in 3/464 subjects (0.6%) with a thyroid of normal volume and in 3/18 (16.6%) subjects with goiter ($\chi^2=24.31$; $p<0.0001$). The prevalence of thyroid nodules was significantly higher in females >35 yr than in those <34 yr ($\chi^2=7.47$; $p=0.0062$). A significant increase (>30%) of nodular volume was found in 5 subjects, while an increased number of nodules was found in 8. In conclusion, thyroid ultrasonography reveals the presence of thyroid nodules in a significant proportion of apparently thyroid disease-free subjects living in a borderline iodine-sufficient urban area. Incidentally discovered thyroid nodules are associated with goiter and are likely to progress in volume and number.

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INTRODUCTION

Thyroid nodules are very frequent in the general population, although the estimation of their prevalence is variable, depending on the method of detection. In large population studies palpable thyroid nodules were present in about 5% of subjects (1). These observations have been confirmed in more recent clinical surveys carried out in iodine-sufficient areas (2, 3), while systematic pathological examinations of thyroid glands in autopsy studies have shown a much higher prevalence of thyroid nodularity (ranging 49-57%) that was asymptomatic during life (4). Similar figures are obtained *in vivo* using thyroid ultrasonography, by which thyroid nodules are detected in 13-50% of the general population (5-12). Several factors may explain such a variability in the prevalence of thyroid nodules detected by ultrasonography, the most important being the iodine intake in the population examined (13, 14). Recently, thyroid ultrasonography was used to assess the prevalence of thyroid nodules in the whole population living in a village of Southern Italy characterized by mild-to-moderate iodine deficiency. Thyroid nodules were rare in children, while their prevalence increased with age, being the highest in the 56-65-yr-old group (15). These findings underscore the role of prolonged exposure to iodine deficiency in the growth of goiter and progression of nodularity (16-18).

The aim of the present study was to assess by thyroid ultrasound the prevalence of non-palpable thyroid nodules in subjects without any known thyroid disease and living in an area with borderline sufficient iodine intake. Our results showed that incidentally discovered thyroid nodules are associated to goiter and are likely to progress in volume and number.

SUBJECTS AND METHODS

Subjects

The study group included 482 healthy volunteers, (256 females, 226 males), recruited from the hospital staff (medical and paramedical) and their relatives willing to participate to the survey. The mean±SD age

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was 37±12.6 yr (range 17-82 yr; median 34 yr). All subjects lived close to the hospital, in an urban area. The use of drugs that might interfere with thyroid function was carefully excluded. The aim of the study was explained to the participants who gave their consent. Subjects with present or past history of thyroid disease were excluded. All subjects with thyroid abnormalities were followed periodically once a year for 3 years, while a randomized sample of 50 subjects with no thyroid abnormalities were re-evaluated 36 months after the first observation.

Thyroid function tests

Serum free thyroxine (FT_4) and free triiodothyronine (FT_3) were assayed by RIA (FT_4 Liso-Phase and FT_3 Liso-Phase kit, Technogenetics s.r.l., Milan, Italy). Serum TSH was measured by a sensitive IRMA (Delphia. Pharmacia, Turku, Finland). Antibodies to thyroglobulin (TgAb) and to thyroperoxidase (TPOAb) were measured by passive agglutination (Serodia Tg, Serodia TPO, AMC, Fujirebio INC, Tokyo, Japan) and expressed as reverse of titer. In subjects with incidentally discovered thyroid nodules, serum calcitonin was measured by IRMA assay (CIS BIO International, France). Urinary iodine excretion was performed by a Koltholofft colorimetric method using an autoanalyzer apparatus (Technicon, Rome, Italy) according to the method modified by Zak (19). The median urinary iodine excretion was 122 µg/l (mean 140.5±56, range 60-274 µg/l), indicating that this area is iodine-sufficient according to the World Health Organization (WHO) criteria (20).

Thyroid ultrasonography

Thyroid ultrasonography was performed by a real-time instrument AU 590 Asynchronous (Esaote Biomedica, Genova, Italy) with a 7.5 MHz linear transducer. The volume of thyroid lobes as well as the volume of nodules were calculated according to the formula of the ellipsoid model: width x length x thickness x 0.52.

Thyroid nodules: Thyroid nodules were classified as solid, mixed (with solid parenchima and fluid content) or cystic (a completely fluid lesion). Solid lesions were defined iso- hypo- or hyperechogenic comparing their echogenicity with that of the normal thyroid tissue. The characteristics of the margins were carefully examined, defining the presence of complete or incomplete surrounding transonic rim (halo sign). Microcalcifications were defined as hyperechoic spots less than 2 mm, with acoustic shadowing. Anechoic lesions <1 cm of diameter, not surrounded by a well-defined capsule, were not considered as nodules but as small colloid lumps.

All ultrasound examinations were performed by the same observer (TR). The intra-observer error for determination of thyroid or nodule volume was estimated to be <10% in 10 subjects with nodular goiter submitted to surgery, in whom thyroid and nodule volumes were calculated by the submersion method. To avoid possible overestimations of variations of thyroid or nodular volumes, and taking into account also variations considered as significant in other studies (21), only modifications of volumes >30% were considered significant both for the whole thyroid and for the nodules.

Body parameters: The body surface area (BSA, m^2) was calculated using the formula: $BSA=W^{0.425} \times H^{0.725} \times 71.84 \times 10^{-4}$, where W is the weight in kg and H the height in cm. Lean and fat body mass were measured

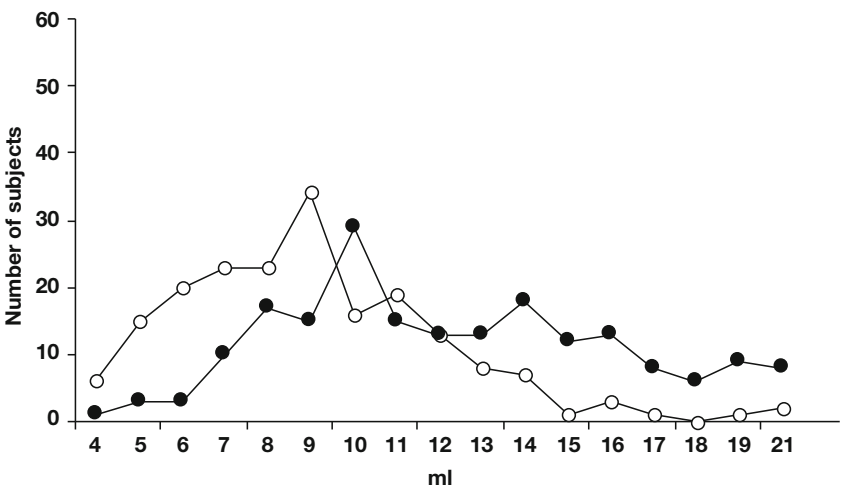

Fig. 1 - *Thyroid volume (median, ml) distribution in females (open circles) and males (closed circles).*

with a body impedance analyzer (BIA 109 Akern, Florence, Italy) and expressed as percentage of body weight.

Statistical analysis

For statistical evaluation parametric tests were used. Results obtained in different groups of subjects were compared by χ^2 test and Student's *t*-test for paired data. Chi-square value was calculated applying the Yates' correction for continuity. Simple regression analysis and normality test were used to define the normal thyroid volume.

RESULTS

Thyroid function

The median of serum FT_4 was 11.2 pg/ml (mean 11.3±2.2; range 6.5-16.2); the median of serum FT_3 was 3.2 pg/ml (mean 3.2±0.5; range 2.0-4.7); the median of serum TSH was 1.2 μU/ml (mean 1.3±0.6; range 0.4-3.3). Five subjects were hypothyroid at the first observation (FT_4: mean 5±2.6 pg/ml, range 1.1-7.5; FT_3: mean 2.8±0.8 pg/ml, range 1.4-3.7; TSH: mean 28.2±45.4 μU/ml, range 4.2-120). One subject was hyperthyroid (FT_4=22 pg/ml; FT_3=5.9 pg/ml; TSH<0.03 μU/ml). In all subjects with thyroid nodules serum calcitonin was undetectable.

Thyroid volume

The mean thyroid volume in the whole study group was 10.9±3.7 ml and was higher in males (12.9±3.6 ml) than in females (9.2±2.9 ml) (p<0.0001). Thyroid volume was normally distributed (Fig. 1) and was correlated with body surface (r=0.55, p=0.0001), height (r=0.50, p=0.0001) and weight (r=0.47, p=0.0001); in contrast to previous studies (22, 23) no correlation was present with lean and fat body mass (Table 1). We defined as goiter thyroid volumes above the mean±2 SD in each sex (males: 12.9±7.2=20.1 ml; females: 9.2±5.8=15 ml). According to these criteria goiter was found in 5/256 females (1.9%) and in 13/226 males (5.7%; χ^2=3.8; p=0.05).

Thyroid nodules

Small anechoic lesions were detected in 37/482 subjects (7.7%) at the first observation. During the follow-up these colloid lumps were not detected in 10 of these subjects anymore. Thyroid nodules were found in 27/482 subjects (5.6 %; 18 females, 9 males). Single nodules were found in 17/464 subjects (3.7%; 13 females, 4 males) with a thyroid gland of normal volume and in 4/18 subjects (22.2%; 1 female; 3 males) with goiter (χ^2=10.21; p=0.001). Multiple nodules were found in 3/464 subjects (0.6%; 1 female; 2 males) with a thyroid of normal volume and in 3/18 subjects (16.6%) with goiter (χ^2=24.31; p<0.0001). The prevalence of thyroid nodules was significantly higher in females >35 yr (14/113; 12,4%) than in those <34 yr (4/143; 2.79%; χ^2=7.47; p=0.0062), while this difference was not significant in males >35 yr (7/134; 5.22%) with respect to those <34 yr (2/92; 2.17%; χ^2=0.6; p=0.41) (Fig. 2). Thyroid echografic characteristics of the nodules are described in Table 2.

Eight nodules, judged clinically relevant for their size or echographic characteristics (29-31), were submitted to fine needle aspiration. Malignancy was excluded in all of them.

Among the 27 subjects with thyroid nodules, a significant (>30%) increase of thyroid volume during the

Table 1 - *Correlation of thyroid volume with body parameters in healthy subjects.*

		Total (no. 482)	Females (no. 256)	Males (no. 226)
Body surface (m^2)	r	0.55	0.38	0.32
	p	0.0001	0.0001	0.004
Height (cm)	r	0.50	0.15	0.37
	p	0.0001	0.12	0.001
Weight (kg)	r	0.47	0.38	0.22
	p	0.0001	0.0001	0.04
Lean body mass	r	0.11	0.22	0.11
	p	0.11	0.02	0.3
Fat body mass	r	0.10	0.21	0.06
	p	0.16	0.02	0.56

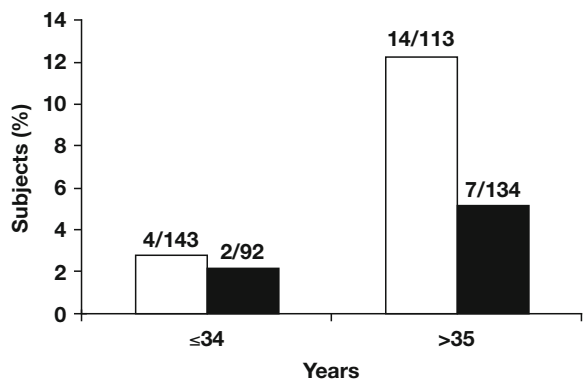

Fig. 2 - *Prevalence of thyroid nodules in females (open columns), in males (closed columns) according to age. The prevalence of thyroid nodules was significanly higher in females >35 yr than in those ≤34 yr (χ^2=7.47; p=0.0062), while no significant difference was found in males >35 years and in those ≤34 years (χ^2=0.6; p=0.41).*

Table 2 - *Volume and echographic characteristics of incidentally discovered thyroid nodules.*

Nodule volume (ml)	Solid		Mixed	Cystic	Total
	Isoechoic	Hypoechoic			
<0.5	5*	7°	-	-	12
0.5-1	5**	1	1	2	9
>1	8	2°°	1	1	12
Total	18	10	2	3	33

*1 had absent halo sign and microcalcifications; **2 had absent halo sign; °1 had absent halo sign; °°1 had microcalcifications.

follow-up was found in 3 (subjects 6-8) (Table 3), a significant increased nodule volume was observed in 5 (subjects 3, 6-9) (Table 3), and an increased number of nodules in 8 (subjects 1-7 and 9) (Table 3). In the group of 50 subjects with no thyroid abnormalities at the first observation no significant increase of thyroid volume and no nodules were detectable during the follow-up, with the exception of small colloid lumps that were detected in 2 subjects.

An echographic pattern of diffuse hypoechogenicity was found in 41 subjects, 12 of them having also positive thyroid autoantibody tests. Two of these 12 subjects were hypothyroid and 3 had subclinical hypothyroidism. Among subjects with normal thyroid echogenicity Tg and/or TPOAb positive tests were more frequently found in subjects with goiter (2/18; 11%) than in those with normal thyroid volume (7/464; 1.5 %; χ^2=4.26, p=0.038) (Table 4).

Table 3 - *Thyroid echographic findings in 9 subjects with incidentally discovered thyroid nodules who had an increase of thyroid volume and/or nodule size or number during the follow-up.*

Case no.	Age (yr)	Thyroid volume (ml) (% change)	Nodule volume (ml) (% change)
1	43	15 → 16 (+7%)	3.2 → 3.2 (0%) Absent → 1.0
2	51	15 → 16 (+7%)	1.3 → 1.4 (+7%) Absent → 0.1 Absent → 0.6
3	54	11 → 13 (+18%)	0.1 → 0.7 (+600%) Absent → 0.4
4	32	19 → 19 (0%)	0.1 → 0.1 Absent → 0.3 Absent → 0.5
5*	59	9 → 8 (-11%)	0.1 → 0.1 (0%) Absent → 0.2
6	56	56 → 77 (+37.5%)	2.5 → 8.0 (+200%) 3.0 → 12.0 (+300%) 4.0 → 5.6 (+40%) Absent → 1.9
7	65	24 → 34 (+42%)	4.0 → 10.0 (+150%) 1.9 → 2.9 (+53%) Absent → 1.7 Absent → 3.4
8	61	41 → 59 (+44%)	9.7 → 10.0 (+30%) 3.9 → 0.5 (-94%) 3.6 → 9.6 (+166)
9	33	16 → 16 (0%)	0.5 → 2.4 (+380%) Absent → 0.5 Absent → 0.2

*This subject had also a diffuse thyroid hypoechogenicity.

Table 4 - *Prevalence of thyroglobulin and/or thyroperoxidase autoantibodies (TgAb and TPOAb respectively) according to thyroid volume.*

TgAb and/or TPOAb	Subjects with normal thyroid volume (no. 464)		Subjects with goiter (no. 18)		Total
	no.	%	no.	%	no.
Positive	7*	1.5	2*	11	9
Negative	457	98.5	16	89	473

*χ^2=4.26; p=0.038

DISCUSSION

In this study we assessed the prevalence of thyroid nodules by thyroid ultrasound in apparently healthy subjects living in an area of bordeline iodine sufficiency and then followed their evolution over 3 yr. Thyroid nodules were detected in 27/482 subjects (5.6%), 9 of whom had an increase in nodule number or volume during the follow-up. Because of the availability of highly sensitive imaging techniques, several papers in recent years have reported a prevalence of incidentally discovered, asymptomatic thyroid nodules ranging from 13 to 50% (5-12). The variability of these observations may depend on several factors such as differences in iodine intake, age of the population examined, inclusion in the study of subjects with known thyroid disease and size of the thyroid lesions considered to be a nodule. Small colloid lumps <1 cm were diagnosed as nodules in some of these papers (5, 8, 9), and not in others (7, 10, 11). In our casistic small colloid lumps were detected in 37/482 subjects (7.7%) and in 10 of these vanished during the follow-up. For the fluid composition and their tendency to vanish, these lesions cannot be considered likely to harbor malignancy. While it is well recognized that iodine deficiency is a major cause of diffuse and nodular goiter (13, 14) in several of these studies iodine intake was not specifically determined. In agreement with these studies, we previously reported a high prevalence of thyroid nodules detected by ultrasound in an iodine-deficient population (median urinary iodine excretion 55 µg/l) living in an extraurban area of Southern Italy. Thyroid nodules were rare in children, and their prevalence increased with age being the highest (28.5%) in the 56-65-yr-old group (12). These results demonstrated the relationship of thyroid nodules with age and length of exposure to iodine deficiency. Thyroid nodules, defined as a solid, mixed or cystic lesion surrounded by a well-defined capsule were found in 27 apparently healthy subjects out of the 482 included in the present study. As observed by other Authors (5, 9-10), the prevalence of thyroid nodules increased with age being higher in females >35 yr than in those ≤34 yr. This difference did not reach significance in males, probably due to the small number of male subjects with thyroid nodules included in this study. As expected and in agreement with previous observations (12), the prevalence of thyroid nodules was higher in subjects with an enlarged thyroid than in subjects with a thyroid of normal volume. Unlike some of the previous reports, the present study was performed in a borderline iodine-sufficient urban area and all subjects with a past or present history of thyroid disorders were excluded. This could explain the overall low prevalence of thyroid incidentalomas detected compared with other studies (5-12). The potential malignancy of thyroid nodules discovered incidentally by ultrasound, although not completely established, is likely to be very low (24). Clinically relevant thyroid carcinoma is relatively rare, being 1-2% of all carcinomas, its incidence ranging approximately from 0.5 to 10/100.000 in the USA (4, 8, 27-29). The discrepancy between the low frequency of clinically relevant thyroid malignancy (30) and the high prevalence of thyroid nodules discovered by ultrasound (5-11) supports the belief that incidental thyroid lesions have little clinical relevance, justifying a conservative approach (27). In the present series thyroid carcinoma was detected in none of 8 nodules submitted to fine needle aspiration, although due to the small number of observations we cannot draw final conclusions on the prevalence of carcinoma in thyroid incidentalomas.

Among the 27 subjects in whom thyroid nodules were detected by ultrasound, an increased number of nodules was found in 8 during the 3-yr follow-up period, and a significant increase in volume in 5 nodules. These data suggest the opportunity of close follow-up and/or L-T_4 suppressive treatment in subjects in whom thyroid nodules are incidentally detected.

A diffuse thyroid hypoechogenicity, suggestive of thyroid autoimmunity (31-34), was found in 12 subjects, all having circulating thyroid autoantibodies positive test, 5 of whom also had overt or subclinical hypothyroidism. Among subjects with normal thyroid echogenicity, thyroid autoantibodies were more frequently detectable in subjects with goiter than in those with normal thyroid volume. Although the number of goitrous subjects included in this study is small, these data confirm previous observations obtained in larger populations showing an association between goiter and low titer of thyroid autoantibodies positivity (35-39).

In conclusion, although thyroid ultrasonography is not likely to detect pre-clinical thyroid carcinoma, it reveals the presence of thyroid nodules in a signif-

icant proportion of apparently thyroid disease-free subjects living in an iodine-sufficient urban area. Incidentally discovered thyroid nodules are associated with goiter and are likely to progress in volume and number.

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