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Selenium and its relationship with selenoprotein P and glutathione peroxidase in children and adolescents with Hashimoto's thyroiditis and hypothyroidism

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ABSTRACT

The essential trace element selenium (Se) is required for thyroid hormone synthesis and metabolism. Selenoproteins contain selenocysteine and are responsible for biological functions of selenium. Glutathione peroxidase (GPx) is one of the major selenoproteins which protects the thyroid cells from oxidative damage. Selenoprotein P (SePP) is considered as the plasma selenium transporter to tissues. The aim of this study was to evaluate serum Se and SePP levels, and GPx activity in erythrocytes of children and adolescents with treated Hashimoto's thyroiditis, hypothyroidism, and normal subjects.

Blood samples were collected from 32 patients with Hashimoto's thyroiditis, 20 with hypothyroidism, and 25 matched normal subjects. All the patients were under treatment with levothyroxine and at the time of analysis all of the thyroid function tests were normal. GPx enzyme activity was measured by spectrophotometry at 340 nm. Serum selenium levels were measured by high-resolution continuum source graphite furnace atomic absorption. SePP, TPOAb (anti-thyroid peroxidase antibody), and TgAb (anti-thyroglobulin antibody) were determined by ELISA kits. T_4, T_3, T_3 uptake and TSH were also measured.

Neither GPx activity nor SePP levels were significantly different in patients with Hashimoto's thyroiditis or hypothyroidism compared to normal subjects. Although GPx and SePP were both lower in patients with hypothyroidism compared to those with Hashimoto's thyroiditis and normal subjects but the difference was not significant. Serum Se levels also did not differ significantly in patients and normal subjects. We did not find any correlation between GPx or SePP with TPOAb or TgAb but SePP was significantly correlated with Se.

Results show that in patients with Hashimoto's thyroiditis or hypothyroidism who have been under treatment with levothyroxine and have normal thyroid function tests, the GPx, SePP and Se levels are not significantly different.

1. Introduction

Thyroid hormones are key regulators of development, growth, differentiation, and many other physiological processes [1]. Among all human tissues, the thyroid gland contains the largest amounts of selenium (Se), and Se concentrations at this site are relatively stable irrespective of dietary intake and availability in the organism [2]. Se can exist in many different chemical forms in biological materials either as organic Se compounds, such as selenomethionine and dimethylselenide, and inorganic selenites and selenates [3]. Selenoproteins are unique as they contain selenium in their active

Abbreviations: Se, selenium; GPx, glutathione peroxidase; SePP, selenoprotein P; TPOAb, anti-thyroid peroxidase antibody; TgAb, anti-thyroglobulin antibody; T_3, triiodothyronine; T_4, tetraiodothyronine; TSH, thyroid-stimulating hormone.

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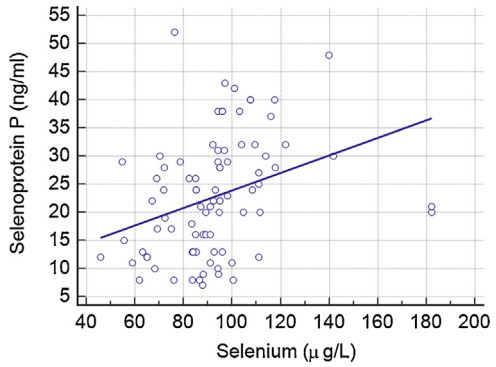

Fig. 1. Correlation between selenoprotein P levels and selenium levels ($r = 0.336$, $P = 0.02$).

site in the form of the 21st amino acid selenocysteine [4]. Selenium can also occur as selenomethionine, which is the main form of Se found in food. Animals cannot synthesize Se-meth or distinguish it from methionine and as a result it is nonspecifically incorporated into proteins as selenomethionine in the place of methionine and is not known to have a physiological function separate from that of methionine [5–8].

The thyroid contains several selenoproteins including iodothyronine 5′-deiodinase, glutathione peroxidase (GPx) which is part of the antioxidant defense mechanism against oxidative stress, thioredoxin reductase type 1, and selenoprotein P (SePP) [9]. Iodothyronine deiodinases are selenoproteins that catalyze the stereospecific and sequential removal of iodine atoms from the pro-hormone T_4, generating active and inactive isomers of both triiodothyronine (T_3) and diiodothyronine (T_2). This biotransformation of thyroid hormones occurs in practically every tissue [10].

The three steps of thyroid hormone biosynthesis are all catalyzed by a single enzyme, thyroid peroxidase (TPO). TPO uses H_2O_2 which is produced in high amounts by thyroid dual oxidases 1 and 2. Thus, in the thyroid, reactive oxygen species (ROS) and free radicals are constantly formed and participate in physiological and pathological processes in the gland, as a consequence of its normal physiological activity [11]. Cells have developed a comprehensive set of antioxidant defense mechanisms to limit the action of ROS. GPx acts as an efficient antioxidant enzyme by eliminating H_2O_2 and thus protects the thyroid cells from oxidative damage [12].

Selenoprotein P (SePP) represents the major selenoprotein in plasma [13]. SePP is an established marker for the nutritional selenium status [14]. Selenium deficiency reduces the plasma concentrations of SePP and selenium [15].

Se is crucial for thyroid gland functioning and thyroid hormone biosynthesis and metabolism [16]. On the other hand, thyroid hormone affects Se metabolism directly or indirectly and affects the serum selenium status and regulates the expression of several selenoproteins [17].

Furthermore, Se has been shown to be important in the regulation of immune function [18], and low selenium levels have been associated with poor immune function [19]. In some conditions, and especially in inflammatory diseases, selenium concentrations decline and selenoprotein biosynthesis is impaired [20]. Se treatment results in reduced inflammatory activity [18]. Severe and persistent selenium deficiency impairs thyroid hormone biosynthesis and also exaggerates destruction of follicular structures and their replacement by fibrotic tissue [18].

The human thyroid gland is the organ most affected by tissue-specific autoimmune diseases [18]. Autoimmune thyroid disease manifests itself in various clinical forms such as classical Hashimoto's thyroiditis. Hashimoto's thyroiditis is the most common form of thyroiditis in childhood and the most frequent cause of pediatric thyroid disease in iodine-replete areas of the world [21,22]. It has been hypothesized that nutritional selenium deficiency may promote the initiation or progression of thyroid autoimmunity [19]. Thus Se levels have been investigated in relation with thyroid disease and some of them have found lower Se levels in patients with autoimmune thyroid disorders. Selenium supplementation have also been examined in various clinical trials but the results have been equivocal [2,9,23–28]. These conflicting findings collectively indicate that the role of selenium and the benefit of its supplementation in the management of thyroid disorders are still unresolved [29].

Most of the studies have focused on the relationship between Se and autoimmune thyroid disorders and Se importance in non-autoimmune hypothyroidism has not been previously investigated. On the other hand, selenium status has not been studied in patients after long-term treatment of hypothyroidism and normalization of thyroid function. Thus, the present study was aimed at exploring the levels of Se and two important selenoproteins GPx and SePP in treated patients with Hashimoto's thyroiditis and non-autoimmune hypothyroidism and their comparison with normal subjects.

2. Subjects and methods

2.1. Subjects

Thirty five patients with Hashimoto's thyroiditis, 22 patients with hypothyroidism, and 30 normal subjects were randomly selected for the study. We tested the hypothesis that selenium is significantly different in patients with Hashimoto's thyroiditis or hypothyroidism compared with normal subjects at the 5% significance level. To detect such a difference, the sample size was calculated on the basis of the results of a previous study of selenium levels in patients with Hashimoto's thyroiditis [30] with 80% power and a confidence interval of 95% using PASS software (version 11). Therefore each study group was calculated to comprise 12 subjects per group. We enhanced the sample size in order to ensure that the required sample size would be achieved in case of missing data and to improve the power of the study.

The presence of Hashimoto's thyroiditis was documented by the increased levels of anti-thyroid peroxidase autoantibodies (TPOAb) and/or anti-thyroglobulin autoantibodies (TgAb). Autoantibodies are found in almost all of the patients with Hashimoto's thyroiditis, however TPOAb are more prevalent than TgAb [31]. Values in excess of 40 IU/mL for TPOAb and 125 IU/mL for TgAb were considered positive for the presence of these autoantibodies. Patients with hypothyroidism had been diagnosed based on elevated thyroid-stimulating hormone (TSH) and low T_4 levels, but normal TPOAb, and TgAb. Both groups of patients were under treatment with levothyroxine and at the time of sample collection they had normal TSH levels. The subjects who were taking any other medications especially those which could affect thyroid function or autoimmunity or Se levels (anti-depressive drugs, anti-psychotic drugs, corticosteroids, immunosuppressants, amiodarone, and preparations containing vitamins or trace elements) were excluded from the study. Case and control subjects were matches for age and body mass index (BMI).

The study was approved by the Ethics Committee of the Tehran University of Medical Sciences and all of the participants provided written informed consent.

2.2. Sample collection

Blood samples were collected after an overnight fast of 12 h. Blood samples for clinical chemistry analysis were clotted and