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Effect of selenium supplementation on thyroid hormone metabolism in an iodine and selenium deficient population

B. Contempré*, N. L. Duale†, J. E. Dumont*, B. Ngo‡, A. T. Diplock§ and J. Vanderpas*

**IRIBHN, Free University of Brussels, Campus Erasme, †Hopital de Karawa, Centre Evangélique de l'Ubangi-Mongala, Zaïre, ‡Public Health School, UNIKIN, Kinshasa, Zaïre and §Guy's Hospital, University of London, UK*

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Summary

OBJECTIVE Severe selenium deficiency has been documented in northern Zaïre, already known as one of the most iodine deficient regions in the world and characterized by a predominance of the myxoedematous form of cretinism. This has been attributed to the double deficiency of essential trace elements. A short selenium supplementation programme was conducted in this area to evaluate the effects of a selenium supplementation on thyroid diseases.

DESIGN Placebo or selenium 50 μg as selenomethionine was administered once daily for 2 months. Blood and urine samples were collected before and after supplementation.

PATIENTS Fifty-two healthy schoolchildren from northern Zaire.

MEASUREMENT Selenium status, thyroid function and urinary iodide were determined.

RESULTS After 2 months of selenium supplementation, mean ± SD serum T4 decreased from 73·1 ± 45·4 to 48·3 ± 23·7 nmol/l ($P < 0·001$), serum FT4 from 11·8 ± 6·7 to 8·4 ± 4·1 pmol/l ($P < 0·01$), and serum rT3 from 124 ± 115 to 90 ± 72 pmol/l ($P < 0·05$), without significant change in serum T3 and serum TSH.

CONCLUSION Deiodinase type I which has been shown to be a seleno-enzyme could account for the changes in thyroid hormones in our subjects. Our data show that selenium plays a definite role in thyroid hormone metabolism in humans. Selenium could be an important cofactor in the clinical picture of iodine deficiency in Central Africa and could be involved in the aetiology of both forms of cretinism.

Correspondence: Dr Bernard Contempré, IRIBHN, Bat C, ULB, Campus Erasme, 808, route de Lennik, B-1070 Brussels, Belgium.

Severe selenium deficiency has been described recently in severe iodine deficient areas of Zaïre, Central Africa (Eastern Zaïre, Goyens *et al.*, 1987; Northern Zaïre, Vanderpas *et al.*, 1990). It has been proposed that selenium deficiency could intervene in the physiopathology of endemic myxoedematous cretinism (Goyens *et al.*, 1987), which is especially frequent (85% of all cases) in central Africa, as compared to neurological cretinism (Lagasse *et al.*, 1980).

Selenium deficiency causes a deficiency of glutathione peroxidase, which detoxifies hydrogen peroxide (H_2O_2) in all tissues and may also catalyse the reduction of lipid hydroperoxides (Virion *et al.*, 1984; Cohen & Hochtein, 1963). In the thyroid, H_2O_2 is the oxidant substrate for the iodination of thyroglobulin; its synthesis is stimulated by elevated TSH (Corvilain *et al.*, 1988). The hypothesis has been proposed that an excess of H_2O_2 in a stimulated gland and a lack of H_2O_2-detoxifying enzyme could contribute to the involution of the gland (Goyens *et al.*, 1987), as observed during the first years of life in myxoedematous cretinism (Vanderpas *et al.*, 1986).

It has also been shown in animal experiments that selenium deficiency enhances protein iodination in the thyroid gland (Golstein *et al.*, 1988) and inhibits the type I deiodinase (Beckett *et al.*, 1987, 1989; Arthur *et al.*, 1988, 1989) resulting in both cases in an increased circulating serum T4.

A selenium supplementation trial has been conducted in northern Zaïre, in order to determine the effect of correction of the lowered selenium states that we have described (Vanderpas *et al.*, 1990). The aim of the present paper is to document the changes in serum thyroid hormones in the non-cretinous subjects of our earlier study. The evolution of the same parameters in cretins has been previously published (Contempré *et al.*, 1991a).

Subjects and methods

In 1988, a selenium supplementation trial was conducted in a group of 52 schoolchildren living in the heart of the northern Zaïre endemic goitre area; it consisted in the administration of one tablet of selenium (50 μg selenium as selenomethionine/day orally) or of placebo during 2 months. Thereafter,

Table 1 Upper part, comparison of the selenium status and the thyroid function before and after 2 months selenium supplementation (50 μg selenium as selenomethionine/day orally). Lower part, before and after 2 months placebo supplementation. $*P<0.05$; $**P<0.01$; $***P<0.001$. NS not significant

	Before selenium supplementation ($n=23$)	After selenium supplementation	Paired t-test	Normal range (Belgium)
Selenium status				
Serum selenium (nmol/l)	343 ± 190	944 ± 285	***	650–2500
rbc-GPX(U/gr Hb)	3·0 ± 1·9	5·8 ± 2·2	***	9–20
Thyroid function				
Serum T4 (nmol/l)	73·1 ± 45·4	48·3 ± 23·7	***	58–160
Serum FT4 (pmol/l)	11·8 ± 6·7	8·4 ± 4·1	**	10–26
Serum T3 (nmol/l)	2·05 ± 0·48	2·24 ± 0·45	NS	1·4–3·0
Serum rT3 (pmol/l)	124 ± 115	90 ± 72	*	140–540
Serum TSH (mU/l)	9·6 (7·0–13·1)	7·2 (5·6–9·3)	NS	0·2–10
	Before placebo ($n=22$)	After two months placebo	paired t-test	Normal range (Belgium)
Selenium status				
Serum selenium (nmol/l)	328 ± 157	489 ± 245	*	650–2500
rbc-GPX (U/gr Hb)	3·6 ± 3·0	3·8 ± 3·0	NS	9–20
Thyroid function				
Serum T4 (nmol/l)	54·8 ± 35·1	55·1 ± 38·0	NS	58–160
Serum FT4 (pmol/l)	7·7 ± 5·0	8·0 ± 5·5	NS	10–26
Serum T3 (nmol/l)	1·73 ± 0·57	1·49 ± 0·51	NS	1·4–3·0
Serum rT3 (pmol/1)	95 ± 66	78 ± 55	NS	140–540
Serum TSH (mU/l)	16·7 (1·8–151)	19·0 (1·6–221)	NS	0·2–10

rbc-GPX is red blood cell glutathione peroxidase activity. TSH is given as range and geometric mean. Other values are mean ± SD.

iodine supplementation (Lipiodol 0·5 ml orally) was administered to all children. The complete design of the study, the biochemical methods and the effects of the selenium supplementation on the selenium status of the subjects of the study have been detailed (Vanderpas *et al.*, 1990).

Data are expressed as means ± 1 standard deviation (SD) in the text and in the table, and as means ± 1 standard error of the mean (SEM) in the figures. Serum TSH and urinary iodide concentration are expressed as geometric means (geometric mean ± 1 SD). Comparison of means and determination of Kendall's rank correlation were performed with the Statistical Package for Social Sciences (SPSSPC+, Chicago, Illinois).

Results

Table 1 presents the parameters of selenium status and thyroid function just before and after 2 months selenium or placebo supplementation. At entry to the study, the children in both groups showed severe selenium deficiency documented by a low mean serum selenium and a low mean red blood cell glutathione peroxidase activity (rbc GPX). In the Se supplemented group, except for mean rT3 which was within the hypothyroid range, the mean thyroid hormonal parameters were initially within the low normal range. In the placebo group, all the mean thyroid parameters were within the hypothyroid range. The difference between the selenium supplemented and the placebo group was however not significant at the entry of the study.

The mean urinary iodide was 226 (102–480) nmol/l in the selenium supplemented group and 197 (86–440) nmol/l in the placebo group; this difference was not significant. Thirty-three per cent of the subjects in the selenium supplemented group and 42% of the subjects in the placebo group presented individual urinary iodide values below 160 nmol/l.

Two months after selenium supplementation, mean serum selenium level increased to within the normal range while the very low rbc GPX activity was partially normalized. At the same time, mean serum T4, FT4 and mean rT3 fell to, respectively, 66, 71 and 73% of the initial value. Despite the decrease of T4 and FT4, serum TSH did not change significantly and serum T3 also remained stable.

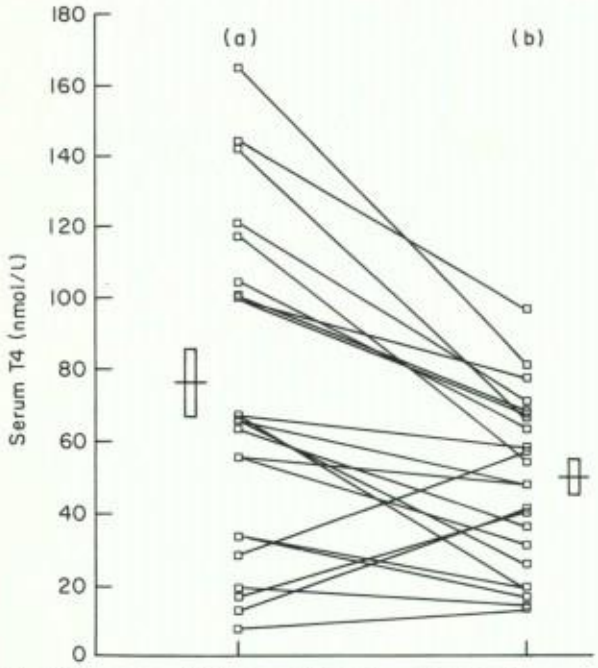

Fig. 1 Comparison of the serum T4 levels a, before and b, 2 months after selenium supplementation (50 μg orally/day); means $\pm$ 1 SEM are also shown.

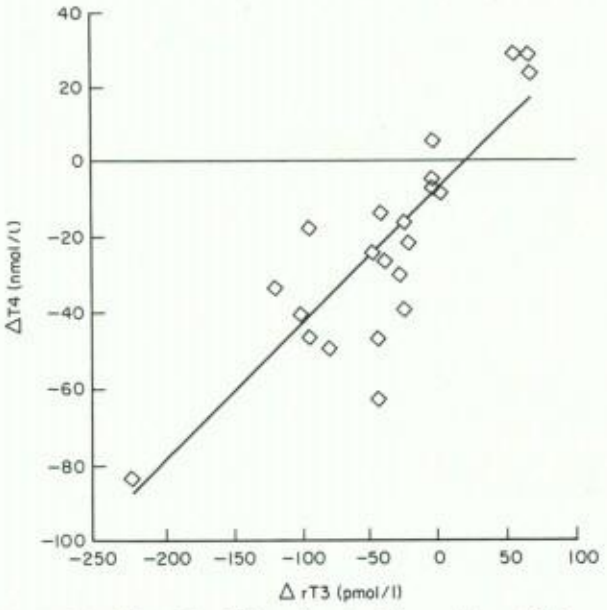

Fig. 2 Correlation (Kendall's rank test) of the variation of T4 before and after 2 months selenium supplementation (ΔT4) with that of rT3 at the same time (ΔrT3). $K=0{\cdot}60$; $P<0{\cdot}001$.

Figure 1 compares the mean and the individual serum T4 values before and after selenium supplementation. For the patients with normal or moderately low serum T4 (but still > 50 nmol/l), all individual values decreased by 10–50% of the initial level, and for five subjects, initially euthyroid according to normal values for Belgians, the values declined below the lower limit of the normal reference range.

For the patients with the lowest serum T4 (< 50 nmol/l), the changes in the individual values were variable from case to case: four of them presented a slight decrease while the three other children presented a moderate increase; all seven cases remained within the hypothyroid range.

Figure 2 shows the relationship of the decrease of serum T4 with that of serum rT3. The variation of rT3 was proportional to that of T4 ($K=0{\cdot}6$; $P<0{\cdot}001$).

In the unsupplemented group, the serum selenium increased slightly without change in red blood cell glutathione peroxidase. The thyroid function parameters remained stable during the whole study period with biological values similar to the initial ones in the treated group (Table 1).

The iodine supplementation which followed the selenium or placebo administration brought hypothyroid parameters to within the normal range but did not overcome the decrease of the high T4 values which occurred after selenium supplementation (data not shown).

Discussion

Severe selenium deficiency endemics have been described in other parts of the world; the clinical entities associated with it are an infantile cardiomyopathy (Keshan disease) and an osteoarthropathy (Kashin–Beck disease); selenium supplementation has proved beneficial in these conditions (Sokoloff, 1985; WHO 1987). However, from these studies, no data indicate an effect of selenium on thyroid function.

In our study, in a group of subjects initially in a severe iodine and selenium deficiency state, serum T4 and rT3 fell significantly after 2 months of selenium supplementation. Paradoxically, this fall was unaccompanied by an increase in serum TSH and serum T3 also remained stable.

A change in TBG amount or affinity could be responsible for such a variation. However, in our subjects, TBG did not change after selenium supplementation.

Several experimental studies document a concomitant variation of thyroid hormones values with selenium status. Golstein *et al.* (1988) showed increased serum T4 and T3 values in selenium deficient rats and proposed that selenium deficiency through an increased availability of H_2O_2, required by the thyroperoxidase for thyroid hormone production, increases iodide organification in the thyroid gland.

On the other hand, selenium deficiency was shown to inhibit type I deiodinase activity (Beckett *et al.*, 1989; Meinhold *et al.*, 1991), also resulting in increased serum T4 values. This deiodinase has recently been shown to be a

selenium containing enzyme in which the selenocysteine residue is essential for the enzyme activity (Behne *et al.*, 1990; Berry *et al.*, 1991a).

Beckett *et al.* (1989) also showed that selenium deficiency exerts an influence on deiodinase type II activity; however, the latest evidence indicates that this deiodinase is not a selenoenzyme and it is suggested that the variation in the enzyme activity is linked to the serum T4 variation itself (Safran *et al.*, 1991; Berry *et al.*, 1991b).

According to the evidence, selenium supplementation to selenium deficient subjects should result in a decrease of serum T4. Nevertheless, in our study, if the effect of selenium is restricted to an alteration in the production of hormones by the thyroid, as suggested by Golstein *et al.* (1988), it is difficult to explain why serum TSH remained stable while serum T4 dropped by 30–50% of its initial level in most of the subjects. Our data are also not in complete agreement with the findings of Beckett *et al.* (1989); in our experiment, serum T3 remained stable while serum rT3 decreased and the reverse was observed by Beckett.

Whatever the exact mechanism by which selenium affects thyroid function, our data show that selenium could play a definite role in thyroid hormone metabolism in humans, and that selenium deficiency as found in Central Africa and possibly in other parts of the world, is severe enough to induce disturbance of thyroid hormone metabolism.

It is interesting to note that inhibition of deiodinase I in selenium deficiency impedes the catabolism of thyroid hormones, diminishes the iodide loss by the kidney, and thus involves a thyroid hormone and iodine economy which, together with a possible increased hormone synthesis in the thyroid gland, could lessen the importance of the iodine deficiency. This has very practical consequences in combined iodine and selenium deficient areas, especially for the pregnant woman and the fetus who could be, in case of selenium deficiency, protected against iodine deficiency and brain damage (Contempré *et al.*, 1991b).

In this case, selenium supplementation alone could involve a more complex change in thyroid metabolism than was foreseen previously and should not be undertaken without concomitant iodine supplementation, at least until further studies are undertaken, since the indiscriminate use of selenium supplements might exacerbate, rather than improve, the situation.

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References

Arthur, J.R., Morrice, P.C. & Beckett, G.J. (1988) Thyroid hormone concentration in selenium deficient and selenium sufficient cattle. *Research in Veterinary Science*, **45,** 122–123.

Beckett, G.J., Beddows, S.E., Morrice, P.C., Nicol, F. & Arthur, J.R. (1987) Inhibition of hepatic deiodination of thyroxine is caused by selenium deficiency in rats. *Biochemical Journal*, **248,** 443–447.

Beckett, G.J., MacDougall, D.A., Nicol, F. & Arthur, J.R. (1989) Inhibition of type I and type II iodothyronine deiodinase activity in rat liver, kidney and brain produced by selenium deficiency. *Biochemical Journal*, **259,** 887–892.

Behne, D., Kyriakopoulos, A., Meinhold, H. & Kohrle, J. (1990) Identification of type I iodothyronine 5′-deiodinase as a selenoenzyme. *Biocohemical and Biophysical Research Communications*, **173,** 1143–1149.

Berry, M., Banu, L. & Larsen, P.R. (1991a) Type I iodothyronine deiodinade is a selenocysteine-containing enzyme. *Nature*, **349,** 438–440.

Berry, M., Kieffer, D. & Larsen, P.R. (1991b) Evidence that cysteine, not selenocysteine, is in the catalytic site of type II iodothyronine deiodinase. *Endocrinology*, **129,** 550–552.

Cohen, G. & Hochtein, P. (1963) Glutathione peroxidase: the primary agent for the elimination of hydrogen peroxide in erythrocytes. *Biochemistry*, **6,** 1420–1428.

Contempré, B., Dumont, J.E., Ngo Bebe, Thilly, C.H., Diplock, A.T. & Vanderpas, J. (1991a) 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. *Journal of Clinical Endocrinology and Metaboloism*, **73,** 213–215.

Contempré, B., Vanderpas, J. & Dumont, J.E. (1991b) Cretinism, thyroid hormones and selenium. *Molecular and Cellular Endocrinology*, **81,** C193–C195.

Corvilain, B., Van Sande, J. & Dumont, J.E. (1988) Inhibition by iodide of iodide binding to protein: The 'Wolff-Chaikoff' effect is caused by inhibition of H_2O_2 generation. *Biochemical and Biophysical Research Communications*, **154,** 1287–1292.

Delange, F. (1985) Adaptation to iodine deficiency during growth. *Pediatrics Adolescent Endocrinology*, Volume 14, pp. 295–326 (Karger, Basel).

Golstein, J., Corvilain, B., Lamy, F., Paquer, D. & Dumont, J.E. (1988) Effect of selenium deficient diet on thyroid function of normal and perchlorate treated rats. *Acta Endocrinologica (Copenh.)*, **118,** 495–502.

Goyens, P., Golstein, J., Nsombola, B., Vis, H. & Dumont, J.E. (1987) Selenium deficiency as a possible factor in the pathogenesis

of myxedematous endemic cretinism. *Acta Endocrinologica (Copenh.)*, **114,** 497–502.

Lagasse, R., Luvivilla, K., Yunga, Y., Gerard, M., Hanson, A., Bourdoux, P., Delange, F. & Thilly, C.H. (1980) 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), pp. 135–141. International Development Research Centre, IDRC 136, Ottawa, Canada.

Meinhold, H., Bohm, G., Haselbach, U., Giencke, R., Gessner, H. & Behne D. (1991) Effects of selenium deficiency on thyroid hormone synthesis and metabolism. Abstract no. 309. 10th International Thyroid Conference. The Hague 3–8 February.

Robinson, M.F. (1988) 1988 McCollum Award Lecture. The New Zealand selenium experience. *American Journal of Clinical Nutrition*, **48,** 521–34.

Safran, M., Farwell, A.P. & Leonard, J.L. (1991) Evidence that Type II 5′-deiodinase is not a selenoprotein. *Journal of Biological Chemistry*, **266,** 13477–13480.

Sokoloff, L. (1985) Endemic forms of osteoarthritis. *Clinics in Rheumatic Diseases*, **11,** 187–202.

Vanderpas, J.B., Contempré, B., Duale, N.L., Goossens W., Ngo Bebe., Thorpe, R., Dumont, J., Thilly, C.H. & Diplock, A.T. (1990) Combined iodine and selenium deficiency in northern Zaïre in relationship to myxedematous cretinism. *American Journal of Clinical Nutrition*, **52,** 1087–93.

Vanderpas, J.B., Rivera-Vanderpas, M.T., Bourdoux, P., Luvivilla, K., Lagasse, R., Perlmutter-Cremer, N., Delange, F., Lanoie, L., Ermans, A.M. & Thilly, C.H. (1986) Reversibility of severe hypothyroidism with supplementary iodine in patients with endemic cretinism. *New England Journal of Medecine*, **315,** 791–795.

Virion, A., Michot, J.L., Deme, D., Kaniewski, J. & Pommier, J. (1984) NADPH-dependent H_2O_2 generation and peroxidase activity in thyroid particular fraction. *Molecular and Cellular Endocrinology*, **36,** 95–105.

WHO (1987) *Selenium*. Environmental Health Criteria 58. WHO, Geneva.