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Hypothyroid patients showing shortened responsiveness to oral iodized oil have paradoxically low serum thyroglobulin and low thyroid reserve. Thyroglobulin/thyrotropin ratio as a measure of thyroid damage

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In Central Africa, all of northern Zaire is very severely deficient in iodine. A peculiar feature of this endemia is that iodine deficiency and the ensuing thyroid gland stimulation not only leads to goitre formation but also to progressive thyroid involution and to myxoedematous cretinism. An iodine supplementation trial based on oral administration of small doses of iodine was made in 81 schoolchildren. All of them received a small dose of iodine (0.1 ml containing 48 mg) per os and the thyroid status was followed during 4 months. Blood and urine samples were collected at the start of the study, then 2 weeks, 2 months and 4 months after iodine administration. Before iodine supplementation, the mean urinary iodine level was 0.18 ± 0.02 μmol/l, and 10% of the subjects had a urinary iodine level below 0.08 μmol/l. Fifty-two percent of the subjects had a serum thyrotropin (TSH) level above 10 mU/l. All the subjects responded to the administration of iodine, and all of them recovered a euthyroid status. Most of them were still euthyroid at the end of the study. However, within 4 or even 2 months, some subjects (15% of the total) reverted to hypothyroidism. At the entry of the study these subjects were all hypothyroid and had elevated TSH and paradoxically low serum thyroglobulin (TG) values. In myxoedematous cretins living in the same area, even lower serum TG levels were found. Together with the absence of goitre, a paradoxically low serum TG suggests a low thyroid reserve, and in the present case a reduced amount of functional thyroid tissue. We show that the serum TG/TSH ratio may be used as a predictive index of thyroid reserve and of positive response to iodine administration. These data further suggest that thyroid damage is not confined to myxoedematous cretins, but is widely distributed in the phenotypically normal population. Widely distributed thyroid damage may render iodine prophylaxis based on oral administration unpredictable.

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Oral administration of iodized oil in severely iodine-deficient areas is one of the possible methods of iodine prophylaxis. Most iodine supplementation trials are aimed at determining the safest and most appropriate single dose of oral iodized oil and the duration of its effect (1–8). The conclusions differ depending on the target populations (e.g. pregnant women, newborn babies, children or adults) and on the endemia studied (for a review, see Ref. 9). However, the conclusions tend to be generalized, not taking into account possible important specificities of the various endemias.

Small doses of orally administrated iodized oil (0.1 ml containing 48 mg) have been shown to correct hypothyroidism for about 1 year in Eastern Zaire (Kivu) (5). In the present study conducted to document better the relations that exist between iodine and selenium, the same dose and the same method of administering the iodized oil were used in Western Zaire (Ubangi).

However, one of the features of the Western Zaire endemia is that severe iodine deficiency and the ensuing persistent stimulation of the thyroid gland does not only lead to the formation of goitres, but also induces thyroid damage in some young subjects, causing a progressive involution of the thyroid gland and irreversible hypothyroidism, eventually leading to myxoedematous cretinism.

An unexpected result of the present study is that in Western Zaire, after iodine supplementation and the correction of their hypothyroidism, some phenotypically normal subjects reverted quickly to a hypothyroid status. They were not distributed at random in the population studied, but were all severely hypothyroid at the entry of

the study and had paradoxically low serum thyroglobulin (TG) values. This paper discusses the causes of the shortened response to iodine and the value of the serum TG in identifying these. Together with the absence of goitre, a low serum TG suggests a low thyroid reserve. It is concluded that thyroid damage in Western Zaire is not only confined to myxoedematous cretins, but is also widely distributed in the normal population. The practical consequence of this finding is that the efficacy of the orally administered iodized oil is much reduced in these subjects, and that its effects become unpredictable at a population scale.

Subjects and methods

The present study was conducted in Central Africa, in the core of a very severe iodine-deficient area in Northwestern Zaire. It was made in phenotypically normal children attending school in the small rural village of Bonudana, situated near the city of Karawa, Ubangi, Zaire. The global prevalence of visible goitre in the children of the school was 43% (grade 2 or 3 according to the WHO classification (10)). Cretinism is prevalent in this area, and most of the cretins present the features of myxoedematous cretins, i.e. mental retardation, severe hypothyroidism, dwarfism and myxoedema (11); for a review, see Ref. 9.

The study was aimed initially at documenting better the interactions that exist between iodine and selenium. It consisted in the administration of oral iodized oil, followed 2 weeks later by 4 months of selenium or placebo supplementation. The analysis of the relations that exist between iodine and selenium is presented in a separated paper. The present paper focuses on a by-product of this study, i.e. the shortened effect of iodized oil in some subjects. One hundred subjects entered the study, After the 4 months of supplementation, 81 of them were still attending school and were present at the last visit and therefore entered the present analysis.

Schoolchildren (9–16 years) of both sexes (male/female ratio = 0.25) were included in the study after prior agreement from the parents, teachers and local medical and administrative authorities. The thyroid volume and consistency were estimated by two independent observers. All the subjects received one single dose (0.1 ml containing 48 mg of iodine) of iodized oil per os (Lipiodol Ultrafluide, Guerbet, Aulnay sous bois, France). The iodized oil was administered with accuracy using an automatic syringe (Eppendorff, Germany).

Blood and urine samples were collected before any supplementation, then 2 weeks, 4 weeks, 10 weeks and 18 weeks after iodine administration. Samples were centrifuged within the day and serum and plasma samples were stored at −20°C and transferred to Belgium for measurements.

Serum samples were assessed for the selenium content by spectrofluorimetry, and serum glutathione peroxidase activity was measured with a commercially available kit (Ransel, Randox, Dublin, Ireland) with cumene hydroperoxide as substrate.

Thyrotrophin, T_4, free T_4 (FT_4), T_3, reverse T_3 (rT_3) and thyroxine-binding globulin (TBG) were determined by radioimmunoassay, with commercially available kits (Behring, Germany for TSH and TBG; Johnson & Johnson Amersham, UK for T_4 and T_3; Clinical Assays Gammacoat, Germany for FT_4; Serono diagnostic Italy for rT_3). Thyroglobulin was determined by IRMA (Pasteur, France). Samples were also assessed for anti-TG (Techland, Radim, Liège, Belgium) and anti-microsomial antibodies (Murex Diagnostics, Dartford, UK).

Urine samples were assessed for iodine and thiocyanate (SCN) concentration, iodine with an automated Technicon analyser and thiocyanate by spectrophotometry (12). All measurements were made in duplicate.

The TG results were compared to those of 19 myxoedematous cretins living in the same area. The other thyroid and selenium measurements made in the cretins subjects were made and published previously (13).

Statistical analysis

Statistical analysis were made using the SPSSPC program. Comparison of the means between groups were made by one-way ANOVA. Comparison of the serum TG and TG/TSH ratio was made using a non-parametric test. Means are expressed as means ± SEM in the tables and in the graphs. Serum TSH and urinary iodine are expressed as log means (95% confidence interval).

Results

Iodine supplementation trial in schoolchildren

Overall, the log mean urinary iodine level was low (0.18 ± 0.02 μmol/l) 54% of all the subjects had a urinary iodine concentration below 0.16 μmol/l and 10% below 0.08 μmol/l. Only 10% or 6% of all the subjects had a urinary iodine concentration above 0.40 and 0.78 μmol/l, respectively. Thyrotropin level was above 10 mU/l in 52% or above 50 mU/l in 42% of the subjects. Serum selenium and serum glutathione peroxidase levels were low (696 ± 15 nmol/l and 175 ± 8 IU/l, respectively). Urinary SCN concentration was elevated (397 ± 48 μmol/l). Serum selenium, serum glutathione peroxidase and serum TBG levels were comparable between the three groups A, B and C at all the moments of the study (not shown). Both anti-TG and anti-microsomial antibodies were negative in all the subjects.

All the subjects responded to iodine administration

and all of them recovered to TSH below 10 mU/l and T_4 > 58 nmol/l during the period studied.

However, after 10 or 18 weeks of iodine supplementation, some subjects were hypothyroid again (TSH > 10 mU/l). They all belonged to the group of subjects who were hypothyroid at the beginning of the study (TSH > 10 mU/l), and represented 25% of them (12/48). This represents 15% of the overall population studied. Those subjects who fell again in the hypothyroid range at the end of the study belonged to both the placebo and the selenium-treated groups. In an attempt to characterize these patients, the subjects of the study were divided a posteriori into two groups according to their TSH level at the beginning of the study (Table 1): (group A) the "euthyroid" group, TSH < 10 mU/l; (groups B and C) the "hypothyroid" groups, TSH > 10 mU/l. The hypothyroid group was further divided according to the TSH level at the end of the study: (group B) "euthyroid", TSH < 10 mU/l); (group C) "hypothyroid", TSH > 10 mU/l.

Thyroid status: a posteriori classification (Table 1 and Fig. 1). At the beginning of the study the "euthyroid" subjects (TSH < 10 mU/l, group A) had mean values within the normal range for all the parameters studied except for the mean TG and the mean urinary iodine level, which were elevated and decreased, respectively. Only six subjects had a TG value within the normal range according to our reference values (<60 μg/l).

The hypothyroid subjects (groups B and C) were comparable for all the parameters studied except for the serum TG. The mean serum TG level was lower in the subjects who were hypothyroid again at the end of the study (group C) as compared to the other hypothyroid subjects (group B). However, the mean serum TG level of the subjects who were hypothyroid again at the end of the study (group C) was comparable to that of the "euthyroid" subjects (group A) (Fig. 1B). Overall, serum TG was correlated with the thyroid hormone (especially the T_3/T_4 ratio), with log TSH and inversely with log urinary iodine (Table 2). For TSH levels below 10 mU/l, the TG values were correlated better with the T_3/T_4 ratio and with log urinary iodine than with serum TSH. All sizes of goitres were found in this group, and no significant influence of goitre size on serum TG level was found. For the elevated TSH values (> 10 mU/l), the best correlation was found with log serum TSH, much less with the thyroid hormones and no longer with log urinary iodine. The serum TG level was significantly lower ($p < 0.05$) in patients having lower thyroid sizes (grades 0, 1a) as compared to goitrous patients (grades 1b, 2, 3).

In the group of subjects with elevated serum TSH levels and paradoxically low serum TG levels, no correlations were found.

The TG/TSH ratio was different between the three groups A, B and C. It was elevated in the "euthyroid" subjects (group A), significantly decreased in the hypothyroid subjects (group B) versus group A, and further significantly decreased in the subjects who were hypothyroid again at the end of the study (group C) (Table 1). Figure 2 shows that the TG/TSH ratio seems to increase within the normal range. For levated TSH values, however, the TG/TSH ratio steadily decreases, showing an abrupt drop for very elevated TSH values.

Two weeks after iodine administration, urinary iodine was within the normal range and similar in the three groups. All the thyroid parameters were in the euthyroid range except for the mean serum TG. The mean TSH level, however, remained more elevated in group C. The serum TG values were decreased comparably in the three groups, but the nadir of the TG values was not yet reached after 2 weeks.

At the end of the study, i.e. after 18 weeks, urinary iodine was low again in the three groups. In groups A and B, the urinary iodine level was still elevated as compared to the values before supplementation. The thyroid parameters were within the euthyroid range except for the mean serum TG. In these groups the serum TG level was not raised as compared to 2 weeks after iodine supplementation.

In the subjects who were hypothyroid again at the end of the study (group C, TSH > 10 mU/l), the urinary iodine level was lower than in both groups A and B and was comparable to the values before iodine supplementation. This group C had lower T_4, FT_4, T_3 and urinary iodine levels and an elevated TSH level as compared to the other groups. The serum TG level was not different compared to the other groups A and B but was raised significantly as compared to 2 weeks after iodine supplementation. The TG/TSH ratio was significantly lower in this group as compared to the other groups.

Thyroid palpation. One of the subjects who was hypothyroid again at the end of the study had a large goitre that was amongst the biggest in the overall population studied. It was non-nodular and soft at palpation. All the other subjects of this group had a small thyroid that was non-palpable in three of them. In the other subjects it consisted of a small, firm and regular thyroid; a single nodule with a smooth surface that was freely movable and very hard; or a small, hard and well-delimited multinodular thyroid. The firmness or hardness of the thyroid was a peculiar feature of the subjects with paradoxically low TG values. The other subjects had a soft thyroid at palpation; sometimes a nodule was found, but the consistency of rubber was never as hard as in the subjects who were hypothyroid again at the end of the study. The palpation was never painful.

Myxoedematous cretins

Table 3 compares the thyroid parameters in the two groups of myxoedematous cretins separated into cretins

Table 1. Serum thyroid hormone parameters, urinary iodine and thiocyanate at different times studied in the three groups of subjects: a posteriori classification according to the TSH level at the start and at the end of the study.[a]

	TSH (mU/l)	TG (μG/l)	TG/TSH (μG/mU)	T_4 (nmol/l)	FT_4 (pmol/l)	T_3 (nmol/l)	rT_3 (pmol/l)	Urinary iodine (μmol/l)	Thiocyanate (μmol/l)
(A) Initially euthyroid subjects (TSH < 10 mU/l) (N = 33)									
Day 0, pre-iodine	2.9 (2.1–3.9)	346 ± 46	112 ± 16	79 ± 6	13 ± 1	2.4 ± 0.1	170 ± 17	0.25 (0.2–0.34)	481 ± 309
14 Days post iodine	1.3 (1.0–1.7)	151 ± 52	112 ± 32	104 ± 4	17 ± 0.6	2.1 ± 0.08	244 ± 12	1.11 (0.81–1.53)	533 ± 653
120 Days post iodine	1.5 (1.2–1.9)	124 ± 18	85 ± 16	88 ± 4	15 ± 0.4	2.1 ± 0.02	201 ± 15	0.34 (0.27–0.44)	499 ± 275
(B) Initially hypothyroid subjects (TSH > 10 mU/l); euthyroid end study (TSH < 10 mU/l) (N = 36)									
Day 0, pre-iodine	93 (65–141)#	1109 ± 130#	18 ± 3.3#	23 ± 3#	4 ± 0.4#	2.0 ± 0.09*	80 ± 3#	0.13 (0.12–0.15)#	430 ± 275 NS
14 Days post iodine	3.5 (2.8–4.1)#	262 ± 44 NS	75 ± 12 NS	89 ± 3*	15 ± 0.5*	2.5 ± 0.08#	182 ± 9#	1.04 (0.83–1.34) NS	396 ± 155 NS
120 Days post iodine	3.1 (2.5–3.8)#	175 ± 24 NS	57 ± 8 NS	75 ± 4#	13 ± 0.5*	2.2 ± 0.08 NS	155 ± 9 NS	0.27 (0.22–0.33) NS	567 ± 430 NS
(C) Initially hypothyroid subjects (TSH > 10 mU/l); hypothyroid again end study (TSH > 10 mU/l) (N = 12)									
Day 0, pre-iodine	104 (52–213) NS	457 ± 105#	7 ± 2.8#	35 ± 6 NS	7 ± 1 NS	1.5 ± 0.12*	90 ± 9 NS	0.17 (0.13–0.24) NS	378 ± 138 NS
14 Days post iodine	8.6 (5.6–13.2)#	204 ± 61 NS	32 ± 16#	91 ± 6 NS	16 ± 0.9 NS	2.2 ± 0.14 NS	186 ± 18 NS	1.15 (0.56–2.37) NS	516 ± 224 NS
120 Days post iodine	32 (16–63)#	252 ± 50 NS	12 ± 4#	49 ± 3#	8 ± 0.4#	1.8 ± 0.09*	83 ± 15#	0.17 (0.13–0.22)*	533 ± 240 NS
Ranges (Belgium)	0.2–4.5	< 60		58–142	9–28	1.4–2.9	140–540	> 0.40	

[a] Results are expressed as means ± SEM, and log means (95% confidence interval) for TSH and urinary iodine. Levels of significance are expressed in B vs A, and in C vs B at the same moment of the study: * $p < 0.05$ and # $p < 0.01$.

with or without palpable thyroid tissue. Both groups of cretins had the same clinical features of cretinism and were comparable for height and weight (100 ± 4 vs 105 ± 4 cm; 15.4 ± 1.5 vs 18 ± 1 kg, respectively). Myxoedematous cretins with some remaining thyroid tissue had more elevated T_3 levels and very elevated TG levels as compared to cretins without palpable thyroid. Clearly, we found two patterns of distribution of TG values in cretins: elevated values (range 750–2800 μg/l) in myxoedematous cretins in whom some thyroid tissue was palpable (estimated goitre size = 1a–1b, according to the WHO classification) with or

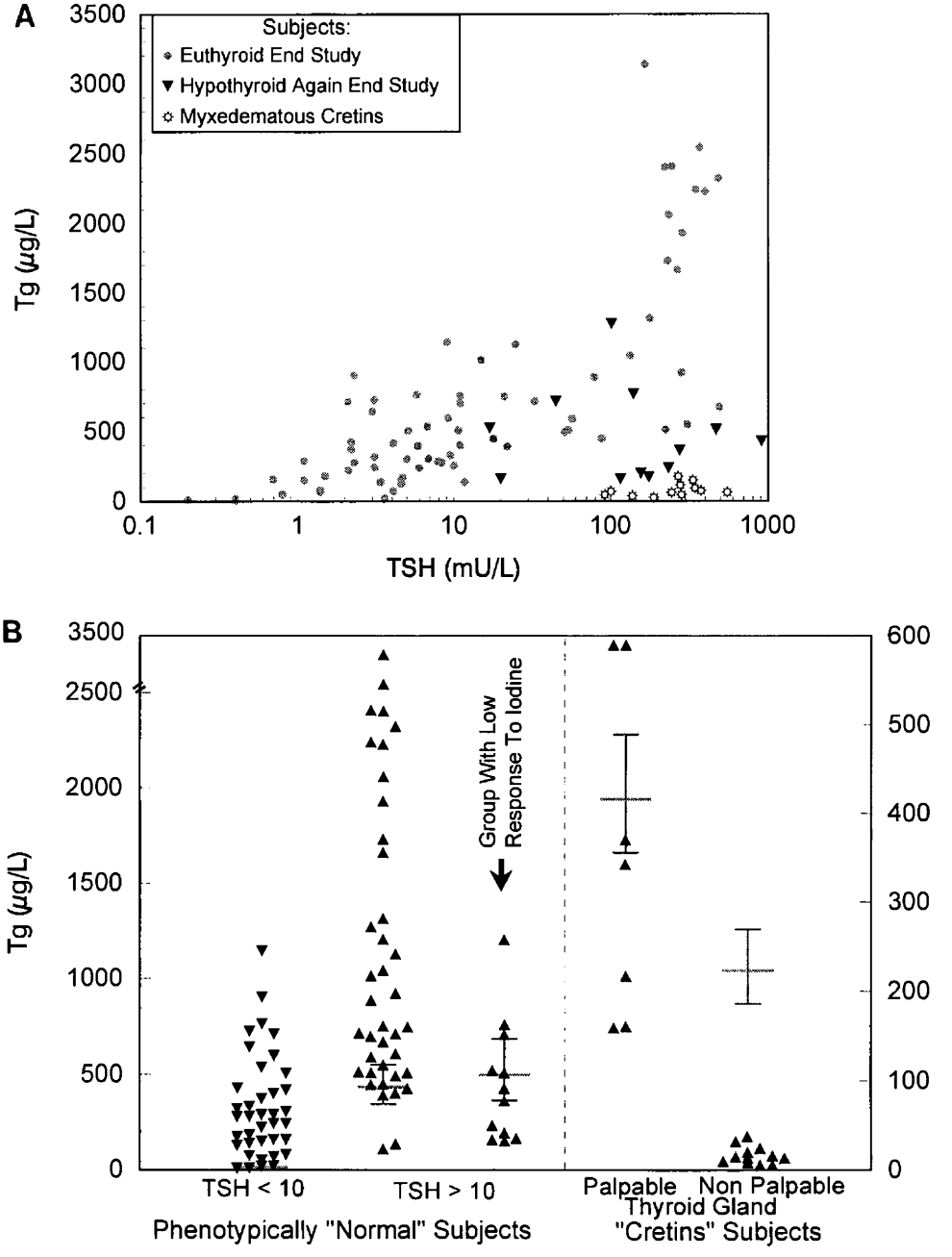

Fig. 1. (A) Serum thyroglobulin (TG) versus serum TSH at the start of the study in the phenotypically normal subjects and in myxoedematous cretins: (●) phenotypically normal subjects, euthyroid at the end of the study; (▼) phenotypically normal subjects, hypothyroid again (TSH < 10 mU/l) at the end of the study; (⊕) myxoedematous cretins without palpable thyroid tissue. (B) Individual serum TG and mean TSH at the start of the study in phenotypically normal subjects and myxoedematous cretins. A posteriori classification according to the TSH level at the start of the study and the thyroid status at the end of the study (as in Table 1). Myxoedematous cretins were separated according to thyroid palpation.

without nodules; and low values (range 26–170 μg/l) in cretins without palpable thyroid tissue (Fig. 1B). Independently of whether the thyroid was palpable, the TG/TSH ratio was low in the myxoedematous cretins as compared to the overall phenotypically normal population (Fig. 2B). The lowest TG/TSH ratio of all the subjects involved in this study was found in the cretins without palpable thyroids.

Discussion

The present results show that in some phenotypically normal subjects the administration of oral iodized oil could not overcome the hypothyroidism for more than 4 or even 2 months. As explanation of the decreased efficacy of the oral iodized oil might be that the subjects failed to receive the correct dose of iodine. In addition,

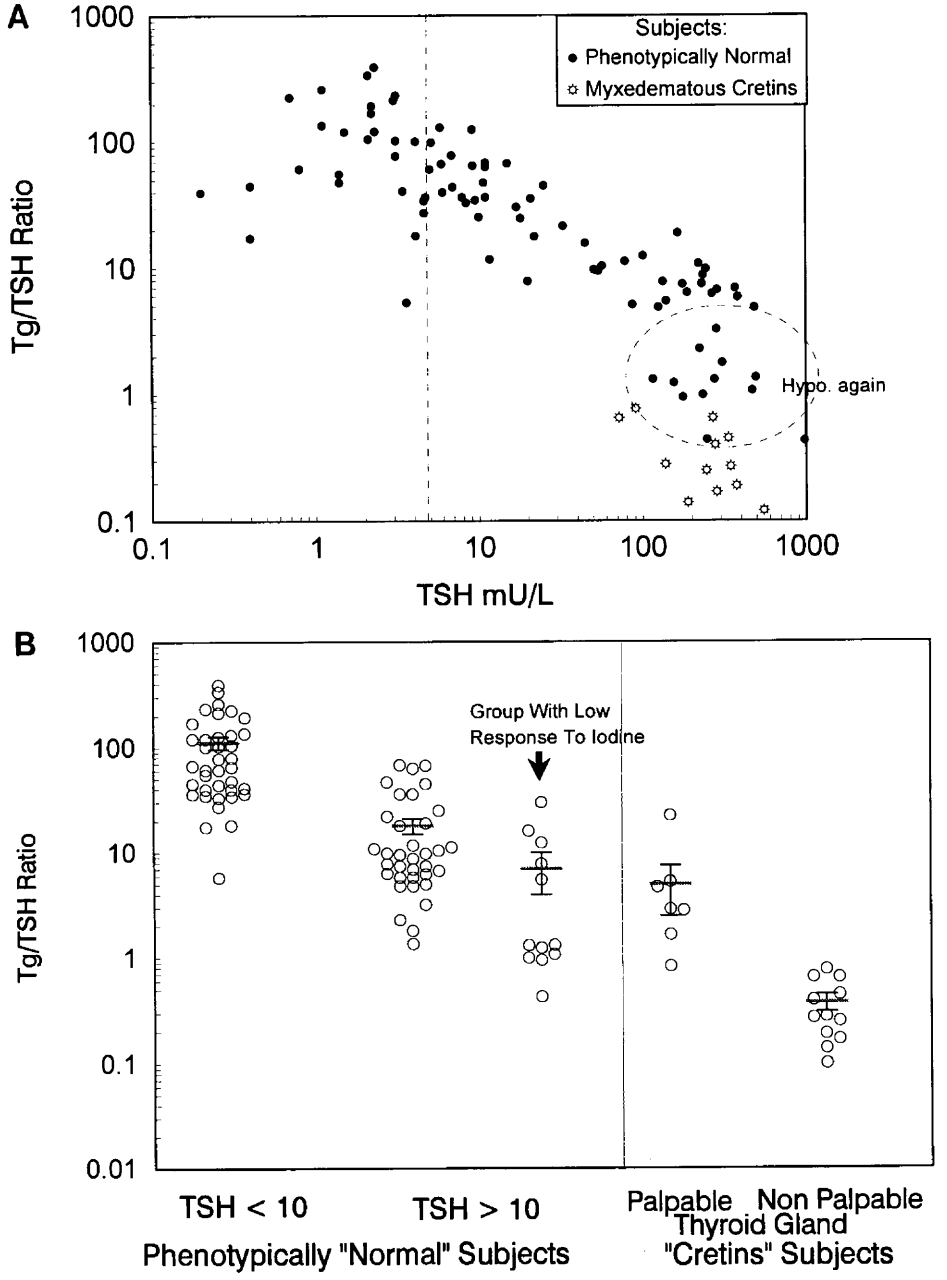

Fig. 2. (A) Serum TG/TSH ratio versus serum TSH at the start of the study in the phenotypically normal subjects and in myxoedematous cretins; (●) phenotypically normal subjects; ⊕ myxoedematous cretins without palpable thyroid tissue. (B) Individual and mean TG/TSH ratio at the start of the study in phenotypically normal subjects and myxoedematous cretins. A priori classification according to the TG/TSH ratio at the start of the study. Myxoedematous cretins were separated according to the thyroid palpation.

Table 2. Correlation coefficients (r) and significance levels (p) of serum thyroglobulin (TG) against serum log TSH, T_4, T_3, T_3/T_4 ratio and log urinary iodine in various groups.[a]

	Log Iodine		Log TSH		T_4		T_3		T_3/T_4	
	r	p	r	p	r	p	r	p	r	p
(A) Euthyroid (N = 34) TSH < 10	−0.558	(0.000)	0.394	(0.023)	−0.647	(0.000)	0.433	(0.012)	0.679	(0.000)
(B) Hypothyroid (N = 30) TSH > 10 (C excluded)	−0.142	(0.456)	0.832	(0.000)	−0.660	(0.000)	−0.346	(0.061)	0.549	(0.002)
(C) TSH > 50, TG < 800 (N = 17)	0.012	(0.962)	−0.058	(0.823)	−0.278	(0.280)	0.306	(0.231)	0.380	(0.132)

[a] Subjects are separated into three groups according to the serum TSH level at the start of the study.

steatorrhoea, tropical sprue or intestine parasitosis may affect the absorption of iodized oil (14). However, the urinary iodine excretion was comparable in all the different groups 2 weeks after the administration of oral iodized oil. Also, the subjects who became rapidly hypothyroid after iodine administration belonged to a distinctive group sharing the same characteristics at the entry of the study. Therefore, the aetiologies of malabsorption or of an error of administration appear unlikely. Actually, although these subjects had no peculiar clinical features that would have allowed them to be identified easily amongst the other schoolchildren, they were all hypothyroid at the beginning of the study. Besides, when compared to the overall group of hypothyroid subjects, the main differences at the clinical examination were the lower goitre size, its firmness or hard consistency at palpation and the paradoxically low serum TG level. In fact, serum TG was the one discriminant parameter among the hypothyroid subjects.

At first, all the subjects corrected their hypothyroidism well after the oral administration of iodized oil. Consistent with previous studies, urinary excretion of iodine returned rapidly to low values (1–8, 15), although the thyroid function remained compensated for a much longer period of time. Consequently, urinary iodine as a variable lacks reliability in the evaluation of the programmes based on oral iodine supplementation. Instead, the follow-up of serum TG and the search for its rise even before a rise in serum TSH occurs has been proposed as an early witness of the efficacy of this method (6, 7). In the course of the follow-up, a new rise in serum TG would point out a lack of iodine at the thyroid level. This would result in a lack of negative control of TSH stimulation by iodine and in a subsequent increased level of stimulation of the thyroid gland (16). Therefore, another administration of iodine would be needed to avoid these subjects returning to hypothyroidism (6, 7).

In fact, serum TG depends on the size of the thyroid and its level of stimulation (17, 18). In goitre endemia, serum TG is indeed reported to be correlated with the thyroid size, with the TSH level and with the serum T_3/T_4 ratio (10, 19–21). The serum T_3/T_4 ratio is in turn inversely related to the concentration of iodine in the thyroid (22), and could be an index of the level of iodination of the TG in the thyroid (22–24). Eventually, the level of iodination itself decreases with increasing goitre size (22, 25, 26). At the start of the present study we found all these correlations. However, in the moderate levels of thyroid stimulation (TSH < 10 mU/l), serum TG was better related to the values reflecting the availability of iodine, through the T_3/T_4 ratio and the urinary iodine level. For elevated levels of thyroid stimulation (TSH > 10 mU/l), serum TG was better correlated with the serum TSH than with the T_3/T_4 ratio and was no longer related to urinary iodine. In this last situation, thyroid size influenced the serum TG level while no correlation could be found for the moderate levels of TSH. Therefore, in the hypothyroid condition, for a given level of serum TSH the serum TG would reflect the thyroid size and would be an index

Table 3. Thyroid hormone parameters in the myxoedematous cretins separated into two groups according to thyroid palpation.[a]

Myxoedematous cretins	TSH (mU/l)	TG (μg/l)	TG/TSH (μg/mU)	T_4 (nmol/l)	T_3 (nmol/l)	TBG (mg/l)	Urinary iodine (μmol/l)
Palpable thyroid (N = 7)	416 (281–616)	1719 ± 556	5.1 ± 2.6	3.6 ± 2.0	1.3 ± 0.2	30 ± 2	0.11 (0.06–0.23)
No palpable thyroid (N = 12)	223 (148–339)	83 ± 14	0.38 ± 0.07	11.9 ± 1.7	0.73 ± 0.1	31 ± 1	0.17 (0.13–0.23)
	NS	p < 0.01	p < 0.01	NS	p < 0.05	NS	NS

[a] Results are expressed as means ± SEM, and log means (95% confidence intervals) for TSH and urinary iodine.

of the functional thyroid tissue. By way of illustration, contrary to the elevated serum TG level found in hypothyroid goitrous subjects, hypothyroid patients with damaged thyroids have reduced or undetectable serum TG. Indeed, serum TG is known to be relatively reduced and even undetectable in patients with hypoplastic or aplastic thyroids, respectively (27–30). Similarly, in the peculiar case of the subjects displaying the features of myxoedematous cretinism, serum TG should also be reduced, although this has not been documented yet. Actually, the thyroid gland of the myxoedematous cretins of Central Africa is known to be palpable in some subjects only (9, 11). In the cretins, the small thyroid has a reduced amount of functional tissue that has been shown to undergo a slow involution process occurring during the first years of life especially (13, 31, 32, 33). Consistent with these previous findings, we report that in spite of the very high TSH values, the myxoedematous cretins without palpable thyroid tissue had paradoxically very reduced serum TG levels. This further supports that under the conditions of elevated thyroid stimulation by TSH, serum TG can be regarded as an index of the thyroid reserve.

By also considering the serum TG level in phenotypically normal subjects, explanations of the shortened efficacy of the iodine administration could be proposed by looking at possible maladaptations of the thyroid gland itself. Indeed, oral iodized oil is absorbed rapidly and most of the absorbed iodine is eliminated rapidly in the urine (1). Therefore, it can be speculated that its efficacy depends mainly on a balance between: the amount of iodide trapped by the thyroid gland during the short peak of serum iodide that follows the oral administration of iodized oil, and further trapped during the recycling of the iodide that originates from the deiodination process; and the rate of release of iodine from the thyroid.

Consequently, at least two maladaptations of the thyroid gland to iodine deficiency could explain a rapid waste of iodine from the thyroid. First, as an optimal adaptation to iodine deficiency, it is suggested that the thyroid gland size should not increase more than twice (35). If it grows more and becomes goitrous, the big colloid goitre would have to hydrolyse a great amount of poorly iodinated TG to reach a sufficient secretion of thyroid hormone. Hence, an increased total iodine secretion from the goitrous thyroids could occur, both organic and inorganic (25). Consequently, in spite of the very elevated trapping capacity of the thyroid, this iodide leakage leads to an increased clearance of iodine through the kidney, which, in turn, has a deleterious effect on the global iodine economy (25, 35). On the other hand, the process of thyroid damage, as shown above in the myxoedematous cretins, leads to a reduced trapping capacity and a fast turnover of iodine (32). Therefore, subjects with a reduced amount of functional thyroid tissue would not be able to trap and store a great amount of iodine, nor would they be able to keep it for long. In short, both oversized goitres and thyroids that are too small could decrease the efficiency of orally administered iodized oil, but the serum TG level would discriminate between the two causes. In the present study, the paradoxically low serum TG level corroborated by the thyroid palpation found in the subjects who became rapidly hypothyroid after iodized oil, strongly suggests thyroid damage and a small thyroid reserve.

The subjects who entered the present iodine supplementation trial were not cretins or cretinoids. However, because nutritional factors are involved in the process of thyroid involution that has touched the cretins (36, 37), it is conceivable that thyroid damage also occurs in the rest of the population. The homogenous distribution of values of serum TG versus serum TSH from the euthyroid subjects to the myxoedematous cretins suggests that, in addition to the myxoedematous cretins, all the degrees of thyroid damage are also present in the rest of the population. Consequently, with respect to thyroid damage, the presence of myxoedematous cretins in an endemia may suggest that they represent only the visible part of the iceberg.

Another question would be to know if the serum TG level could be used further *a priori* to identify the subjects with a low thyroid reserve and a low thyroid efficacy. In fact, the serum TG level was discriminant among the hypothyroid subjects but was not discriminant at the whole population scale. However, serum TG through the TG/TSH ratio was discriminant between the three groups of subjects as presented in Table 1. In the euthyroid range, the TG/TSH ratio ranged above 10 μg/mU. It then decreased with increasing TSH stimulation (Fig. 2). In the hypothyroid range, the subjects with a TG/TSH ratio below 10 μg/mU comprised not only the cretins and the subjects with a paradoxically low serum TG level but also many, but not all, of the hypothyroid subjects with elevated TG levels (Fig. 3). The TG/TSH ratio did not seem to be influenced by the thyroid size itself, but measured the efficacy of the response of the thyroid gland to TSH. However, not all our subjects with a low TG/TSH ratio had a decreased response to iodine administration. Unfortunately, this study did not provide any precise information about iodine metabolism in the different subjects. However, it is conceivable that a low TG/TSH ratio in a goitrous subject identifies a maladapted oversized thyroid (25, 35). Therefore, the TG/TSH ratio might also be used as a predictive index of positive response to iodine administration. Its use may help to define a schedule of iodine administration that would take into account specificities of the various endemias, whatever they are.

Indeed, the probability of evolving to large goitre or to thyroid involution varies widely between endemias and does not merely depend on the severity of the iodine deficiency. It also depends on the number and on the

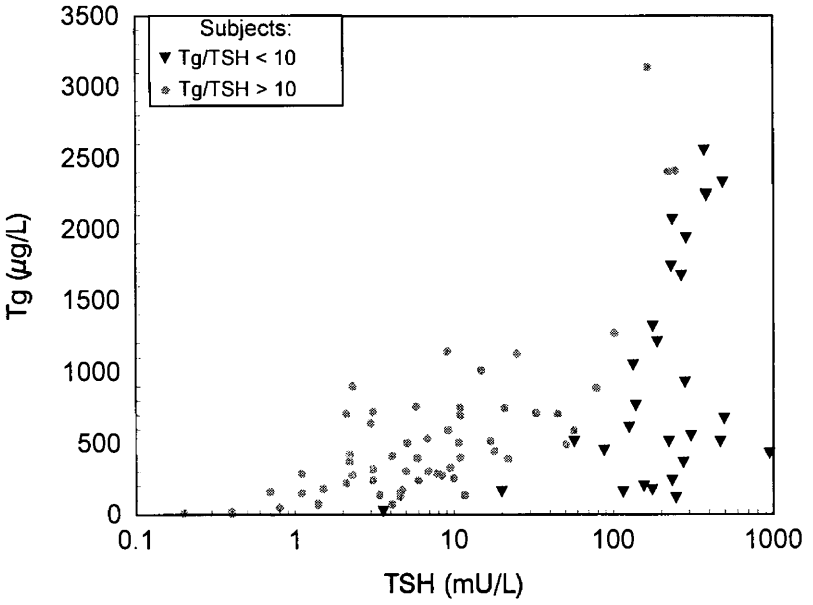

Fig. 3. Serum thyroglobulin (TG) versus serum TSH at the start of the study in the phenotypically normal subjects: (●) phenotypically normal subjects, TG/TSH ratio >10 at the start of the study; (▼) phenotypically normal subjects, TG/TSH ratio <10 at the start of the study.

severity of various local environmental factors (cassava, millet, pollutants, selenium, etc.) (9, 35, 36). All these factors may cause variable responses to iodine between individuals in a given endemia, as well as between endemias. Ignoring them could jepoardize the objectives of a supplementation programme based on oral administration of iodine. Indeed, following an inappropriate schedule, some subjects would swing back and forth between hypothyroidism and euthyroidism between successive iodine administrations. In an area with myxoedematous cretinism, these subjects would be, at first, those hypothyroid subjects having the most damaged thyroids, which could lead to some side effects. Indeed, it is noticeable that at a serum concentration very probably reached after oral iodine administration, iodide itself induces thyroid necrosis if the thyroid is iodine deficient (38). Therefore, although there is no doubt that iodine supplementation and the benefits of the ensuing euthyroidism overwhelm the problem of transient thyroid damage, it is questionable whether an inappropriate schedule would be beneficial or if repeated acute iodine administration to iodine-deficient thyroids would also take part in the process of thyroid damage.

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