Selenium deficiency mitigates hypothyroxinemia in iodine-deficient subjects

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ABSTRACT Studies were performed to assess the role of combined selenium and iodine deficiency in the etiology of endemic myxedematous cretinism in a population in Zaire. One effect of selenium deficiency may be to lower glutathione peroxidase activity in the thyroid gland, thus allowing hydrogen peroxide produced during thyroid hormone synthesis to be cytotoxic. In selenium-and-iodine-deficient humans, selenium supplementation may aggravate hypothyroidism by stimulating thyroid hormone metabolism by the selenoenzyme type I iodothyronine 5'-deiodinase. Selenium supplementation is thus not indicated without iodine or thyroid hormone supplementation in cases of combined selenium and iodine deficiencies. Am J Clin Nutr Suppl 1993:57:271S-5S.

KEY WORDS Iodine deficiency, selenium deficiency, myxedematous cretinism

Introduction

Twenty-five years ago, radiolabeled selenomethionine was used as a marker of protein synthesis in the thyroid to help in the differential diagnosis of cold nodules (1). The interest in using selenium in thyroidology has declined with time as more specific and more sensitive clinical and technical diagnostic tests became available. However, since the demonstration that selenium intervenes in thyroid hormone metabolism in 1987, interest in selenium has been revived (2). Our purpose is to review the data concerning the role of selenium in the thyroid hormone metabolism of humans, taking advantage of the studies conducted in one of the most severely iodine-and-selenium-deficient populations in the world (3-5).

Northern Zaire has an endemic-goiter belt with 4 million people over a 2000-km² area. This endemic is characterized by a peculiarly elevated frequency of myxedematous cretinism, characterized by a clinical picture similar to that of sporadic cretinism—persistent hypothyroidism since early infancy resulting in dwarfism, infantile morphotype, and mental deficiency. This form of cretinism has to be differentiated from neurological cretinism (6). The classical concept of two types of endemic cretinism, already described in 1908 (7), has recently been somewhat modified by the observation in China of a similar degree of neurological dysfunction in neurological cretins and in myxedematous cretins. Actually, in myxedematous cretins of Western China at least (8), an irreversible loss of thyroid function seems to be superimposed on the neurological impairment (9). Epidemiological and experimental data strongly support the hypothesis that neurological cretinism results from fetomaternal hypothyroidism during the end of the first trimester of pregnancy (10-12); during this period, the fetal gland is not yet working (fetal thyroid hormones are not synthesized before 10 wk of gestation), and the normal development of the central nervous system is critically dependent on an adequate placental transfer of thyroid hormones of maternal origin. According to the studies in China, fetomaternal hypothyroidism during the first trimester of pregnancy should involve neurological cretinism, whereas a persistent hypothyroidism during childhood should involve an involution of the thyroid gland, rendering the child definitely hypothyroid.

Contrasting with the observations in China, central Africa has a high incidence of the "pure" form of myxedematous cretinism: in a very careful examination of 80 cretins in Ubangi, Zaire, 62 (78%) were myxedematous and 18 (22%) were clear examples of "pure" neurological cretinism (ie, without stunted growth or myxedema). Of the 62 cretins found to be myxedematous, 36 had no signs indicative of neurological cretinism; ie, they did not have deaf-mutism, spastic-dystonic motor disorders, or evidence of lower-motor-neuron-cell loss (13).
The epidemiological data suggest, then, that in Central Africa, but likely not in other iodine-deficient areas, that the developing fetus is less frequently exposed to hypothyroidism during a critical period at the end of the first trimester while the factors causing juvenile hypothyroidism and the evolution through myxedematous cretinism are present.

Recent investigations have been oriented toward the role of combined iodine and selenium deficiency in the etiology of endemic myxedematous cretinism in Zaire (14); the initial hypothesis was that iodine deficiency involves an increase in hydrogen peroxide (H₂O₂) synthesis in the thyroid stimulated by thyroid-stimulating hormone (TSH) (15). An excess of H₂O₂ in a thyroid gland depleted of one of the essential antioxidant mechanisms (selenium-glutathione peroxidase) could involve the progressive involution of thyroid function characteristic of myxedematous cretinism (16, 17).

To test this hypothesis, a selenium-supplementation trial was conducted in schoolchildren and in cretins of Ubangi, Zaire, in 1988, when the unique known function of selenium was that of being a cofactor of glutathione peroxidase. The time course of thyroid-function indexes was analyzed after selenium supplementation.

**Experimental studies**

In the first part of this study, the data documenting the progressive loss of thyroid functional capacity with age in cretins are presented (16). In a second part, presented here, the effect of selenium supplementation on the thyroid function of cretins and schoolchildren is presented.

The responsiveness of the thyroid gland to iodine supplementation decreases with age in cretins

Cretins aged 0–42 y were selected on clinical criteria and on biochemical criteria (TSH > 40 mU/L and thyroxin (T₄ < 64 nmol/L) in rural villages of Ubangi, and iodized oil (0.5 mL Lipiodol IM; Guerbet, Aulnay-sous-Bois, France) was administered. **Figure 1** shows the distribution of the individual TSH values before and 5 mo after iodine supplementation. Before treatment, the individual serum TSH values were homogeneously distributed according to age, with a mean serum TSH concentration (geometric mean ± 1 SD) of 220.1 mU/L (range 105.6–458.9 mU/L) (n = 64). Five months after treatment, serum TSH was < 10 mU/mL in the 14 cretins < 4 y old, but in older cretins, an increasing proportion of subjects with age kept elevated serum TSH values; the mean serum TSH concentrations after treatment increased progressively with age: aged 0–4 y, 1.8 mU/L (0.5–6.4 mU/L) (n = 14); aged 5–15 y, 13.0 mU/L (2.4–71.7 mU/L) (n = 36) (P < 0.001 vs 0–4 y); aged 15–42 y, 40.6 mU/L (9.6–170.6 mU/L) (n = 14) (P < 0.001 vs 5–15 y). **Figure 2** shows the distribution of the individual values of serum T₄ before and 5 mo after iodine supplementation. Before treatment, the individual serum T₄ values were homogeneously distributed according to age, with a mean serum T₄ concentration (arithmetic mean ± 1 SD) of 19.3 ± 17.1 nmol/L (n = 65). Five months after treatment, serum T₄ was > 77
nmol/L in the 15 cretins < 4 y old, but in older cretins, an increasing proportion of subjects remained hypothyroxinemic; the mean serum T₄ concentrations after treatment decreased progressively with age: 0–4 y, 162.9 ± 41.2 nmol/L (n = 13); 5–15 y, 119.2 ± 55.8 nmol/L (n = 37) (P < 0.001 vs 0–4 y); 15–42 y, 66.4 ± 36.0 nmol/L (n = 14) (P < 0.001 vs 5–15 y).

**Selenium supplementation in iodine-and-selenium-deficient subjects aggravates hypothyroxinemia**

Schoolchildren and cretins of villages surrounding Karawa were supplemented for 2 mo with a physiological dose of selenium (50 μg Se/d as selenomethionine per os) in the absence of iodine supplementation. Serum selenium was very low at entry into the study and was similar in schoolchildren and in cretins [1 ± 1 SD: schoolchildren, 343 ± 190 nmol/L (n = 23); cretins, 296 ± 116 nmol/L (n = 9)]. Selenium was in the normal range (60–250 nmol/L) in all subjects after 2 mo of selenium supplementation, with a mean serum concentration of 944 ± 285 nmol/L in the 23 schoolchildren and of 1725 ± 547 nmol/L in the 9 cretins. Erythrocyte glutathione peroxidase activity was very low at entry into the study, with lower activity in cretins than in schoolchildren [schoolchildren, 2.97 ± 1.84 U/g Hb (n = 24); cretins, 1.42 ± 1.71 U/g Hb (n = 9) (P < 0.05)]; after 2 mo of selenium supplementation, mean erythrocyte glutathione peroxidase activity increased significantly in both groups without reaching the normal reference range in schoolchildren (9–16 U/g Hb) [schoolchildren, 5.76 ± 2.19 U/g Hb (n = 23) (P < 0.01 vs entry into the study); cretins, 10.33 ± 5.31 U/g Hb (n = 9) (P < 0.001 vs entry in the study)].

Figure 3 shows individual values and the mean concentrations of serum T₄ before and 2 mo after selenium supplementation in schoolchildren and in cretins. In schoolchildren, at entry into the study, the individual values of serum T₄ were distributed in the normal (9 cases, 39%) and in the hypothyroxinemic range (14 cases, 61%); 2 mo after selenium supplementation, all individual values of serum T₄ initially in the normal range (> 77 nmol/L) decreased, and only three cases of the nine initially euthyroxinemic schoolchildren kept a serum T₄ in the normal range; mean serum T₄ concentration in schoolchildren decreased from 72.74 ± 45.21 nmol/L to 47.97 ± 23.39 nmol/L (n = 23) (P < 0.001). In cretins, at entry into the study, all nine individual values of serum T₄ were severely decreased (< 30 nmol/L); 2 mo after selenium supplementation, all eight detectable (≥ 1.3 nmol/L) serum T₄ values decreased further, whereas the unique serum T₄ value initially at the limit of detection remained at that level 2 mo later; mean serum T₄ decreased from 12.8 ± 5.1 nmol/L to 2.5 ± 2.5 nmol/L (n = 9) (P < 0.001).

The other thyroid-function indexes in schoolchildren and in cretins evolved as follows (4, 5). In schoolchildren, the serum free thyroxin (FT₄) index decreased from 11.8 ± 6.7 nmol/L to 8.4 ± 4.1 nmol/L (n = 23) (P < 0.01), and serum reverse triiodothyronine (rT₃) decreased from 12.4 ± 11.5 nmol/L to 9.0 ± 7.2 nmol/L (n = 23) (P < 0.05); mean serum T₃ and mean serum TSH remained stable during the selenium-supplementation trial. In cretins, the serum FT₄ index remained the same or decreased to an undetectable level in all nine cretins; mean serum T₃ concentration decreased from 0.98 ± 0.72 nmol/L to 0.72 ± 0.29 nmol/L (n = 9) (P = NS), and the two cases of
that selenium plays a role in the pathogenesis of myxedematous
cretinism, it is proposed that selenium deficiency involves a lack
glutathione peroxidase activity in the thyroid, and the synthesis
of H₂O₂ in excess due to thyrotropin stimulation induces cyto-
toxicity. Figure 4 shows also that selenium is the cofactor of
iodothyronine 5'-deiodinase, as recently proven (18, 19). This is
likely the mechanism by which serum T₄ and serum reverse T₃
decrease after selenium supplementation in iodine-and-sele-
nium-deficient subjects. Schoolchildren and cretins differ in the
remaining functional capacity of the gland: in schoolchildren after
selenium supplementation, the lowering of serum T₄ is not ac-
 companied by a decrease in serum T₃; it is not evident, then,
that the aggravation of hypothyroxinemia means an aggravation
of hypothyroidism, at least for a few months; a better intracellular
conversion of T₄ to T₃ could even mitigate hypothyroidism, as
the decrease in serum TSH after selenium supplementation in
initially hypothyroxinemic children suggests (20). By contrast,
in cretins, the depleted thyroid gland is unable to adapt to the
increased metabolism of serum T₄, and the aggravation of hy-
pothyroxinemia is clearly associated with an aggravation of hy-
pothyroidism.

Considering the relatively low frequency of neurological cre-
tinism in Northern Zaire, it is proposed that selenium deficiency
mitigates maternal hypothyroxinemia during the critical phase,
when the development of the fetal central nervous system is

cretins who were initially in a normal range of serum T₃ (1.32-
2.90 nmol/L) presented T₄ values outside the lower limit of nor-
mal after selenium supplementation. Serum rT₃, was initially at
the undetectable level in the nine cretins (3.0 pmol/L), and it
remained so 2 mo after selenium supplementation. Mean serum
TSH increased significantly from 262 mU/L (218–316 mU/L.)
to 363 mU/L (304–432 mU/L) (n = 9) (P < 0.001).

Discussion

Persistent hypothyroidism since early life in cretins of northern
Zaire is associated with a progressive loss of thyroid functional
capacity. This degenerative process is mainly postnatal, and it is
not until 5 y of age that the thyroid becomes incapable of
restoring a euthyroid state after iodine supplementation.

The frequency of this "pure" form of myxedematous cretinism
is peculiarly elevated in Central Africa, whereas in other endemic
areas, myxedematous features seem to be superimposed on neu-
rological cretinism, resulting in a clinical picture of "mixed"
cretinism (neurological cretinism combined with myxedematous
features) (8).

This clinical epidemiological observation has not been con-
tradicted by various independent observers (6, 13, 16) who have
worked in the field, and it raises two questions: 1) Why should
myxedematous cretinism be more frequent in Central Africa
than in other endemic areas? 2) Why should myxedematous
cretins be protected from neurological disorders in Central Africa
and not in other endemic areas?

The observation of a severe selenium deficiency combined
with iodine deficiency offers an attractive unifying hypothesis
to answer both questions (Figure 4). Concerning the hypothesis

FIG 3. Mean concentrations and individual values of serum T₄ before
and 2 mo after selenium supplementation (50 µg selenium/d as sele-
no-methionine tablets) in schoolchildren aged 9–15 y (left panel) and in
cretins aged 8–25 y (right panel). The normal reference range of serum
T₄ is indicated by the hatched area in the left panel. Note that the serum
T₄ scale is 10 times lower in the right panel than in the left panel.

FIG 4. Proposed model of interaction of selenium deficiency with
cretinism. Selenium is the cofactor of two enzymes, glutathione peroxidase
(Se-GPX) and type I 5'-deiodinase (Se-DIase I). A lack of Se-GPX in the
thyroid could involve a decrease of the defense mechanisms against hy-
drogen peroxide (H₂O₂) and an increased cytotoxicity, resulting in an
involution of the thyroid functional capacity characteristic of endemic
myxedematous cretinism. On the other hand, a lack of Se-DIase I could
involve a decrease in the conversion of serum T₄ into T₃ mainly in the
liver, and, in pregnant women, could increase the availability of T₄ of
maternal origin for the fetus during the critical period of brain devel-
oping when the pool of thyroid hormones in the fetus is entirely de-
pendent on an adequate supply of maternal thyroid hormones by plac-
cental transfer (before the 10th wk of gestation).
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It is closely dependent on an adequate supply of thyroid hormones of maternal origin. Moreover, selenium deficiency in the fetus could diminish the utilization of T4 in the peripheral tissues, and keep it preferentially for the central nervous system (CNS); in the case that type II 5'-deiodinase, which converts T4 to T3, in the CNS, is not a selenoenzyme, this would favor fetal CNS.

Despite the speculative nature of this proposed model, it is clear that selenium supplementation should not be undertaken without concomitant iodine supplementation in an iodine-and-selenium-deficient population.

References