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Iodine deficiency in Calabria: Characterization of endemic goiter and analysis of different indicators of iodine status region-wide

G. Costante*, L. Grasso**, E. Schifino*, M.F. Marasco*, U. Crocetti*, C. Capula*, R. Chiarella*, O. Ludovico*, M. Nocera*, G. Parlato***, and S. Filetti*

*Department of Experimental and Clinical Medicine and *** Institute of Biochemistry, Physics and Molecular and Cellular Pathology, Service of Clinical Chemistry, Faculty of Medicine and Surgery, University of Catanzaro, Catanzaro; **Chair of Endocrinology, University of Pisa, Pisa, Italy

ABSTRACT. The distribution of goiter prevalence in schoolchildren (no.=13,984, age 6-14 yr), the neonatal TSH results obtained from the congenital hypothyroidism screening program and the urinary iodine excretion values (no.=284) were employed for the assessment of iodine deficiency in Calabria, a Southern Italy region. Data were collected during the years 1990-1996. In the inland territory, goiter prevalence ranged from 19 to 64%. At sea level, there was a great variability of goiter prevalence, with values varying from 5.3 to 25.7%. The analysis of the neonatal hypothyroidism screening program data (no.=21,078) showed a 14.8% frequency of TSH levels >5 μU/ml whole blood in newborns from the inland territory and a 14.1% frequency at sea level. Urinary iodine excretion resulted (mean±SD) 53.8±43.4 μg/l (range: <20 to 189 μg/l) in the inland territory and 89.6±59.8 μg/l (range: 26 to 333 μg/l) at sea level. Median urinary iodine excretion values in 13 villages or small towns of the inland territory ranged from 31 to 57 μg/l. In 2 major towns located at sea level, the median iodine excretion values were 72 μg/l in Crotone main city and 94 μg/l in Reggio Calabria main city. The data indicated that moderate, with pockets of severe iodine deficiency is present in the inland region while iodine supply varies from sufficient to marginally low in the coastal areas. Mild iodine deficiency was found in a major town located at sea level.
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INTRODUCTION

Iodine nutritional deficiency still represents a major public health problem worldwide (1). At present, approximately 1 billion people are exposed to the risk of iodine deficiency disorders (IDD), including endemic cretinism, other neurological manifestations and endemic goiter (2).

During the last decades, iodine prophylaxis programs have been implemented for the correction of IDD in many countries (3). In particular, the diffusion on a large scale of salt fortified with iodine has played a pivotal role in the eradication of endemic goiter (1-4). In Europe, pockets of iodine deficiency are still present and normal iodine supply has been documented only in The Netherlands, France and Slovakia (5).

IDD prophylaxis with iodized salt can be performed in Italy on a voluntary basis. For this reason iodized salt consumption in the country still accounts for less than 2% of the total salt used for domestic purposes (6). In the absence of a generalized prophylaxis, iodine nutritional status nationwide varies from sufficient to severely deficient (5-9). Thus, endemic goiter as well as other IDD such as cretinism and other neurological manifestations have been documented in the country over the last 2 decades (8, 10).

Goiter and its complications (*i.e.* thyroid nodularity, functional autonomy and hyperthyroidism due to toxic nodular goiter) represent a great proportion of patients attending our endocrinology outpatient clinics, from different areas of Calabria. In addition, preliminary reports have shown the presence of iodine deficiency *foci* in the region (7, 9), suggesting a great heterogeneity in iodine supply among different areas. Therefore, the aim of the present study was to precisely define the map of endemic goiter

Key-words: Iodine deficiency, endemic goiter, neonatal TSH, congenital hypothyroidism.

Correspondence: Dr. Giuseppe Costante, Dipartimento di Medicina Sperimentale e Clinica, Università di Catanzaro, Via T. Campanella 115, 88100 Catanzaro, Italy.

E-mail: costante@unicz.it

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and to characterize iodine deficiency in the whole Calabrian territory. For this purpose, clinical parameters and 2 different biochemical indicators of IDD status were analyzed according to the latest WHO (World Health Organization)-ICCIDD (International Council for Control of Iodine Deficiency Disorders)-UNICEF (United Nations Children's Fund) *ad hoc* committee recommendations (11). In particular, the distribution of goiter prevalence in a large schoolchildren sample representative of the different geographical areas of the region, the urinary iodine excretion values and the neonatal TSH results obtained from the congenital hypothyroidism screening program were analyzed as impact factors for the assessment of iodine nutritional supply.

SUBJECTS AND METHODS

Description of the region

Calabria (Fig. 1) is a Southern Italy region comprising 5 provinces, with an area of 15,080 km^2 and a population of about 2.2 million inhabitants. Geographically, it is a peninsula almost entirely composed of foothills and steep slope mountains, frequently culminating in uplands. These mountains form the Calabrian Appennins and are divided into four major ridges: the Pollino, the Sila, the Serre and the Aspromonte. Only 9% of the regional territory consists of small plains, spread along ~800 km of rugged coastline.

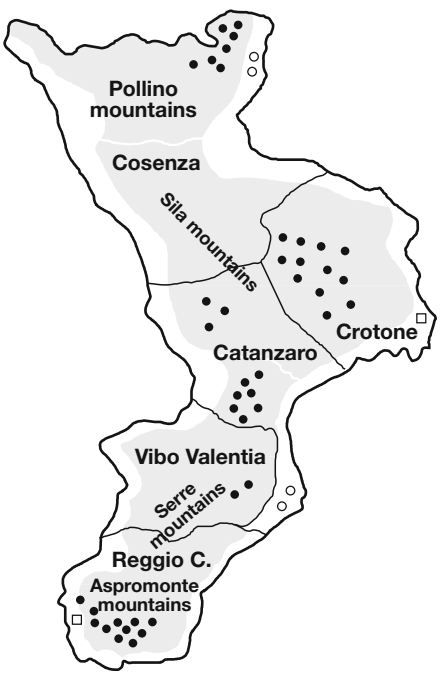

Fig. 1 - *Calabria region. Shaded areas represent the inland territory. Villages and small towns are identified with black circles. Areas at the sea level are indicated by open circles. Two main towns at the sea level are identified by open squares.*

Epidemiological survey for endemic goiter

Schoolchildren (no.=13,984; females=6812; males=7172) aged 6-14 yr were examined for the presence of goiter by palpation. The survey was performed during the years 1990-1996. Because of the great heterogeneity in terms of access to main roads and/or to highways as well as eating habits among different areas of the region, a balanced sample representative of the different geo-morphological, socioeconomical and cultural conditions of the region was selected, including villages, small towns and major cities. Altogether, the schoolchildren examined represented about 15% of children in this age range living in Calabria. In particular, 10,243 schoolchildren lived in 42 villages and small towns located from 350 to 920 m altitude, on all 4 major mountain ridges (Fig. 1). A sample of 3741 schoolchildren resident in 4 small and in 2 chief towns located at sea level was also examined. In-field data were obtained by 2 trained examiners and were classified according to WHO recommendations (12). Discrepant grading between the 2 observers occurred in 15% of children. In such instances, the final decision was made by recording the lower assigned score.

Urinary iodine excretion

Urine samples (no.=284) were randomly collected during the morning on a voluntary basis, from children undergoing thyroid size evaluation in the provinces of Crotone and Reggio Calabria. The measurement of urinary iodine concentration was performed using a Technicon Autoanalyzer (13).

Screening for congenital hypothyroidism

The congenital hypothyroidism screening program in Calabria is performed according to the double assay strategy, by measuring both TSH and T_4 on dried blood spotted filter paper, as previously described (14). The data analyzed in the present study were obtained from January 1 to December 31, 1993. The total number of infants screened was 22,384 (99% coverage; 51.1% males, 48.9% females). Only the results obtained at days 4 and 5 of life were considered and all TSH values >20 μU/ml were excluded, to avoid the interference of both congenital hypothyroidism and neonatal hyperthyrotropinemia. On the whole, neonatal TSH results included for the present study were 21,078.

Statistics

Mean, SD and frequency distribution were used for data analysis.

RESULTS

Distribution of goiter prevalence in the different areas of the region

The average goiter prevalence resulted 40.7% in the inland territory and 16.3% at sea level (Table 1). Detailed data of goiter prevalence distribution in the region are illustrated in Figure 2. In the inland territory, the highest values were observed in the area of the Sila mountains belonging to the Catanzaro and Crotone provinces. In individual villages, goiter prevalence ranged from 30 to 64% in the Catanzaro province and from 30 to 68% in the Crotone province. Slightly lower goiter prevalence was recorded in the area of the Pollino mountains in the province of Cosenza (range prevalence: 25-46%), in the Aspromonte mountains of Reggio Calabria province (range prevalence: 20-51%) and

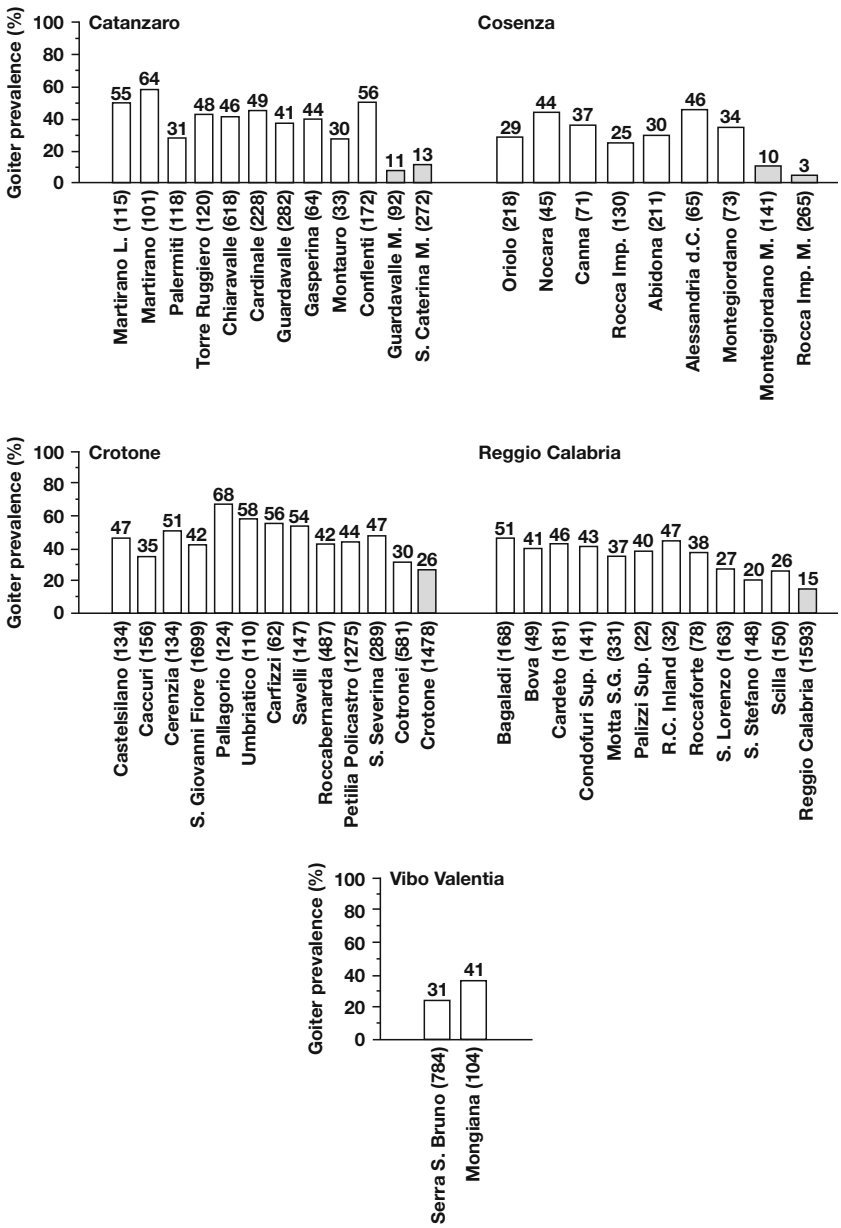

Fig. 2 - *Distribution of goiter prevalence in the 5 provinces of the Calabria region. Darker bars represent areas at the sea level. The number of examined schoolchildren is indicated in parentheses. Individual prevalences are reported on top of each bar.*

in the Serre mountains of Vibo Valentia province (range prevalence: 310-41%).
At sea level, there was a great variability of goiter prevalence, the lowest values being recorded in the Ionian coastal areas belonging to the provinces of Cosenza (5.3%) and Catanzaro (11.6%). Surprisingly, goiter prevalence in 2 main towns located at sea level was 14.7% in Reggio Calabria main city and 25.7% in Crotone main city.

Distribution according to sex, age and grade of goiter

A progressive increase in goiter prevalence with age was observed in both sexes. In males, the average prevalence resulted 28.2%, ranging from 26% at 6-8 yr of age to 31% at 12-14 yr. The average goiter prevalence in females was 42.8%, varying from 29.1% in 6-8-yr-old females to 46% in girls at post-puberty (Fig. 3, upper panel).
When pooled data from the whole region were examined according to goiter grade (Fig. 3 lower panel), a grade 1a goiter was observed in 23.5% of males and 29.6% of females. The difference between the 2 sexes was even more apparent for higher goiter grades. In fact, the prevalence of grade 1b goiter was 3 times more elevated in females than in males (14.1% and 4.2%, respectively). Grade 2 goiters were observed almost exclusively in females after the onset of puberty, with a prevalence of 2.3%. Children with palpable thyroid nodules were classified as grade 2 goiter. The proportion of schoolchildren presenting nodular goiter was 0.47% of the total males and 0.79% of the females. No child with palpable thyroid nodules was observed below 8 years of age.

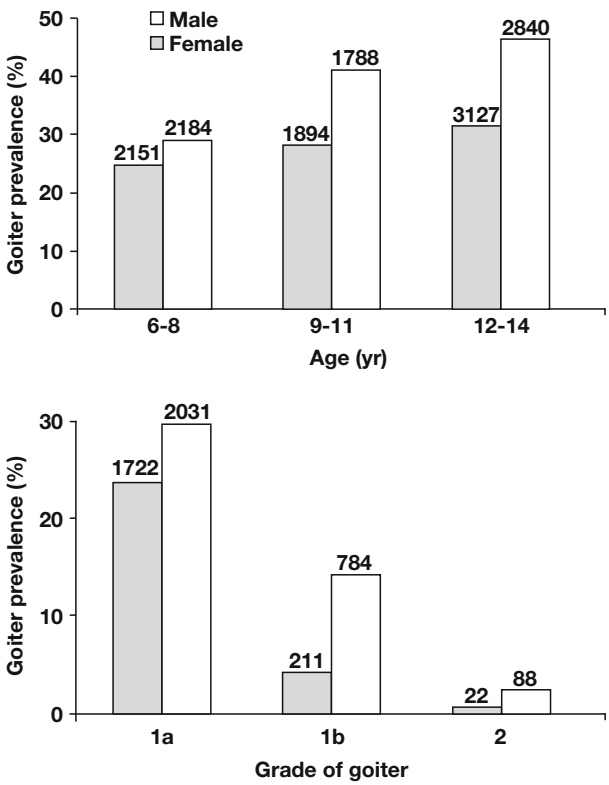

Fig. 3 - *Upper panel: Distribution of goiter prevalence according to age and sex. The number of examined schoolchildren is indicated on top of each bar. Lower panel: Distribution of goiter prevalence according to goiter grade and sex. The number of examined schoolchildren is indicated on top of each bar.*

Assessment of biochemical iodine deficiency parameters

In addition to goiter prevalence, the frequency of neonatal TSH >5 µU/ml and urinary iodine excretion were used to characterize iodine deficiency in the region. The overall results are summarized in Table 1.
The analysis of the neonatal hypothyroidism screening program data showed a 14.8% frequency of TSH levels >5 µU/ml whole blood in newborns from the inland territory and a 14.1% frequency in children born to mothers living at sea level.
In keeping with both goiter prevalence and frequency of neonatal TSH levels >5 µU/ml whole blood, urinary iodine excretion resulted (mean±SD) 53.8±43.4 µg/l (range: <20 to 189 µg/l) in the inland territory. Values somewhat higher (mean±SD: 89.6±59.8 µg/l; range: 26 to 333 µg/l) were obtained at sea level.
Urinary iodine excretion results were also examined according to the area of origin. Median urinary iodine excretion values were calculated in 13 villages or small towns of the inland territory and ranged from 31 to 57 µg/l. In the 2 major towns located at

Table 1 - *Goiter prevalence, neonatal TSH 97% cut off and urinary iodine excretion (expressed as mean±SD) and in the Calabrian territory. The number of subjects examined is indicated in parenthesis.*

Territory	Goiter prevalence (%)	Frequency of neonatal TSH >5 µU/ml whole blood	Urinary iodine excretion (µg/l)
Inland	41.3% (10243)	14.8% (9957)	53.8±43.4* (191)
Sea level	17.4% (3741)	14.1% (11121)	89.6±58.8* (93)

*p=0.0001.

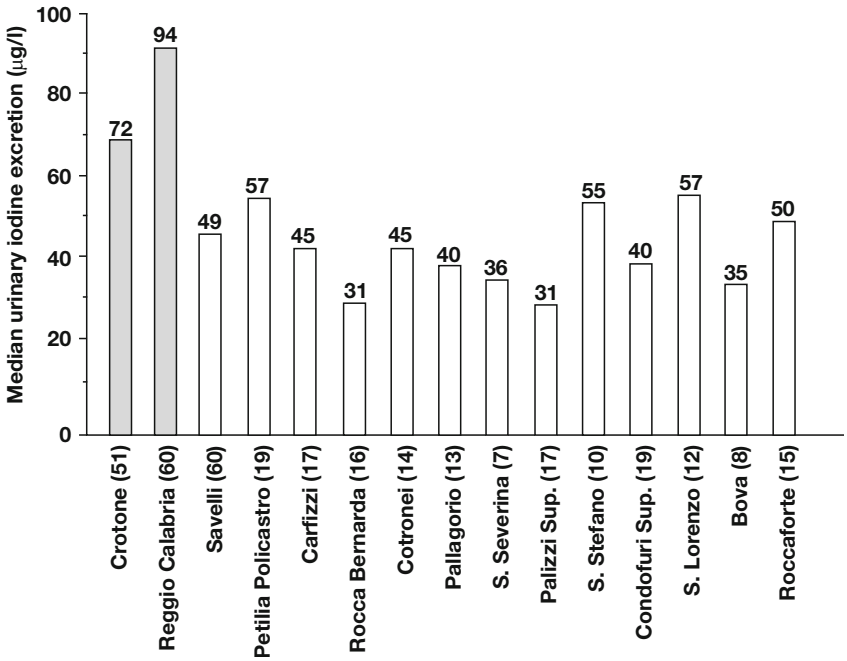

Fig. 4 - *Median urinary iodine excretion in 2 main towns located at the sea level (dark bars) and in 13 villages and small towns of the inland region (white bars). The number of examined samples is indicated in parentheses. Individual prevalences are reported on top of each bar.*

sea level, the median iodine excretion values were 72 µg/l in Crotone main city and 94 µg/l in Reggio Calabria main city (Fig. 4).

DISCUSSION

Classically, goiter prevalence in schoolchildren represents a very sensitive tool to assess iodine deficiency (2).

Both palpation and ultrasonography can be used for the evaluation of thyroid size. Ultrasound examination is, however, more precise and reproducible than palpation (11, 15). The former technique has the disadvantage that thyroid volume measurements should be related to normative values established in iodine repleted children, as a function of age and body surface area for each population group (11, 15).

When the present study was originally designed, ultrasonography was not easy to perform in large scale "in field" studies and normative values for ultrasound thyroid volume measurement in children living in iodine-sufficient areas were not well established. The survey for endemic goiter was therefore performed by palpation, according to the WHO recommendations (12). In terms of precision, it should be emphasized that the inter-observer variation rate in the present survey was 15%, in agreement with those reported by other investigators (15). Assigning the lowest score in case of discrepant grading between the two observers also minimized the risk of overestimation.

Based on the results obtained in Calabria during the present survey, endemic goiter was severely present in the inland territory (40.7% average prevalence), with a rather homogeneous distribution regionwide. Surprisingly, only one out of 3 areas located at sea level resulted free from endemic goiter. In fact, goiter prevalence resulted marginally elevated in Reggio Calabria main town (14.7%), while values of mild endemia were observed in Crotone main town (25.7%).

Analysis of the results according to sex, age and grade of goiter, further strengthened the epidemiological impact of goiter prevalence data. As expected, goiter prevalence was remarkably lower in males than in females. The difference between sexes was particularly evident after the onset of puberty. In fact, a sharp increase in goiter prevalence as well as a relatively elevated rate of high grade goiters were observed in peripubertal girls, probably as a consequence of estrogen effect on thyroid economy (16) and consistent with the universally higher prevalence of goiter observed in adult women.

Goiter prevalence data were mainly confirmed by the results of 2 different biochemical parameters used to assess iodine deficiency: neonatal TSH from the congenital hypothyroidism screening program and urinary iodine excretion.

Neonatal TSH data analysis has been shown to rep-

resent a sensitive method for the surveillance of iodine deficiency (17). The latest WHO-ICCIDD-UNICEF report has established that in the absence of iodine deficiency, less than 3% of newborns have TSH levels above 5 μU/ml whole blood (11). In the present report, a frequency of approximately 15% of TSH levels above 5 μU/ml whole blood was observed. These results are compatible with mild to moderate iodine deficiency (18). It is important to point out that at sea level the frequency of TSH levels >5 μU/ml was higher than one could expect according to goiter prevalence data and resulted almost as elevated as in the inland territory. This apparent discrepancy cannot be readily explained. Probably, in mild iodine deficiency conditions the frequency of neonatal TSH levels >5 μU/ml is not a parameter sensitive enough to reveal small differences of iodine supply. In this respect, we have previously demonstrated that the determination of the 97th percentile of neonatal TSH values represented a valuable tool, allowing to dissect the territory according to the risk of endemic goiter and other IDD (14).

Urinary iodine excretion is presently considered the most useful impact indicator to evaluate the severity of iodine deficiency (11). In Calabria the urinary iodine excretion results confirmed that both the inland territory and the coastal areas of the region are exposed to various degrees of iodine deficiency. In the inland territory, the median iodine excretion values were in perfect agreement with goiter prevalence data, indicating a condition of moderate iodine deficiency. At the sea level, urinary iodine excretion resulted marginally low in Reggio Calabria main town, with values comparable to those reported in other Italian coastal areas (19). However, a situation of mild iodine deficiency was found in Crotone in spite of the localization at sea level. The peculiarity of these results deserves particular consideration. In fact, goiter prevalence in Crotone main city was even higher than one could expect based on urinary iodine excretion values. The strong immigration rate from the inland territory and the water supply provided from sources located on the Sila ridges could contribute in determining such a situation. Theoretically, the presence of goitrogens (*i.e.* thyocyanate) in the foodstuff (1) should also be considered, even though this seems unlikely. The eating habits in the town, in fact, do not include major use of nutrients rich in natural goitrogens. Indeed, other genetic or epigenetic factors might also be involved.

In conclusion, this study indicates that endemic goiter is present region-wide in Calabria and is associated to mild-moderate iodine deficiency. Such a situation has been described in other Southern Italy regions (10, 19).

In terms of public health, our data represent an important baseline for future monitoring of IDD in Calabria and suggest that a generalized iodine prophylaxis program should probably be taken into consideration, even though it could transiently lead to an increased risk for hyperthyroidism (20, 21).

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