THYROID
Volume 7, Number 4, 1997
Mary Ann Liebert, Inc.

Thyrotropin and Thyroglobulin as an Index of Optimal Iodine Intake: Correlation with Iodine Excretion of 39,913 Euthyroid Patients

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ABSTRACT

The recommendations for the dietary allowance of iodine are 150 μg per day for adolescents and adults. Thyrotropin (TSH) and thyroglobulin (Tg) can be used as surveillance indicators for assessing iodine deficiency disorders. We compared the relation between TSH and Tg, free triiodothyronine, and thyroxine serum levels with urinary iodine excretion in 2311 untreated euthyroid patients using our modified cericarsenite method. An adequate iodine intake may be assumed when TSH and Tg values are at the lower end of the normal range. Patients were grouped according to urinary iodine excretion and goiter size. In the group with an iodine excretion between 201 and 300 μg of iodine per gram of creatinine, the lowest TSH values and even low Tg levels could be shown. We conclude that an iodine intake of approximately 250 μg/day is associated with the lowest TSH stimulation to thyrocytes. In the groups separated according to thyroid size, significantly higher Tg levels were found in the patients with uninodular and multinodular goiter as a result of longstanding iodine deficiency, whereas actual urinary iodine excretion did not differ significantly.

Additionally, iodine excretion of 39,913 euthyroid patients between 1984 and 1996 was examined. In Austria iodized salt (10 mg KI/kg) was introduced by law in 1963 and increased to 20 mg KI/kg salt in 1990. An initial increase of iodine excretion until 1993 was followed by a decrease in 1994 and 1995 without further changes in 1996.

These results show that iodine intake has improved since 1984; however, in 1996 iodine excretion in one-third of the investigated patients was under 100 μg per gram of creatinine and more than 80% had less than 200 μg per gram of creatinine.

INTRODUCTION

IT IS A FACT THAT IODINE DEFICIENCY is a main cause for endemic goiter. Like almost every country in the world, Austria was a classic endemic goiter country until 1963; in 1963, iodized salt (10 mg KI/kg) was introduced by law (1); in 1990 iodine salt supplementation was increased to 20 mg KI/kg (2) on account of a still elevated goiter prevalence (3). According to the recommendations of the World Health Organization (WHO), the dietary requirement of iodine is 150 μg/day for adolescents and adults (4).

Thyrotropin (TSH), thyroglobulin (Tg), urinary iodine excretion, and goiter grade are reliable indicators of iodine supplementation of a population (5–8). To monitor the daily iodine intake the urinary iodine excretion can be used (9).

The aim of this study was to determine the optimal amount of iodine intake by correlating the iodine excretion with TSH, Tg, free triiodothyronine (FT_3), free thyroxine (FT_4) serum levels, goiter size, and age in untreated euthyroid patients and to compare these results with the status of iodine supplementation within the last 13 years.

PATIENTS AND METHODS

Part 1

Two thousand nine hundred seventy-two euthyroid patients (TSH between 0.4 and 3.5 mU/L; 1018 males, mean age 60 ± 14.6 years; 1954 females, mean age 61 ± 15.6

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years), who were referred to our department in 1994, were investigated.

Two thousand three hundred eleven of these had neither received thyroid hormone therapy nor antithyroid drugs or lithium therapy. In all patients investigated serum levels of FT_3, FT_4, and TSH were determined; moreover, in 1050 of these Tg was assessed as well.

Patients were divided into five groups according to iodine excretion: A: <50; B: 50 to 100; C: 101 to 200; D: 201 to 300; E: >300 μg iodine per gram creatinine.

TSH, Tg, FT_3, and FT_4 levels were compared between the groups. The correlation between patient's age and TSH was examined.

Two thousand one hundred forty-eight of these patients, who had had no prior thyroid surgery, were further divided into four groups according their goiter size estimated either by ultrasound or by palpation (no goiter, diffuse thyroid enlargement, uninodular goiter, multinodular goiter). TSH, Tg levels, urinary iodine excretion, and age were compared between the groups.

TSH, Tg, FT_3, and FT_4 serum levels were measured with commercially available kits (TSH: TSH IRMA Henning DYNO Test [Berlin, Germany], normal range 0.4 to 3.5 mU/L;. Tg: Thyreoglobulin IRMA Henning Berlin, normal range 2 to 70 ng/mL; FT_3: FT_3 RIAgnost. Behring [Marburg/Lahn, Germany], normal range 3.0 to 6.2 pmol/L; FT_4: FT_4 RIA Clinical Assays [Stillwater, MN], normal range 12 to 28 pmol/l).

Urinary iodine levels were measured by the modified method of Lorenz-Wawschinek (10) based on the reduction of ceric ammonium sulphate in the presence of arsenic acid, as described by Sandell and Kolthoff (11). This method was elaborated in our own laboratory and had been accepted as a suitable epidemiological assessment of iodine deficiency because of its simplicity, speed, low cost, and high accuracy. This novel method had been suggested by WHO as the best screening method available (12,13).

The results are given as means ± standard error of the mean. To compute the significance of FT_3, FT_4, TSH, Tg levels and age between the groups an ANOVA analysis was applied (Fisher least significant difference). The level of significance is taken to be 95%. To study the cross-classification of iodine excretion, Tg, and goiter grade the chi squared test was applied. Correlation between TSH and age was determined with Spearman's rank correlation test.

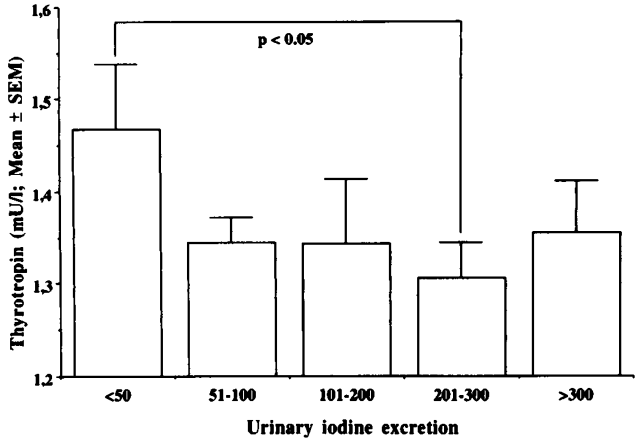

FIG. 1. Means ± SEM of thyrotropin levels of 2308 untreated euthyroid patients sorted according to their iodine excretion. Lowest TSH values could be observed in the group with iodine excretion between 201 and 300 μg iodine per gram creatinine ($p < .05$ compared with group A).

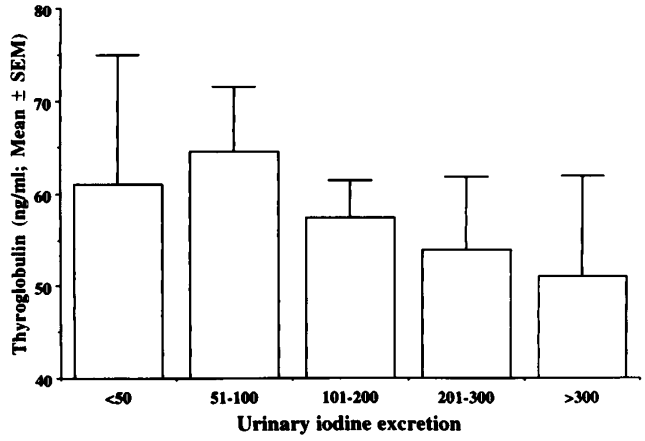

FIG. 2. Means ± SEM of thyroglobulin levels of 1050 untreated euthyroid patients sorted according to their iodine excretion. Decreasing thyroglobulin values could be observed with increasing urinary iodine excretion.

Part 2

Between January 1984 and December 1996 39,913 euthyroid patients (TSH between 0.4 and 3.5 mU/L) from all parts of Styria, a federal state of Austria, were referred to our department. According to their urinary iodine excretion the patients were split into the five groups mentioned above. The results are shown as a percentage of each group per year and as median per year.

In the period between 1984 and 1996 the following TSH kits were used in our laboratory: TSH RIA Henning, TSH IRMA Henning DYNO Test, TSH IRMA Immunotech (Marseille, France), TSH IRMA Cis (Paris, France).

RESULTS

The results of Part 1 are shown in Figs. 1 to 4. The lowest TSH serum levels were found in group D (urinary iodine excretion between 201 and 300 μg of iodine per gram of creatine). This group had a lower TSH ($P < .05$) than group A (<50 μg of iodine per gram of creatine). Although Tg levels showed no significant differences within the five groups investigated, there a marked decrease in thyroglobulin appeared with increasing urinary iodine excretion, ie, the higher the urinary iodine excretion the lower the thyroglobulin values. FT_3 values were significantly higher in patients of the groups with the lowest iodine excretion (group A and B) compared with all other groups. FT_4 values were lowest in group C (101 to 200 μg of iodine per gram of creatine) and differed significantly from groups A and B.

Dividing patients according to goiter size showed that compared with patients with normal sized thyroid glands, significantly lower TSH levels were found in patient groups

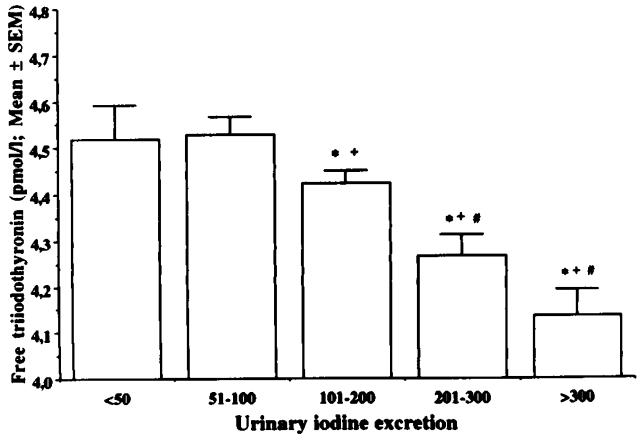

FIG. 3. Free triiodothyronine (FT_3) levels of 2308 untreated euthyroid patients (means ± SEM). In the groups with lower iodine excretion compensatory higher FT_3 levels were observed. *, significant difference compared with group A ($p < .0$); †, significant difference compared with group B ($p < .05$); #, significant difference compared to group C ($p < .05$).

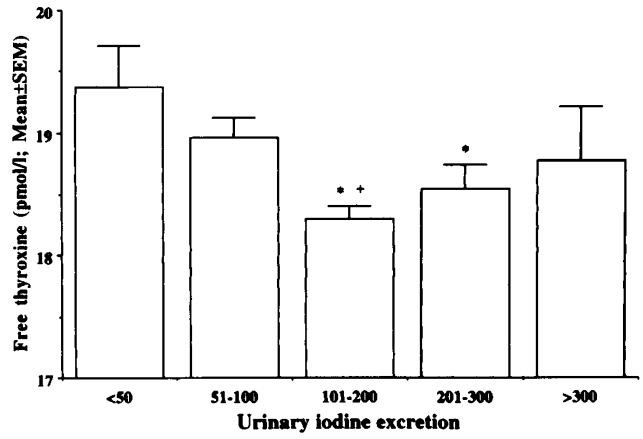

FIG. 4. Free thyroxine (FT_4) levels of 2308 untreated euthyroid patients (means ± SEM). *, significant difference to group A ($p < .05$); †, significant difference to group B ($p < .05$).

with goiter. Tg values in patients with uninodular and multinodular goiter were significantly higher than in patient groups with normal sized thyroid glands or diffuse thyroid enlargement (Table 1).

The TSH values showed a weak but significant negative correlation with age ($r = -0.133$, $P < .0001$).

The analysis of the cross-classification of iodine excretion and goiter size showed no significant correlations (Table 2).

Part 2

The changes of urinary iodine excretion during the period of 1984 to 1996 are shown in Table 3.

A decrease in the percentage of subjects in group A (iodine excretion <50 μg of iodine per gram of creatine) and B (50–100 μg of iodine per gram of creatine) was observed within the period between 1984 and 1993. However, an increase in both groups was found in the following 3 years. Opposite results were seen in the remaining group C (iodine excretion between 101 and 200 μg of iodine per gram of creatine), D (201 to 300 μg of iodine per gram of creatine), and E (>300 μg of iodine per gram of creatine): an initial rise was observed up to 1992 and 1993; subsequently, a slow drop occurred until 1995 and 1996 respectively.

The median of iodine excretion showed an increase until 1993 with a subsequent decrease over the next 2 years and no further change in the last year of our observation period (Fig. 5).

DISCUSSION

As is generally known, iodine deficiency disorders (IDD) affect at least one billion people throughout the world (14). Within recent decades, IDD was generally no longer considered a significant public health problem. However, surveys carried out in the early 1980s and in the 1990s (15) clearly demonstrated the persistence of moderately or even severely affected regions.

We attempted to evaluate optimal iodine intake and investigated changes in the iodine intake of the Styrian population during the last 13 years. Our results from euthyroid patients show that TSH values are lowest at an iodine excretion rate between 200 and 300 μg of iodine per gram of creatine. In this group, Tg levels were low as well. From this we conclude that an optimal daily intake of iodine is approximately 250 μg.

However, the levels we found are considerably higher than those published earlier (16) in 112 probands. By investigating a larger group, ie, 2311 patients, we could establish a higher daily demand.

The significantly higher FT_3 values for low iodine excretion groups (groups A and B) seem to represent a compensatory mechanism for iodine deficiency (7). To some extent, FT_4 values differed significantly, but additional information cannot be derived from this finding.

When grouping the patients according to thyroid size, we found significantly lower TSH values in groups with nodular goiter compared with patients without enlarged thyroids. In iodine deficient areas, autonomous cells can be found in goiters (17). In case of increased iodine intake,

TABLE 1. MEANS ± SEM OF TSH AND TG OF THE PATIENTS GROUPED BY THEIR GOITER SIZE

	No goiter	*Diffuse goiter*	*Uninodular goiter*	*Multinodular goiter*
TSH	1.44 ± 0.019	1.05 ± 0.047	1.25 ± 0.042	1.11 ± 0.031
Tg	22.6 ± 2.78	30.8 ± 8.75	65.5 ± 6.91	96.9 ± 6.53

TSH values were significantly lower and Tg levels significantly higher in patients with thyroid enlargement compared with normal subjects.

TABLE 2. CROSS-CLASSIFICATION OF IODINE EXCRETION AND GOITER GRADE*

Iodine Excretion	*No goiter*	*Diffuse goiter*	*Uninodular goiter*	*Multinodular goiter*
<50	77	8	14	17
51–100	373	35	69	101
101–200	639	53	134	223
201–300	148	13	44	50
>300	102	8	19	21

*No statistically significant differences could be observed.

TABLE 3. IODINE EXCRETION OF 39,913 EUTHYROID PATIENTS FROM ALL PARTS OF STYRIA BETWEEN JANUARY 1984 AND DECEMBER 1996

	Ranges of iodine excretion (μgl/gCr)					
Year	*<50*	*50–100*	*100–200*	*200–300*	*>300*	*Median μg of iodine per gram of creatine*
1984	38.48	44.24	13.88	1.56	1.84	59
1985	25.53	51.52	19.81	1.25	1.89	70
1986	6.68	44.60	42.07	4.36	2.29	98
1987	7.41	42.92	43.33	4.41	1.94	99
1988	6.69	38.63	43.99	6.49	4.17	106
1989	4.17	24.70	50.29	13.34	7.43	133
1990	5.72	31.52	46.79	10.07	5.78	118
1991	3.18	22.15	51.15	15.91	7.54	140
1992	3.36	18.38	53.70	15.78	8.78	143
1993	3.07	18.39	52.08	16.61	9.84	146
1994	4.58	23.39	52.08	13.75	6.20	133
1995	6.37	31.19	45.09	9.94	7.41	118
1996	7.21	28.93	45.68	11.68	6.50	122

According to the iodine excretion, the patients are divided into 5 groups (results are shown as a percentage of each group and as median per year).

these cells can cause latent or even manifest hyperthyroidism. We presume that this group consists of patients who developed multinodular goiter with increasingly autonomous cells during an extended period of iodine deficiency. After improving iodine intake, the first sign of an increase in thyroid hormone production seems to be a decrease of TSH. As also described by other authors, we found a significant negative correlation between age and TSH.

Tg levels, which represent an indicator for chronic iodine deficiency (6), were significantly higher—as a result of extended iodine deficiency—in groups with uninodular and multinodular goiter than in both other groups. Iodine secretion, however, showed no significant differences among the various groups. This indicates steady iodine intake by the investigated population during the 1-year observation period (6).

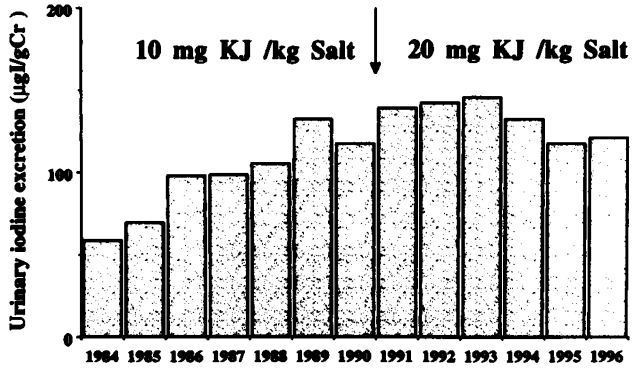

FIG. 5. Medians of iodine excretion during the time period between 1984 and 1996. In 1991, iodine supplementation was increased from 10 mg to 20 mg KJ per kilogram salt.

Taking the results of the first part into consideration, the investigation of 39,913 euthyroid patients over a period of 13 years indicated that a majority suffer at least from some iodine deficiency.

During the whole observation period, median urinary iodine excretion was significantly below desired levels. At best, adequate iodine intake could be established for 16.6% of investigated patients in 1993.

Before 1990, ie, prior to the increase of iodine supplementation to 20 mg KI/kg salt, we observed improvement in iodine supply in our Styrian patients. These results are probably caused by information of the population concerning additional iodine sources. Despite such efforts, approximately one-third of the local population was still below 100 μg of iodine per gram of creatine. Until 1993, a further improvement could be established. Even in that year almost 22% of all patients had iodine excretion below 100 μg of iodine per gram of creatine. However, in the following 2 years (1994 and 1995) iodine excretion declined again.

In 1996 iodine excretion in more than one-third of patients was under 100 μg of iodine per gram of creatine and

more than 80% were under the ideal excretion rate of 200 μg of iodine per gram of creatine.

A possible explanation for this is the propagating of low-salt diets for patients with hypertensive vascular disease or cardiac insufficiency. Furthermore, it should be mentioned that noniodized salt has been available in supermarkets when Austria joined the European Union (EU) over a period of 2 years.

Compared with the results of the first part of the study we have been able to show that iodine prophylaxis in Austria seemed to be initially successful but deteriorated in recent years. It is imperative to monitor the iodine prophylactic program and to promote a higher iodine supplementation by additionally controlling the iodine content of salt in production, marketing, and households (18).

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