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Trace elements in hypothyroidism in relation to L-thyroxine therapy

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ABSTRACT

Hypothyroidism is a common disorder in the population with a female predominance. Most hypothyroidism cases were found in the age group range of 30–35 in both the sexes of individuals but women were more prone to develop it. Disturbance or imbalance in the thyroid hormone levels is the underlying cause of resultant hypothyroidism. A comparative study of serum T3 (triiodothyronine), T4 (thyroxine), TSH (thyroid stimulating hormone), copper, zinc, magnesium and iron was done in 100 normal individuals as controls (Group I). 100 Hypothyroid patients showing Good Response to Levothyroxine Therapy – GRLT as (Group II A) and 100 Hypothyroid patients showing Poor Response to Levothyroxine Therapy – PRLT as (Group II B) over a period of 1 and half year in the age group of 20 to 45 years. The levels of TSH were found to be elevated in hypothyroid patients with relatively lower levels of serum T3 and T4 as per our study conducted in hypothyroid patients with PRLT when compared with the healthy subjects and patients in GRLT group. A study of implementation of levothyroxine therapy in hypothyroid subjects showed improvement in the patients with all the hormone levels returning back to the pre – hypothyroid state in majority of the hypothyroid patients with GRLT in comparison with the controls. Results of the study indicate a significant decreased levels of serum copper, zinc and iron in hypothyroid patients showing poor response to levothyroxine therapy whereas the magnesium levels in the serum of hypothyroid individuals with poor response to levothyroxine was found elevated. The serum levels of all the trace elements studied i.e., copper, zinc, magnesium, and iron in GRLT hypothyroid individuals and controls were within the normal ranges. Further studies are however needed on these parameters for establishing serum levels of trace elements in hypothyroidism in relation to response to levothyroxine therapy.

1. Introduction

Hypothyroidism is a syndrome that results from the deficiency of thyroid hormones –thyroxine (T4) and triiodothyronine (T3) leading to generalized slowdown of metabolic processes and is one of the most common endocrine disorders affecting 2 – 15% of the population worldwide and in India, it is found to affect 1 in 10 adults in the population with higher incidence in females.[1] Hypothyroidism is further divided into overt and subclinical hypothyroidism, both of them showing elevated serum thyroid stimulating hormone (TSH) levels.[2] Hypothyroidism is characterized by a broad spectrum that ranges from an overt myxedema state, end-organ effects, and multi-system failure to an asymptomatic or subclinical condition with normal levels of thyroxine and triiodothyronine and mildly increased levels of serum TSH. Hypothyroidism is divided into three types namely – primary due to auto immune disease (Hashimoto's

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thyroiditis) is the commonest form and accounts for 85 – 90%, secondary occurs if the pituitary gland does not produce enough TSH to induce the thyroid gland but produces sufficient quantities of thyroid hormones and accounts for 5 – 10% and tertiary wherein there is hypothalamic failure to produce sufficient Thyrotropin Releasing Hormone (TRH) accounting for 5%.[3]

Thyroid hormones T3 and T4 are helpful in normal functioning of all the organs and play an important role in cell differentiation. Alteration of the thyroid hormone results in abnormal metabolic process leading to damage to various tissues and organs. Thyroid hormones affect the trace element metabolism at many levels including excretion and transport.[4]

Trace elements are essential in a number of biological processes as activators or inhibitors of enzymes, hormone secretion and activity and binding to target tissue. Hormones in turn influence the metabolism of trace elements at their level of action, excretion, and transport.[5]

Role of trace elements in hypothyroidism is not well established, different studies showing varied results. Copper (Cu) is an integral component of tyrosinase, an important enzyme in thyroid hormone biosynthesis and superoxide dismutase. A decrease in serum copper levels were seen in patients with hyperthyroid goiter suggesting increased activity of the above enzymes and depletion of the copper levels.[1] Other studies have demonstrated no significant change in serum copper in patients with hypothyroidism.[5] Strong association between copper and thyroid hormones was demonstrated in early postnatal life[6] and serum copper levels were shown to be decreased in patients with hypothyroidism.[2]

Zinc (Zn) is involved in binding of T3 to its nuclear receptor and participation in protein synthesis including the formation of Thyrotropin releasing hormone (TRH).[5] Serum zinc levels were significantly decreased in hypothyroidism,[2,5] whereas other studies showed a significant decrease in hyperthyroidism.[1]

Serum magnesium (Mg) levels were shown to be significantly higher in patients with subclinical hypothyroidism[7] and low magnesium clearance was demonstrated in hypothyroid subjects.[8]

Iron (Fe) deficiency anemia is a relatively frequent finding in overt hypothyroidism which responds to T4 replacement[9] and conversely it has been hypothesized that iron deficiency leads to increased rate of thyroid disorders.[10]

There are numerous studies on the serum levels of trace elements in hypothyroidism with controversial findings. Though many trace elements affected the thyroid status in a number of ways, the role of trace elements in the development of hypothyroidism has not been established as yet.[1–10] The present study was planned to investigate the possible involvement of trace elements in hypothyroidism and their levels in the serum of the patients along with the thyroid hormones.

2. Aims and Objectives

To study the serum levels of trace elements copper, zinc, magnesium, iron, and thyroid hormones (T3, T4) and TSH in hypothyroid patients on levothyroxine therapy and assess their response to therapy in GRLT (Good Response to Levothyroxine Therapy) and PRLT (Poor Response to Levothyroxine Therapy) groups and compare them with normal healthy subjects.

3. Materials and Methods

A hospital based cross-sectional case control study was conducted on total of 200 hypothyroid patients over a period of 1 year and 6 months with convenient sampling of patients attending the medical out-patient department of Owaisi Hospital and Research Center and Princess Esra Hospital, Deccan College of Medical Sciences, Hyderabad, Telangana, India. The patients were compared with 100 normal healthy age matched controls.

Post Institutional Ethical Clearance informed consent was obtained from the patients and controls.

Various study parameters were estimated by the following methods in cases and controls –

1. T3, T4, and TSH: Enzyme Linked Fluorescent Assay (ELFA) on Minividas Hormone Analyzer.
2. Copper: Colorimetric method (Di-Br PAESA Method) on Chem – 7 Semi auto analyzer.
3. Zinc: Colorimetric method (Nitro – PAPS Method) on Chem – 7 Semi auto analyzer.
4. Magnesium: Xylidyl Blue Method on Chem – 7 Semi auto analyzer.
5. Iron: Ferrozine Method on Cobas C311 auto analyzer.

4. Results and Discussion

The results obtained for mean and standard deviation of various parameters in controls and cases were tabulated as follows:(Tables 1 and 2)

In this study, the levels of Serum T3 and T4 in Controls vs GRLT cases were significantly increased (P – value >0.05). Serum TSH, Cu, Zn, Mg and Fe levels were significantly decreased (P – value <0.05) in Controls vs GRLT group.

All the parameter levels were decreased in Controls vs PRLT and GRLT vs PRLT cases groups and highly significant statistically (P – value <0.01) in hypothyroid cases as compared to their age matched controls.

The mean and standard deviation values of all the parameters in cases as well as control subjects were calculated and were represented in the graphical form as bar diagram using MS Excel Software.

Table 1: Mean and Standard deviation of various parameters in controls and cases

S. No.	Parameter	Mean & SD of group – I Controls	Mean & SD of Group – II A (GRLT) Cases	Mean & SD of Group – II B (PRLT) Cases
1.	Age (Years)	32.5±7.27	35.4 ± 6.40	34.84 ± 7.10
2.	Serum T3 (nmol/L)	1.77± 0.51	1.82± 0.44	0.60 ± 0.11
3.	Serum T4 (nmol/L)	94.08± 21.68	94.44± 19.87	22.91 ± 8.77
4.	Serum TSH (uIU/mL)	2.36±1.19	3.21± 0.92	29.72±15.60
5.	Serum Copper (ug/dL)	123.18 ± 8.53	128.62± 9.01	71.20 ± 11.10
6.	Serum Zinc (ug/dL)	70.16± 8.46	85.38± 14.93	50.42 ± 6.49
7.	Serum (mg/dL) Magnesium	2.09± 0.19	2.31± 0.34	3.12 ± 0.14
8.	Serum Iron (ug/dL)	105.24+ 26.40	63.98+ 25.80	25.70 + 5.60

Table 2:

S. No.	Parameter	P – Value of Controls vs GRLT Cases	P – Value of Controls vs PRLT Cases	P – Value of GRLT vs PRLT CaseS
1.	Serum T3 (nmol/L)	0.4750*	0.00002***	0.00002***
2.	Serum T4 (nmol/L)	0.9027*	0.00002***	0.00002***
3.	Serum TSH (uIU/mL)	0.00004***	0.00002***	0.00002***
4.	Serum Copper (ug/dL)	0.00002***	0.00002***	0.00002***
5.	Serum Zinc (ug/dL)	0.00000***	0.00002***	0.00002***
6.	Serum (mg/dL) Magnesium	0.00002***	0.00002***	0.00002***
7.	Serum Iron (ug/dL)	0.00002***	0.00002***	0.00002***

*P>0.05 is considered statistically significant.
***indicates P<0.01 is highly statistically significant.
Parameter values expressed as mean + SD.

The mean values were compared between the cases (GRLT & PRLT Groups) and normal healthy individuals. The P – Values were also calculated using student's paired T test to find out the statistical significance of various parameters.

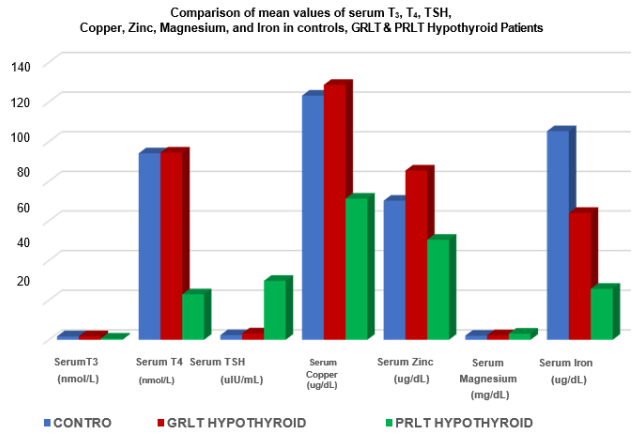

Fig. 1: Comparison of mean of various parameters in controls and cases

Our present study included 100 normal healthy individuals who are not on any kind of medications or supplementation, constituted the control group or group I, 200 hypothyroid patients were taken as cases for the study purpose and were further divided into two subgroups namely Group II A and Group II B. Group II A comprised of 100 hypothyroid individuals whose TSH was within the normal range whereas group II B was formed by hypothyroid subjects showing elevated TSH levels in the serum and included 100 subjects. The Group II A individuals responded well to the levothyroxine therapy and were called Good Response to Levothyroxine Therapy (GRLT) individuals. On the other hand, the hypothyroid patients who did not respond well to levothyroxine therapy were termed as

Poor Response to Levothyroxine Therapy (PRLT) group or Group II B. In our study, the serum levels of the thyroid hormones namely T3, T4, TSH were determined along with the trace elements copper, zinc, magnesium, and iron and were compared among various groups. In both GRLT & PRLT groups the age group of 30 – 35 showed the maximum number of cases and female predominance when compared with their male counterparts in all the age groups and controls included same number of both the sexes of individuals.

The thyroid gland undergoes important functional changes during aging and a prevalence of thyroid dysfunction is higher in the elderly as compared to the younger population. Aging is a complex process involving biochemical and morphological changes in single cells, in organs in the whole organism. Studies have shown that the imbalance in the composition of trace elements may cause different types of pathology as the aging process

advances. There is an increase in the serum copper levels with age progression between hypothyroidism and controls. Slight decrease in zinc concentration was noticed with advancement of age. With the process of aging, the serum magnesium levels were seen to be decreased. Iron content increases with the increase in patient's age and the age group above 45 years is more prone to develop hypothyroidism. This is consistent with previous studies.[11]

The sex distribution showed female predominance in both GRLT as well as PRLT hypothyroid subjects when compared to Control groups. Although the various trace elements serum concentrations showed slight differences according to gender, it is noticed that female patients were more prone to develop hypothyroidism than male patients. The values of thyroid hormones studied in relation to both ages and gender and the results obtained showed that there is a maximum increase in the concentration of TSH hormone and significant decrease in T4 and T3 serum levels for the age group of 30 – 35 in hypothyroid patients than the age groups below 30 years and above 35 years. There is significant increase in TSH values for both men and women with hypothyroidism when compared to the healthy people. The results obtained from our study showed that there is an increase in the concentration of TSH along with significant decrease in the concentration of T3 and T4in hypothyroid patients with poor response to levothyroxine therapy compared to healthy controls and hypothyroid subjects with good response to levothyroxine therapy.

Al-Jeebori K et al studies were in accordance with our studies with increased levels of TSH and decreased levels of serum T3 and T4.[12] The other studies which showed similar results included the study conducted by Yaqoob Y[2] et al, Unnikrishnan[3] et al. Mortoglou A et al showed the elevated TSH hormone levels with relatively lower levels of triiodothyronine and thyroxine.[13] Pal Y et al studied the thyroid hormones levels in hypothyroid patients and concluded the depletion of T3 and T4 with high TSH values. The rise in TSH level and reduction in the serum levels of T3 and T4 with high TSH values. The rise in TSH level and reduction in the serum levels of T3 and T4 in patients with hypothyroidism may be due to Hashimoto's disease which is a self-immune thyroid inflammation caused due to presence of antibodies produced and present in the blood of these patients. These antibodies inhibit immunoglobulin, attack, and destroy the tissue of thyroid and thus reduce the TSH effectiveness in stimulating thyroid gland growth and its hormone production.[14] The levels of all the thyroid hormones were normal within 6 months once the levothyroxine therapy was initiated. Thus, the therapy was found to be beneficial in majority of the hypothyroid patients.

The levels of serum TSH were increased in cases of hypothyroidism which showed poor response to the levothyroxine therapy and on the other hand, its levels were found to be within normal limits or ranges in healthy subjects and in hypothyroid patients who showed good response to levothyroxine therapy. The levels of the hormones T3 and T4 were decreased in the hypothyroid individuals showing poor response to levothyroxine therapy and good response to levothyroxine therapy group along with the control group showed normal levels of both the thyroid hormones.

Many trace elements play a vital role in numerous biological processes acting either as activators or inhibitors of enzymes involved in the body metabolism by competing with other elements and proteins for binding sites, by influencing cell membrane permeability or through some other mechanisms.. Trace elements influence hormones at the level of action that includes hormonal secretion and activity and target tissue binding. Thyroid hormones in turn influence trace elements metabolism at their levels of action which includes transport and excretion of trace elements. The status of different trace elements in hypothyroidism is not well-established and showed varied results according to various studies.[6]

In our study, the levels of trace elements were found to be within normal range in the control groups along with GRLT group. In PRLT group some trace elements showed decreased serum levels while some were elevated. Among the low serum levels of trace elements which we studied were copper, zinc and iron. The trace element which showed increased serum levels was magnesium.

The study undertaken by Blasig S et al,[6] Mittag J et al,[15] Jain R et al,[16] Arora M et al,[17] and Baloch S et al,[18] Anna A, Alebic F et al[19] also showed decreased levels of serum copper in hypothyroid subjects. Copper was correlated positively with serum T3 and negatively correlated with TSH suggesting the elevated serum copper levels are a risk factor for development of hypothyroidism. According to Akcay G et al, the zinc deficiency in the body leads to increased absorption of copper from the intestine and may lead to copper toxicity. The role of copper in production of thyroid hormones involves the stimulation of production of T4 since copper is a cofactor for tyrosinase and indirectly copper controls the body's calcium levels and prevents the over absorption of T4 in the blood cells. Other studies have suggested that the deficiency of copper in hypothyroidism may be a result of T4 insufficiency rather than the cause of it and thyroxine supplementation may help to correct copper deficiency.[2] Copper levels in the serum are regulated by the thyroid hormones predominantly by enhancing synthesis and export of hepatic ceruloplasmin while downregulating competing intracellular Cu-binding proteins. Copper is a component of ceruloplasmin which helps in the transport of iron to the cells. This relationship of copper and iron points to the deficiency of both copper and iron in hypothyroidism.[20]

Zinc levels in serum were found to be on the lower side in hypothyroid patients when compared to the controls. The study conducted by Ertek S et al,[20] Sudeep K et al,[21] Nisa F et al,[22] Kandhro G et al,[23] showed similar results as our study. Yoshida K et al, showed that hypothyroidism had a negative influence on gastrointestinal absorption of zinc. The decrease in serum zinc concentration can be explained by decrease in the gastrointestinal absorption of zinc or a change in the zinc distribution like sequestration of zinc by the liver or other tissues in hypothyroidism subjects.[2] The modulation of gene expression by thyroid hormones occurs with the help of transcription factors which contain zinc bound to cysteine residues. Zinc facilitates the secretion of thyroid hormones by acting as a cofactor for Iodothyronine deiodinase (IDI) enzyme and regulates the genesis and function of TRH.[4] Zinc deficiency can lead to hypothyroidism and hypothyroidism in turn lead to zinc deficiency thereby, forming a vicious cycle. Nishiyama S et al, reported that serum levels of thyroid hormones can be normalized by oral zinc supplementation which highlights the importance of trace element zinc in maintenance of thyroid homeostasis.

As per our study the magnesium levels in the serum of patients with hypothyroidism were elevated. Other studies of Al-Hakeim et al,[24] Wang K et al,[25] Sridevi D et al,[26] Susanna Y et al,[27] Kaur J et al,[28] Murgod R et al,[29] Ryan M et al.[30] Studies have shown conflicting results of serum magnesium in hypothyroid patients. Some authors have shown a decrease in serum magnesium in hypothyroidism whereas S Porta et al have shown a significant decrease in total serum magnesium in hyperthyroid patients. According to Shrestha S et al[31] both plasma magnesium and ionized magnesium were increased in hypothyroidism when compared to controls. In hypothyroidism, filtered magnesium is reabsorbed more as the thyroid hormone has a direct effect on renal tubules resulting in renal retention of magnesium if thyroid hormones are chronically absent.[32] The mechanism of changes in serum magnesium levels due to thyroid dysfunctions were not described in literature except a few mentioned earlier. Hence, this parameter of trace elements needs to be further explored on a large-scale basis.

Our study showed decreased serum iron which was in accordance with the studies conducted by Dahiya K et al,[32] Eftekhari M et al,[33] Mishra A et al,[34] Cinemere H et al,[35] Onat A et al,[36] Bashboosh N et al,[37] and Kammak M et al,[38] Shukla A et al[39] showing anemia in hypothyroidism condition. Iron is considered a co-factor in catalysis of various important biological enzymes including Thyroperoxidase affecting the overall thyroid hormone metabolism.[2] Iron deficiency not only impairs the thyroid metabolism but also reduces the peripheral conversion of T4 to T3. On the other hand, deficiency of thyroid hormones may lead to bone marrow repression and decrease in erythropoietin production due to decreased oxygen requirement. Iron is important in the transport of thyroid hormones into the cells and lack of iron results in pooling of thyroid hormone and a metabolically hypothyroid state. The gene expression of transferrin is also regulated by thyroid hormones. Hence, hypothyroidism is associated with iron deficiency and vice versa iron deficiency increase the risk for hypothyroidism.[10] Shukla et al reported increased incidence of microcytic anemia in hypothyroidism.[39]

As the copper, zinc and iron levels are decreased significantly in PRLT group as compared to controls and GRLT group, the deficiency of these elements may lead to a high TSH level despite taking the adequate dose of levothyroxine in these patients.[2] Supplementation of levothyroxine therapy in hypothyroid patients was found beneficial in some individuals as the levels of the thyroid hormones namely– thyroid stimulating hormone, triiodothyronine, thyroxine was brought back to the normal levels in the serum of hypothyroid patients. The serum levels of the trace elements which we studied included copper, zinc, magnesium and iron also showed improvement in some hypothyroid patients once the levothyroxine therapy was initiated while in others it showed poor response.

Our study was limited by its retrospective design. Additionally, the list of potential confounders for electrolyte disorders is long. The study could not be carried out on large scale basis due to financial constraints and limited duration of study period. An unknown proportion of patients presented in the study suffered from acute illness influencing both trace elements as well as thyroid hormone homeostasis. Some of our patients also presented with minor problems such as simple viral infections of the upper respiratory tract or small traumas which was discovered later on. A detailed case by case review would be necessary in order to rule out all other potential causes for changes of serum trace elements and considered all these elements was not possible for the short duration of study.

Whether hypothyroidism lead to the depletion or elevation of the trace elements or the deficiency/excess intake of the trace elements lead to the development of the hypothyroidism in the studied patients remains controversial for which large scale population based studies should be undertaken. Further the role of levothyroxine therapy in hypothyroid needs to be enlightened as the therapy in a few individuals with hypothyroidism showed good response while in others poor response was noted. Though utmost care has been taken to undertake the strict inclusion of patients and after exclusion criteria being set, the exact cause for varied response to the levothyroxine therapy in hypothyroid individuals could not be found and require further studies.

5. Conclusion

Our study concluded that the levels of magnesium and TSH were significantly found on higher side and T3, T4, copper, zinc, iron were significantly decreased in PRLT group when compared to their normal counterparts and GRLT group.

Whether hypothyroidism led to the development of abnormality in all the above parameters or the parameters posed as risk factors contributing to the development of hypothyroidism remain unknown for which large scale multi-centric population-based studies to establish the role of various parameters should be undertaken which would prove to be beneficial in future studies.

6. Source of Funding

None.

7. Conflict of Interest

None.

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