0021-972X/91/7301-0213$03.00/0
Journal of Clinical Endocrinology and Metabolism
Copyright © 1991 by The Endocrine Society

Vol. 73, No. 1
Printed in U.S.A.

EFFECT OF SELENIUM SUPPLEMENTATION IN HYPOTHYROID SUBJECTS OF AN IODINE AND SELENIUM DEFICIENT AREA : THE POSSIBLE DANGER OF INDISCRIMINATE SUPPLEMENTATION OF IODINE-DEFICIENT SUBJECTS WITH SELENIUM.

CONTEMPRE B, DUMONT JE, NGO BEBE, THILLY CH, DIPLOCK AT and VANDERPAS J.

Institute of Interdisciplinary Research, School of Medicine, Free University of Brussels, Route de Lennik 808, CP 602, Brussels, Belgium and Division of Biochemistry, United Medical and Dental Schools, University of London, Guy's Hospital, London, United Kingdom.

ABSTRACT : Selenium and seleno dependent glutathione peroxidase (GPX) deficiency has been described in endemias of myxedematous cretinism. In northern Zaire, a selenium supplementation trial has been conducted. Beside correcting the GPX activity, two months of selenium supplementation was shown to modify the serum thyroid hormones parameters in clinically euthyroid subjects and to induce a dramatic fall of the already impaired thyroid function in clinically hypothyroid subjects. These results further support a role of selenium in thyroid hormone metabolism. In an iodine deficient area, this selenium deficiency could lead to opposite clinical consequences : protect the general population and the fetus against iodine deficiency and brain damage; and in turn, favour the degenerative process of the thyroid gland leading to myxoedematous cretinism.

Iodine deficiency is a major public health problem throughout the world, and its most severe manifestation is endemic cretinism. The incidence of the two forms of cretinism (neurological and myxedematous) varies from one endemia to another; in central Africa, myxedematous cretinism is predominant; and typical forms of neurological cretinism are rarely observed (1); in the Andean areas the reverse situation exists. Several hypotheses have been proposed to explain the cause of thyroid failure in myxedematous cretinism. Thiocyanate overload resulting from consumption of poorly detoxified cassava worsens the iodine deficiency (2).However, intense stimulation of the thyroid gland is a feature of all endemia and thyocyanate overload or iodine deficiency are only slightly worse in northern Idjwi, where endemic cretinism is prevalent, than in South Idjwi where it is not.(3).

A more recent hypothesis proposed that a lack of protection against peroxidative damage induced by H2O2 in the thyroid cell could explain the progressive destruction of the gland (4-6). Defective glutathione peroxidase due to selenium deficiency could account for the higher sensitivity to H2O2 of an already overstimulated gland (7,8). A very severe selenium deficiency and a concomitant decrease in selenium dependant glutathione-peroxidase (Se-GPX) activity, have been demonstrated in the eastern Zaire (Idjwi Island, Kivu lake) and the Ubangi (northern Zaire), which are African endemias of myxedematous cretinism (5,6); moreover the Se-GPX activity was twice lower in cretins than in normal subjects. A selenium supplementation trial in this area showed the correction of the SE-GPX activity both in normal and in cretin subjects (6). This supplementation also induced an unexpected change in the serum thyroid hormone parameters, ie. a lowering of serum T4 unaccompanied by increased serum TSH (9). In order to assess directly the effects of selenium on the severity of hypothyroidism in cretins and cretinoids the effect of selenium supplementation was studied in these patients. It is shown that selenium deficiency protects against some consequences of iodine deficiency but that correcting selenium deficiency before improving the iodine status of the patient would be expected to be unwise or even dangerous.

SUBJECTS AND METHODS

In 1988, a selenium supplementation was conducted in a group of 52 schoolchildren and 26 cretins living in the core of the northern Zaire goitre area; it consisted in the administration of one tablet of selenium as selenomethionine 50 ug/day per os or of placebo during two months. Thereafter iodine supplementation (lipiodol 0.5 ml per os once) was administred to all children. To assess thyroid function and selenium status, blood samples were collected at the beginning of the study, after two months selenium supplementation, just before the iodine administration and, after six months, at the end of the study. Urinary iodide concentration was determined at the entry and at the end of the study. The complete design of the study, biochemical methods, and the effects of selenium supplementation on the selenium status of all subjects have been detailed and published previously (6). The effects of selenium supplementation on the thyroid parameters of non cretin subjects have been reported in a former paper and are summarized in this one (9). The aim of this paper is to present the effects of selenium supplementation on the thyroid parameters of cretin subjects. Statisticals parameters are expressed as means ± 1 standard deviation of the mean in the text and in the tables and as means ± 1 standard error of the mean in the figures. For serum TSH, the statistical parameters are expressed as geometric means (Geom - 1 SD, geom + 1 SD). Comparison of the means and all statistical analyses were performed with the statistical package for social sciences (SPSSPC+, Chicago, Illinois).

Submitted January 21, 1991. Supported by FRSM n°3.4535.90 and CCE Research Found n°130/2522. Aknowlegment to Mr R. Matthews, Wassen International, Leatherhead, Surrey, U.K. for providing the selenium and placebo tablets used in this study.

RESULTS

Figure 1 compares the mean concentrations and individual values of the thyroid function parameters in normal schoolchildren and in cretins. In normal schoolchildren, there was a spread of T4, FT4 and TSH values from the normal range to the severe hypothyroid range; in cretins, serum T4, FT4 and TSH were in an hypothyroid range in all cases. Normal serum T3 was preserved in most (92%) of the schoolchildren (48/52); it was decreased in the majority (73%) of cretins (19/26).

Serum TBG was normal or moderately elevated in all schoolchildren (25.8 ± 4.8 mg/l, n = 53) and in all cretins (30.2 ± 4.8 mg/l, n = 21) with a greater mean serum TBG concentration in cretins ($p < 0.01$). Erythrocyte GPX was very low in normal schoolchildren (3.3 ± 2.4 U/gr Hb, n = 46), and it was even lower in cretins (2.0 ± 2.4 U/gr Hb, n= 27, $p<005$). Twenty five percent of the cretins presented undetectable erythrocyte GPX. The mean urinary iodide concentration was very low in both cretins (228 nmol/l (39 - 1180), n = 26) and schoolchildren (276 nmol/l (86 - 944), n = 53). Mean serum selenium was very low in cretins (481 ± 291 nmmol/l n = 24) and lower in schoolchildren (342 ± 177 nmol/l n = 52, $p < 0.05$).

Table 1 compares the mean values and fig 2 shows the evolution of the individual values of the thyroid and selenium parameters of cretins before and after two months selenium supplementation alone. Initially, the mean serum thyroid hormone concentrations (T4,FT4,T3,rT3) were in a very low range while mean serum TSH value were elevated. This thyroid status became worse after two months selenium supplementation : the mean serum T4 fell while the mean serum TSH increased significantly; the other serum thyroid hormone concentrations also decreased after selenium supplementation (FT4, T3, rT3) but these decreases were not statistically significant. Mean serum FT4 decreased at the limit of detection after selenium supplementation. Mean serum T3 was initially very low and

	BEFORE SE (n = 9)	AFTER 2 MONTHS SELENIUM	paired t-test	Normal range (Belgium)
Se (nmol/l)	291 ± 116	1722 ± 544	***	630-2500
GPX (U/gr Hb)	1.4 ± 1.7	10.33 ± 5.306	***	9-20
T4 (nmol/l)	12.8 ± 5.1	2.5 ± 2.5	***	58-160
FT4 (pmol/l)	0.26 ± 0.26	0.13 ± 0.00	NS	10-26
T3 (nmol/l)	0.98 ± 0.72	0.72 ± 0.29	NS	1.32-2.90
rT3 (pmol/l)	3.0 ± 0.00	3.0 ± 0.00	NS	140-540
TSH (mU/l)	262 (218-316)	363 (304-432)	***	0.2-7.0
TBG (mg/l)	30.4 ± 2.7	31.8 ± 2.5	NS	16-32

Table 1 Evolution of the thyroid and selenium parameters before and after two months selenium supplementation in nine cretin subjects. Values are presented as means ± 1 st. dev. TSH is expressed as geometric mean (geom mean - 1 std dev, geom mean + 1 std dev). Significance of the paired t-test : * = $p < 0.05$; ** = $p<0.01$; *** = $p < 0.001$; NS = not significant.

decreased still further of one third of the initial value, after selenium supplementation. Mean serum rT3 was at the limit of detection at the entry of the study and remained at the same level during selenium supplementation. All these results suggest a deterioration of the thyroid function. Considering the results of selenium supplementation, it was decided for ethical reasons to discontinue the trial and not to extend the sample of patients investigated.

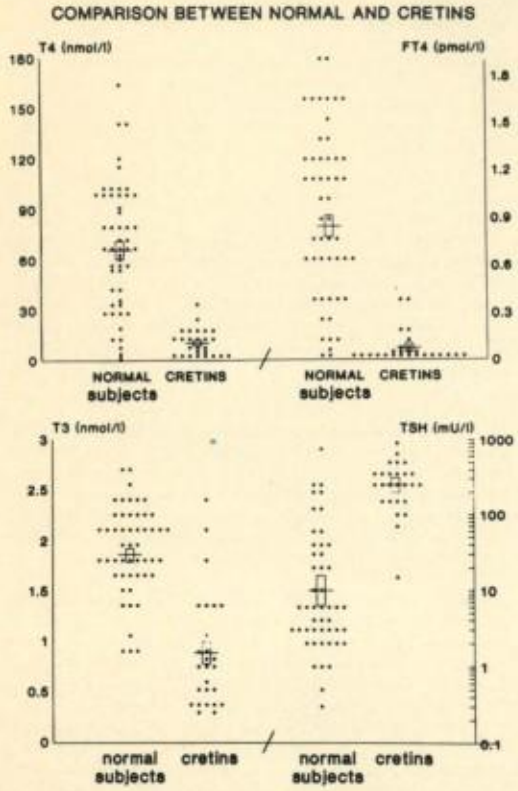

Figure 1: comparison of the means ± 1 standard error and the individual values of the thyroid parameters between the normal subjects and the cretins of the study.

Figure 3 shows the evolution of the thyroid parameters (T4, FT4, T3, TSH) after four months of iodine supplementation which was provided just after the two months of selenium supplementation. In most of the subjects the decline of all the thyroid parameters was reversed. This improvement was very obvious in younger subjects although only two of them recovering normal thyroid function after iodine supplementation.

CASE REPORT : One of the normal schoolchildren received selenium for six months and because of an administrative error made by the family, failed to receive iodine after two months like all the other subjects. His thyroid parameters were initially T4 : 7.7 nmol/l, FT4 : 0.13 pmol/l, T3 : 1.3 nmol/l, TSH : 114 mU/l. And after six months selenium supplementation, T4 : 1.3 nmol/l, FT4 : 0.13 pmol/l, T3 : 0.92 nmol/l, TSH : 163 mU/l.

DISCUSSION

The subjects of the present study were classified as normal or cretins according to the clinical examination. Serum hormonal values were normal or reflected juvenile hypothyroidism in schoolchildren, with a preserved serum T3 value in most cases. They were in the severe hypothyroid range in cretins, even for serum T3 in most cases. Thus, the clinical classification as normals or cretins corresponded to the hormonal profiles. Low T4 with normal T3 is an adaptative process to iodine deficiency in juvenile hypothyroidism, and this mechanism is decompensated in cretins (10-11).

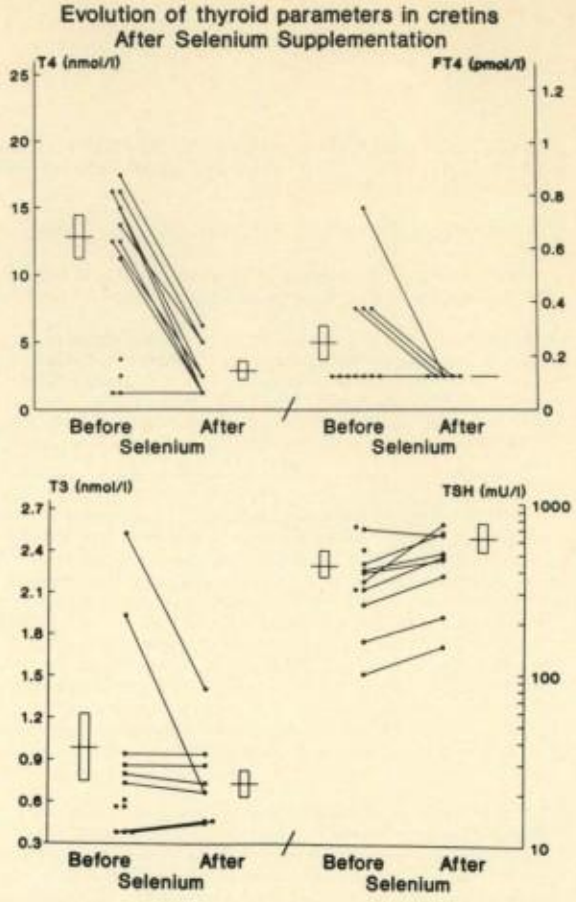

Figure 2: Evolution of the means ± 1 standard error and of the individual values of the main thyroid parameters of cretins subjects of the study before and after two months selenium supplementation.

In a former paper (9), we reported the effects of selenium supplementation on the thyroid function parameters in normal subjects of our study. The main results were that selenium supplementation caused a decrease of serum T4 without a concomitant increase of serum TSH. It was not possible to conclude whether the main effect of selenium supplementation involved the thyroid or extra-thyroid tissues; in the intra-thyroid model, as demonstrated in experimental rats in vivo, selenium supplementation corrects thyroid glutathione peroxidase deficiency and decreases serum T4 presumably by diminishing the availability of hydrogen peroxide substrate for T4 synthesis; furthermore, consonant with the decreased T4, serum TSH is enhanced (12). In the extra-thyroid model, also demonstrated in rats, selenium supplementation increases the conversion rate of T4 to T3 which should induce a decrease in in serum TSH level (13); both mechanisms lead to a decrease of serum T4 in case of selenium supplementation. The combination of both mechanism could explain why in normal subjects serum TSH remained stable after selenium supplementation.

The present results show that selenium supplementation in cretins does not induce a compensated modification of the thyroid parameters by contrast to that observed in normal subjects (9), but rather a dramatic fall of the already impaired thyroid function.

Why did cretins decompensate their thyroid function while normal subjects only modified the thyroid parameters without evident decompensation? Myxoedematous cretins are known to have a small fibrosed thyroid gland with decreased iodide uptake in comparison with normal subjects within the same area; cretins also have an acceleration of all steps of iodine metabolism and hormone secretion in the thyroid gland (14). We can argue that if cretins have a small fibrosed gland, they may

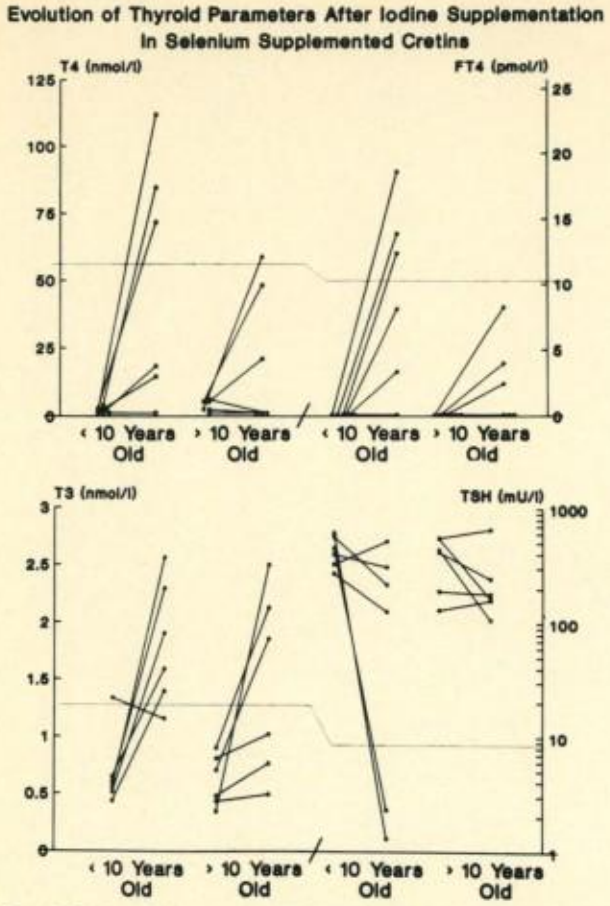

Figure 3: Evolution of the means ± 1 standard error of the mean and of the individual values of the cretins subjects of the study before and four months after iodine supplementation (0.5 ml lipiodol p.os) following two months selenium supplementation alone.

have too little functional thyroid tissue for thyroid hormone synthesis to face an increased requirement of thyroid hormone when the deiodinase activity is enhanced after selenium supplementation (13). An increased requirement for thyroid hormones secretion in cretins would therefore lead to a faster exhaustion of the little iodine reserves stored in the gland and to a faster decompensation of the thyroid status (15). However, most of the cretins partially improve their thyroid function after iodine supplementation, which demonstrates that, in these subjects, the iodine availability before iodine supplementation, and not only the amount of thyroid tissue, was a limiting step in the thyroid hormone synthesis.

Actually, selenium deficiency seems to mitigate the severity of hypothyroidism in iodine-deficient cretins. The iodine intake of these subjects could be too poor to allow a sufficient thyroid hormone synthesis in case of normal selenium status and deiodinase activities.

As summarised in the figure 4, selenium deficiency by improving thyroid hormone synthesis and by decreasing T4 deiodination, maybe also at placenta level in pregnant women, would protect the iodine deficient and thiocyanate overloaded patient. Selenium deficiency would therefore maintain serum T4 level which in the early pregnancy is the main source of fetal brain T3 supply (16-17). It is interresting in this regard that selenium deficiency affects differently the various organs in experimental rats with selective maintenance of brain glutathione peroxidase (12). Thus selenium deficiency would rather protect the fetal brain T4 supply. It could be a protective factor for the early brain development which could in turn explain the scarcity of nervous cretinism in African endemia where both iodine and selenium deficiency prevail. We do not know what would have happened in normal schoolchildren after a prolonged selenium supplementation (more than two months) without concomitant iodine supplementation; but supported by the case report, we suspect that it would

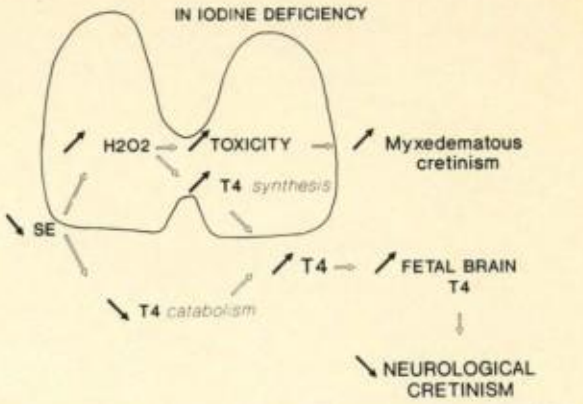

Figure 4: Hypothesis of action of selenium on thyroid function at central and peripheral levels, and the possible related effects on endemic cretinism.

lead to progressive decompensation of thyroid function. In this case, the indiscriminate introduction of selenium supplementation in these regions, in which selenium deficiency could be an important public health problem, could aggravate rather than improve the situation for both children with borderline hypothyroidism and for fetuses of pregnant mothers. Selenium supplementation should therefore only follow iodine supplementation.

Althought not proving an etiological role for selenium in the pathogenesis of endemic cretinism, these results reinforce the data obtained from normal children, and strongly suggest a role for this trace element in human thyroid hormone metabolism. Furthermore, in a severe iodine deficiency area, selenium deficiency seems to mitigate the severity of the iodine deficiency in the global population, and could protect the fetus against brain damage and neurological cretinism, but would favour thyroid destruction and myxoedematous cretinism.

REFERENCES

1. Lagasse R, Luvivilla K, Yunga Y, Gerard M, Hanson A, Bourdoux P, Delange F, Thilly CH. Endemic goitre and cretinism in Ubangi. In: role of cassava in the etiology of endemic goitre and cretinism (Eds A.M. Ermans, N.M. Mbulamoko, F. Delange & R. Ahluwalia). Ottawa: International Development Research Centre, 1980; 136:135-41
2. Ermans AM, Kinthaert M, Van Der Velden M, Bourdoux P. Studies of antithyroid effects of cassava and of thiocyanate in rats. In: Role of cassava in the etiology of endemic goitre and cretinism (Eds A.M Ermans, N.M. Mbulamoko F. Delange & R. Ahluwalia) Ottawa: International Development Research Centre, IDRC. 1980; 136:93.
3. Delange F, Ermans AM. Role of cassava in the etiology of endemic goitre in Idjwi Island. Am J Clin Nutr 1971;24:1354.
4. Vanderpas J B, Rivera-Vanderpas M T, Bourdoux P, Luvivila K, Lagasse R, Pertmulter-Cremer N, Delange F, Lanoie L, Ermans A M, Thilly C H. Reversibility of severe hypothyroidism with supplementary iodine in patients with endemic cretinism. New Engl J Med. 1986; 315:791-795
5. Goyens P, Golstein J, Nsombola B, Vis H, Dumont JE. Selenium deficiency as a possible factor in the pathogenesis of myxedematous endemic cretinism. Acta Endocrinol (Copenh).1987; 114:497-502
6. Vanderpas JB, Contempre B, Duale NL, Goossens W, Ngo Bebe, Thorpe R, Dumont JE, Thilly CH, Diplock AT. Iodine and selenium deficiency associated with cretinism in northern Zaire. Am J Clin Nutr. 1990;52:1087-93.
7. Dumont JE. The action of thyrotropin on thyroid hormone metabolism. Vitamin and Hormones. 1971; 29:287-412.
8. Cohen G, Hochtein P. Glutathione Peroxidase:the primary agent for the elimination of hydrogen peroxide in erythrocytes. Biochemistry 1963;6:1420-1428
9. Contempre B, Vanderpas J, Dumont JE, Duale NL, Ngo Bege, Ntambue K Diplock AT, Thilly CH. Effect of selenium supplementation on thyroid hormone metabolism in an iodine and selenium deficient population. Clin Endocr. (subemitted)
10. Chopra IJ, Hershman JM, Hornabrook W. Serum thyroid hormone and thyrotropin levels in subjects from endemic goiter regions of New Guinea. J clin Endocrinol Metab. 1975; 40:326-333
11. Delange F. Adaptation to Iodine Deficiency during growth. Pediatrics Adolescent Endocrinol (Karger, Basel). 1985; vol 14:295
12. Golstein J, Corvilain B, Lamy F, Paquer D, Dumont JE. Effect of Selenium deficient diet on thyroid function of normal and perchlorate treated rats. Acta Endocrinol (Copenh). 1988; 118:495-502
13. Beckett GJ, MacDougall DA, Nicol F, Arthur JR. Inhibition of type I and type II iodothyronine deiodinase activity in rat liver, kidney and brain is produced by selenium deficiency. Biochem J. 1989;259:887-892
14. Dumont JE, Delange F, Ermans AM. Endemic cretinism in:Endemic Goiter Pan American Health Organisation (ed JB Stanbury) 1969;91-98
15. Delange F. Endemic goitre and thyroid function in Central Africa. Monogr Peadiatr (Karger Basel). 1974; vol2:1-171
16. Calvo R, Obregon MJ, Ruiz de Ona C, Escobar Del Rey F, Morreale De Escobar G. Congenital hypothyroidism, as studied in rats. J Clin Invest. 1990;86:889-899.
17. Larsen PR. Maternal thyroxine and congenital hypothyroidism. N. Engl. J. Med. 1990;321:44-46.