Original Article

Estimation of Serum Copper, Manganese, Selenium, and Zinc in Hypothyroid Patients

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Summary:

Background: Decreased thyroid hormone synthesis and low levels of circulating thyroid hormones result in clinical and biochemical changes in hypothyroidism. As deficiency of thyroid hormones causes many metabolic processes to slow down, therefore; the maintenance of optimal health requires an adequate supply of carbohydrates, proteins and lipids, and macronutrients, micronutrients, and trace elements.

Objective: Study the effect of the changing in serum level of the trace elements; Zn, Cu, Mn, and Se in hypothyroid patient.

Patients and Method: Thirty seven hypothyroid patients and fifteen normal healthy control persons were participated in this study.

Serum zinc and copper were determined using flame atomic absorption spectrophotometer. While determination of manganese and selenium were done using flameless atomic absorption spectrophotometer.

Results: Serum Zn and Se level were significantly decreased in hypothyroidism, while there was significant increase in serum Mn level as compared with control group. Furthermore there was no significant difference in serum Cu level between groups.

Conclusion: the results of this study suggest that the metabolism of Zn, Mn, and Se is abnormal in hypothyroid patients.

Key words: hypothyroidism, Copper, Manganese, Selenium, and Zinc

Introduction:

The maintenance of optimal health requires an adequate supply of carbohydrates, proteins and lipids, and macronutrients, micronutrients, and trace elements [1].

Many trace elements play an essential role in a number of biological processes through their action as activators or inhibitors of enzymatic reactions, by competing with other elements and proteins for binding sites, by influencing the permeability of cell membranes, or through other mechanisms.

Trace elements are known to influence hormones at levels of action, including hormone secretion and activity and binding to target tissue. Conversely, hormones influence trace metals metabolism at several levels of action, including excretion and transport of trace metals [2]. Hence, trace elements assay in biological fluids can be used as diagnostic or prognostic aid in patients with different hormonal disturbances alongside with other biochemical parameters.

Thyroid hormones play an important role in human body metabolism. After binding with specific nuclear receptor, T3/T4 induces transcription of genetic code via mRNA and regulates proteosynthesis in most tissues. Thyroid hormones regulate rate of metabolic processes and consequently development of organism [3].

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Decreased thyroid hormone synthesis and low levels of circulating thyroid hormones result in biochemical and/or clinical hypothyroidism. This condition occurs more frequently in women; the over all incidences are about 3% of the general population [4, 5].

Hypothyroidism can be congenital or acquired. The acquired from may follow thyroid gland or pituitary gland failure [6]. Hypothyroidism, like hyperthyroidism, probably is initiated by autoimmunity against the thyroid gland in addition to different other causes [7]. The thyroid glands of most of these patients first have autoimmune "Thyroiditis", which means thyroid inflammation. This causes progressive deterioration and finally fibrosis of the gland, with resultant diminished or absent secretion of thyroid hormone. Several other types of hypothyroidism also occur, often associated with development of enlarged thyroid glands called thyroid goiter [8].

Deficiency of thyroid hormones causes many metabolic processes to slow down. Symptoms of hypothyroidism include enlargement of thyroid gland-or goiter, impairment of cognition slowing of mental and physical performance, increased risk of coronary heart diseases many and different other symptoms [9].

In this work, the serum content of the trace elements; Zn, Cu, Mn, and Se in hypothyroidism patients was determined and compared to that of normal subjects.

Materials and Methods:

Patients:

Seventy-three hypothyroid patients, their age range between (19-64) years, (41)females and (32) males participated in this study. The patients were diagnosed depending on the results of: clinical examinations, serum hormones (T3, T4) and TSH, computed tomography (CT scan), Pathological examination, and fine needle aspiration (If needed).

Normal Controls:

Fifty normal healthy persons aged (19-55) years (29 females and 21 males) were used as control.

Samples Collection and Preparation:

About Five milliliters of venous blood from fasting subjects were drawn by utilizing disposable plastic syringes in the morning and transferred into sterile test tube. The blood was allowed to clot and centrifuged at 4000g for10 minutes. Sera were separates and stored at -20ºC until analysis.

Analysis of Trace Elements:

Determination of Zinc and Copper:

Serum zinc and copper was determined using flame atomic absorption spectrophotometer (AA-646) (Shimadzu, Japan). Samples were diluted 1:10 with 6% n-butanol solution as diluents. This method achieved 30% increase in sensitivity compared to the use of deionized water only [10]. This effect is due to decrease viscosity and difference in droplet formation and this technique is widely used [11]. Level of sera zinc and copper were calculated after application of absorbencies on suitable calibration curve for each element made from standard solutions.

Determination of Manganese & Selenium:

Serum samples were diluted with equal volume of deionized water for estimation of serum Manganese and diluted two fold with deionized water to estimate serum selenium. Flameless Atomic Absorption Spectrophotometer (Perkin-Elmer Model 503) was used to estimate the level of these elements in the diluted sera. Level of sera Manganese & Selenium were calculated after application of absorbencies on suitable calibration curve for each element from standard solutions.

Results

Table (1) showed the results of serum trace elements expressed as (mean± standard deviation). Serum zinc and selenium level of hypothyroidism patients are significantly lower ($p<0.05$) than the level in normal subjects as shown in Table (2). A significant increase in serum manganese level was demonstrated in patients as compared with that of the normal subjects while there is no significant difference between the groups ($p>0.05$) in serum copper as shown in Table (1).

Table (1): The serum concentration of Trace Elements in Hypothyroidism patients and normal patients expressed as (mean ± standard deviation).

Trace Elements	Normal serum µmol/L	Hypothyroidism µmol/L
Zinc	**9.08±2.48**	**8.09±2.31**
Copper	**21.73±6.44**	**19.55±7.42**
Manganese	**0.70±0.37**	**0.94±0.17**
Selenium	**1.35±0.44**	**1.17±0.54**

Table (2): Probability values and significance of difference for the comparison between hypothyroidism patients and normal control groups in the serum concentration of the studied trace elements.

Trace Elements	P-value	Significance
Zinc	**0.020**	**Significant**
Copper	**0.067**	**Non-Significant**
Manganese	**0.009**	**Significance**
Selenium	**0.027**	**Significant**

Discussion:

The significant decrease in the level of Zn hypothyroidism patients in comparison to that of normal subjects are observed in other different researches [12, 13]. One possible explanation for these findings, that gastrointestinal absorption of zinc is severely impaired in hypothyroidism subjects. An alternative explanation would be a change in zinc distribution; the low zinc level may reflect sequestration of zinc by the liver or other tissues [12]. Other explanation is due to the significant influence of TSH in the variation of the concentration of iodine, selenium and zinc in normal and altered human thyroid tissues [14].

In one research, the serum zinc levels in hyperthyroid patients were clearly higher than in the hypothyroid patients group [15].

Zinc has important roles in thyroid metabolism [16, 17] and a fundamental role in protein synthesis [17, 18]. It is involved in T3 binding to its nuclear receptor, and participates in the formation and mechanism of action of TRH [19]. Olivieri *et al* [20] reported in hypothyroid patients, thyroid hormones did not correlate with indices of zinc status; although, in rats and humans [13, 21], zinc deficiency has decreased iodothyronine levels and also they found a strong positive association between zinc and FT3 levels [20]. Hence, the correlation between hypothyroidism and serum zinc is not a simple correlation and needs more specific studies.

The decrease in serum selenium levels in hypothyroidism patients is in agreement with the studies of other researchers indicating the important role selenium in controlling the thyroid gland functions [22, 23].

There was statistically significant correlations among indexes of selenium status and indexes of thyroid hormone metabolism and function. Especially dangerous are concomitant deficiencies of both key elements for thyroid hormone metabolism; I and Se from the point of thyroid hormone regulative functions [3].

In other studies used animals, selenium deficiency in rats inhibited the production of (T3) from (T4). It is concluded that, since both T3 production and catabolism are inhibited by selenium deficiency, there is little change in hepatic T3 stores [24]. Selenium deficiency in

rats is characterized by elevated serum T4 and decreased serum T3 concentrations, and low liver iodothyronine 5'-deiodinase I and brain iodothyronine 5'-deiodinase II ctivities [25].

The iodothyronine deiodinases, which are responsible for the conversion of thyroxine (T4) to its active form, triiodothyronine (T3), are selenoenzymes [26, 27, 28]. Selenium deficiency may cause reduced growth rates owing to a feed back response, which lowers triiodothyronine mediated synthesis of growth hormone in the pituitary [29]. However, another data reported that in hypothyroid patients, a poor Se status was associated with a diminished 5́-deiodinase, leading to increase T4 levels and decreased T3/T4 ratios [3, 30, 31].

Selenium supplementation caused an increase in plasma selenium values (32, 33) but did not affect the activity of the selenoenzyme glutathione peroxidase used as a marker of selenium status and caused a significant decrease in thyroglobulin values [33]. Furthermore, serum T3 increase as well as a highly significant decrease in the serum T4/T3-ratio, which pointed to improved peripheral T4 intoT3 conversion during sodium selenite therapy medication. [28].

In conclusion, when selenium is depleted, there is less Se to form the deiodinase enzymes which convert T4 to T3, resulting in low T3 and hypothyroidism. In addition, there is less selenium to form glutathione peroxidase, one of the body's prime antioxidants. This results in greater levels of reactive oxygen species and hydrogen peroxide, which lead to increase the damage to the thyroid gland.

There is no significant change in serum copper in patients with hypothyroidism as compared to that of normal subjects. There is no precise evidence, in literature, corresponding the correlation between serum copper and hypothyroidism. More investigations are required using larger sample size and severe hypothyroidism to be sure about lack of correlation between the disease and different copper indexes.

A significant increase in manganese levels of hypothyroidism patients was seen in comparison to that of normal subjects (Table (1 and 2)). The direct cause for the increase in serum Mn is not understood and there is no direct correlation between serum manganese and hypothyroidism. Only one research reported an indirect correlation between serum manganese and workers exposed to manganese. Misiewicz, *et al* [34], reported a significantly lower blood serum concentrations of T3 and T4 accompanied by a significantly higher concentration of thyrotropin (TSH) in workers exposed to the environmental presence of manganese, iron chromates and other agents as compared to the control group (differing with respect to the environmental exposure to manganese only). Hence it may be not due to the exposure to manganese only. More studies are needed to explain the real cause about the increase in serum manganese in hypothyroidism. In this work it is the first report about the increase in serum manganese in hypothyroidism patients.

References:

1. *Solomons N. (1993)" Trace Elements". In 'Clinical Nutrition: Parenteral Nutrition' 2nd edition. Philadelphia, pp 150-183.*
2. *Henkin, RI. "Trace Elements in Endocrinology" Medical Clinics of North America (1976); 60: 779.*
3. *Kvicala,-J; Zamrazil,-V. Effect of iodine and selenium upon thyroid function. Cent-Eur-J-Public-Health. 2003 Jun; 11(2): 107-13*
4. *Ingbar SH, Woeber KA: (1974) "The Thyroid Gland". In Williams RH, editor: 'Text book of endocrinology', 5th edition, Philadelphia, WB Saunders.*
5. *Standbury JB., Kroc RL., (2000)"Human Development and the Thyroid Gland" : Relation to Endemic Cretinism, Plenum Press, New York, p 19.*
6. *Vanderpump-MP; Tunbridge-WM; French-JM; Appleton-D; Bates-D; Clark-F; et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin-Endocrinol-Oxf. 1995 Jul; 43(1): 55-68*
7. *Wartofsky L., The scope and impact of thyroid disease. Clin-Chem. 1996 Jan; 42(1): 121-4*
8. *Meng-W. [Diagnosis and therapy of hypothyroidism in adulthood] Z-Arztl-Fortbild-Jena.(1996) Feb; 90(1): 43-49. (English abstract).*
9. *Surks M I, Ocampo E., subclinical thyroid diseases. Am. J. Med. (1996); 100; 217-223.*
10. *Meret S., Henkin K.I. (1971): Clin.Chem.17:369. Cited by: Gowenlock H.A., McMurray R.J., McLauchlan M.D. (1988): Varly's Practical Clinical*

Biochemistry. 6th Ed. Heinemann Medical Books. London.

11. *Taylor A., Bryant T.N. (1981) Clin.Chim.Acta.110:83.Cited by Gowenlock H.A., McMurray R.J.,Mclauchlan M.D.(1988): Varly's Practical Clinical Biochemistry. 6th Ed.Heinemann Medical Books. London.*
12. *Yoshida, K., Kiso, Y., Watanabe, T., Kaise, K., Kaise, N., Itagaki, M. "Erythrocyte zinc in hyperthyroidism: reflection of integrated thyroid hormone levels over the previous few months." Metabolism (1990); 39(2): 182-186.*
13. *McConnell, RJ., Menendez, CE., Smith, FR., Henkin, RI. "Defects of taste and smell in patients with hypothyroidism." Am J Med (1975); 59: 354-364.*
14. *Bellisola,-G; Bratter,-P; Cinque,-G; Francia,-G; Galassini,-S; Gawlik,-D; et al. The TSH-dependent variation of the essential elements iodine, selenium and zinc within human thyroid tissues. J-Trace-Elem-Med-Biol. 1998 Nov; 12(3): 177-82*
15. *Aktuna-D; Buchinger-W; Langsteger-W; Meister-E; Sternad-H; Lorenz-O; et al [Beta-carotene, vitamin A and carrier proteins in thyroid diseases] Acta-Med-Austriaca. 1993; 20(1-2): 17-20. (English abstract)*
16. *Arthur, JR., Nicol. F., Beckett, GJ. "Selenium deficiency, thyroid hormone metabolism, and thyroid hormone deiodinases." Am J Clin Nutri (1993); 57: 236S-239S.*
17. *Fabris, N. "Neuroendocrine-immune aging: an integrative view on the role of zinc." Ann NY Acad Sci (1994); 719: 353-368.*
18. *Freake,-H-C; Govoni,-K-E; Guda,-K; Huang,-C; Zinn,-S-A. Actions and interactions of thyroid hormone and zinc status in growing rats. J-Nutr. 2001 Apr; 131(4): 1135-41*
19. *Pekary, AE., Lukaski, HC., Mena, I., Hershman, JM. "Processing of TRH precursor peptides in rat brain and pituitary is zinc dependent." Peptides (1991); 12: 1025-1032*
20. *Olivieri, O., Girelli, D., Stanzial, AM., Rossi, L., Bassi, A. "Selenium, zinc, and thyroid hormones in healthy subjects: low T3/T4 ratio in the elderly is related to impaired selenium status." Biol Trace Elem Res. (1996); 51: 31-41.*
21. *Ruz, M., Codoceo, J., Galgani, H. "Single and multiple selenium-zinc-iodine deficiency affect rat thyroid metabolism and ultrastructure." J Nutr. (1999); 129: 174-180.*
22. *Ravaglia, G., Forti, P., Mabiola, F., Nesi, B., Cucinotta, D., Savarino, L. "Blood micronutrient and thyroid hormone concentrations in the oldest-old." J Clin Endocrinol Metab (2000); 85: 2260-2265.*
23. *Golstein, J., Goyens, P., Nsombola, B. "Selenium deficiency as a possible factor in the pathogenesis of myxoedematous endemic cretinism." Acta Endocrinologica (1987); 114: 497-502.*
24. *Beckett-GJ; Russell-A; Nicol-F; Sahu-P; Wolf-CR; Arthur-JR . Effect of selenium deficiency on hepatic type I 5-iodothyronine deiodinase activity and hepatic thyroid hormone levels in the rat. Biochem-J. 1992 Mar 1; 282 (Pt 2): 483-6*
25. *Chanoine-JP; Safran-M; Farwell-AP; Tranter-P; Ekenbarger-DM; Dubord-S; et al. Selenium deficiency and type II 5'-deiodinase regulation in the euthyroid and hypothyroid rat: evidence of a direct effect of thyroxine. Endocrinology. 1992 Jul; 131(1): 479-84.*
26. *Arthur, JR. "Regulation of selenoproteins gene expression and thyroid hormone metabolism." Biochem.Soc. Trans. (1996); 24: 348-388.*
27. *Chanoine, JP. "Selenium decreases thyroglobulin concentrations but dose not affect the increased thyroxin-to-triiodothyronine ratio in children with congenital hypothyroidism." J-Clin-Endocrinol-Metab. (2001); 86(3): 1160-1163.*
28. *Kauf-E; Dawczynski-H; Jahreis-G; Janitzky-E; Winnefeld-K. Sodium selenite therapy and thyroid-hormone status in cystic fibrosis and congenital hypothyroidism. Biol-Trace-Elem-Res. 1994 Mar; 40(3): 247-53.*
29. *Arthur, JR., Nicol, F. "Effect of selenium deficiency on thyroid gland and on plasma pituitary thyrotropin and growth hormone concentrations in the rat." Clin. Chem. Enzymol. Commun. (1990); 3: 209-214.*
30. *Becktt, GJ., Arthur, JR. "The iodothyronine deiodinases and 5'-deiodination." Clin Endocrinol Metab (1994); 8: 285-304.*
31. *Campos, A., Meinhold, H., Walzog, B. "Effects of selenium and iodine deficiency on thyroid hormone concentrations in the central nervous system of the rat." Eur J Endocrinol (1997); 136: 316-323.*
32. *Van-Lente-F; Daher-R. Plasma selenium concentrations in patients with euthyroid sick syndrome. Clin-Chem. (1992) Sep; 38(9): 1885-8.*

33. *Chanoine,-J-P; Neve,-J; Wu,-S; Vanderpas,-J; Bourdoux,-P. Selenium decreases thyroglobulin concentrations but does not affect the increased thyroxine-to-triiodothyronine ratio in children with congenital hypothyroidism. J-Clin-Endocrinol-Metab. (2001) Mar; 86(3): 1160-3.*
34. *Misiewicz, A., Radwan, K., Karmolinski, M., Dziewit, T. "Effect of occupational environment containing manganese on thyroid function." Br J Nutr (1979); 41: 253-261.*