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Study of Zinc and Selenium in Hypothyroidism and Grave's hyperthyroidism in comparison with Euthyroidism – A Cross-sectional study in northern Andhra Pradesh

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Abstract

Background: Thyroid disease is widespread in India with the prevalence of Hypothyroidism at 10.95%. The prevalence of Thyroid disease increases with age and is more common in women. Zinc and Selenium are microelements that are needed by humans in small concentrations. Zinc plays an important role in Thyroid metabolism. Zinc is part of the Deiodinase enzyme which catalyses the peripheral conversion of Thyroxine (T4) to Triiodothyronine (T3). Selenium is also important for the production of Thyroid hormones. Zinc and Selenium have an intricate association with Thyroid metabolism. The deficiency of these parameters affects the concentration of Thyroid hormones.

Aim: This study evaluates the status of Serum Zinc and Selenium levels in Hypothyroidism and Grave's Hyperthyroidism with Euthyroid subjects as control.

Materials and methods: This is a hospital-based Cross-Sectional study that included 100 cases of Hypothyroidism and 60 cases of Grave's Hyperthyroidism with 100 Euthyroid subjects as control. All the subjects were between 15-60 years of age. After Detailed case history and Examination, the Blood sample is collected and analysed the same day for FreeT3, FreeT4, TSH, Serum Zinc, and Serum Selenium levels.

Result: Compared to Euthyroid subjects, Patients with Clinical Hypothyroidism have statistically significant (P-value <0.05) lower levels of Serum Zinc and Serum

Selenium. The scenario is the same in the case of Grave's Hyperthyroidism patients. Our study found Statistically significant (P-value <0.05) lower levels of Serum Zinc and Selenium levels in Grave's Hyperthyroidism patients.

Conclusion: Our study found a strong association between Serum Zinc and Selenium levels and Thyroid profile. The deficiency of these parameters can lead to both Hypothyroidism and Hyperthyroidism.

Keywords: Zinc, Selenium, Thyroid profile, Cross-sectional study, Hypothyroidism, Grave's Hyperthyroidism.

Introduction

Thyroid disease is widespread in India and the world. There is a significant burden of thyroid diseases in the Community, among which Hypothyroidism is prevalent. The prevalence of hypothyroidism in India was 10.95% [1] compared with only 2% in the UK and 4·6% in the USA. The prevalence of Hyperthyroidism was found to be

1.6% [2]. The prevalence of Thyroid disease increases with age and is more common in women. The prevalence of subclinical Hypothyroidism is higher than Clinical Hypothyroidism, which goes undiagnosed most of the time[3.] Thyroid hormones are Thyroxine (T4) also called Tetraiodothyronine and Triiodothyronine (T3) secreted by the thyroid gland. They are essential for the normal growth of the body, metabolism, and tissue differentiation. Thyroid hormones stimulate the Basal metabolic rate, increase glycogenolysis, gluconeogenesis and lipolysis and enhance the synthesis of proteins [4].

Zinc and Selenium are microelements that are needed by humans in small concentrations. Zinc plays an important role in metabolism. Zinc is part of the Deiodinase enzyme which catalyses the peripheral conversion of Thyroxine (T4) to Triiodothyronine (T3) [5]. Zinc is also required for the synthesis of Thyrotropin-releasing hormone (TRH). Selenium is Important for the production of Thyroid hormones. iodothyronine deiodinase is an important enzyme that converts T4 to T3 in tissues during the production of thyroid hormone [6]. selenium through Selenoproteins also has antioxidant activity in Thyroid glands which maintain the health of Thyroid gland [6].

There were few studies done in India to correlate Zinc and Selenium levels in Hypothyroidism and Hyperthyroidism separately. There was no study conducted in India where the association between Zinc and Selenium was assessed in Hyperthyroidism and Hypothyroidism in comparison to Euthyroidism in the same research. Hence the purpose of this study.

Materials and methods

Study design: This was a hospital-based Cross-Sectional study conducted at our Institution. The study included 100 newly diagnosed cases of Hypothyroidism, and 60 newly diagnosed cases of Grave's Hyperthyroidism in comparison with 100 Euthyroid subjects with age 15 - 60 years who attended the Department of Medicine, Department of Ophthalmology of Institution for 1.5 years from 01.01.2021 to 30.06.2022. the study protocol was approved by the institutional ethics committee. Informed consent was taken from all the study participants.

Inclusion Criteria

All the cases and controls belonged to the age group of 15-60 years. Newly diagnosed and untreated cases of Hypothyroidism and Grave's Hyperthyroidism who attended OPD of Medicine and Ophthalmology Department, MIMS, Nellimarla were selected as cases. Healthy age and sex-matched 100 subjects were enrolled as controls.

Exclusion Criteria

Exclusion criteria included pregnant, menopause or lactating women, acute or Chronic illness, Liver or Renal disorders, intake of Oral contraceptive pills, Thyroid malignancies, Subjects on Iron supplements, and Subjects on any medication that can alter Thyroid status or Iron status in blood.

Methods

Clinical history was taken from all the subjects who participated in the study. General examination of these patients, including weight, height, Heart rate, and Blood pressure measurement was done and recorded in a structured protocol format. Grave's Hyperthyroidism subjects were examined in detail for Exophthalmos in the Department of Ophthalmology and recorded details. After obtaining Informed consent from the subject, 5 mL of the blood sample was collected from all subjects under aseptic conditions. After adequate clotting, the serum tube was centrifuged. The serum which gets separated in the test tube was aliquoted. It was used for testing thyroid profile (Free T3, Free T4, TSH) and Serum levels of Iron, Total Iron Binding Capacity (TIBC). The aliquoted sample was stored at - 20◦C.

The following Instruments and methods were used for analysing the parameters. Free T3 - Electrochemiluminescence immunoassay (ECLIA)

Free T4 - Electrochemiluminescence immunoassay (ECLIA), TSH – Electrochemiluminescence immunoassay (ECLIA)

Serum Zinc: Spectrophotometric method using Nitro-PAPS reagent – ERBA EM200 analyser

Serum Selenium: Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-EOS) method.

Statistical methods

Data were analysed using IBM SPSS Statistics Version 21.0. Qualitative variables were expressed as frequency and percentages. Quantitative variables were expressed in Mean and Standard deviations. ANOVA with post hoc analysis was used for the comparisons between three groups and multiple comparisons. Karl-Pearson correlation coefficient was used to explore the association between study variables. For all statistical analyses, $P < 0.05$ was considered statistically significant.

Results

Mean±SD of FT3 and FT4 (Table 1) were significantly lower in Hypothyroidism ($P<0.05$) and significantly higher in Grave's Hyperthyroidism ($P<0.05$) in comparison with Euthyroid subjects. Table 2 analysed and compared the Mean±SD of Serum Zinc and Serum Selenium levels in various groups. Mean±SD of Serum Zinc was found to be 38.21±8.72 µg/dl in the Hypothyroid group and 46.89±6.98 µg/dl in the Hyperthyroid group compared to 93.39±13.72 µg/dl In Control subjects. This was depicted in the Mean plot (Fig.1). A strong association was established during comparison ($P<0.05$). Similar results were found with Serum Selenium. Mean±SD of Serum Selenium was found to be 53.32±13.53 µg/L in the hypothyroid group and 49.55±7.86 µg/L in the hyperthyroid group compared to 102.57±20.4 µg/L In Control subjects. This was depicted in the Mean plot (Fig.2). Similar strong association was established during comparison ($P<0.05$). Table 1.3 did a post-hoc analysis of the Variables. Our previous findings were confirmed by ANOVA with post-hoc analysis. all the major comparisons were found to be $P<0.05$. Table 4, and 5 showed Pearson Correlation and P-value within various study groups.

Table: 1: Mean, SD, and P-Value of various Thyroid parameters.

		Number	Mean	Std. Deviation	Std. Error	P-Value
FT3	Euthyroid	100	318.8458	37.77513	3.77751	0.000
	Hypothyroid	100	149.2950	20.30577	2.03058	
	Hyperthyroid	60	581.0800	64.94884	8.38486	
FT4	Euthyroid	100	1.8435	.43223	.04322	0.000
	Hypothyroid	100	.4434	.20087	.02009	
	Hyperthyroid	60	4.3807	.71971	.09291	
TSH	Euthyroid	100	2.2318	.90688	.09069	0.000
	Hypothyroid	100	42.1734	18.87280	1.88728	
	Hyperthyroid	60	.0977	.09473	.01223	
	Total	260	17.1015	23.05463	1.42979	

FT3 – Free T3, FT4- Free T4, TSH – Thyroid Stimulating Hormone, Std: Standard; P<0.05 was considered significant: Table is Original

Table: 2: Mean, SD, and P-Value of Serum Zinc and Selenium in groups.

		Number	Mean	Std. Deviation	Std. Error	P-Value
Serum Zinc	Euthyroid	100	93.3904	13.72224	1.37222	0.000
	Hypothyroid	100	38.2154	8.72655	.87265	
	Hyperthyroid	60	46.8902	6.98762	.90210	
S Selenium	Euthyroid	100	102.5732	20.40818	2.04082	0.000
	Hypothyroid	100	53.3216	13.53246	1.35325	
	Hyperthyroid	60	49.5500	7.86847	1.01582	
	Total	260	71.3942	29.24536	1.81372	

Std: Standard; S Selenium - Serum Selenium, P<0.05 was considered as significant: Table is Original.

Mean Plots of Serum Zinc and Serum Selenium:

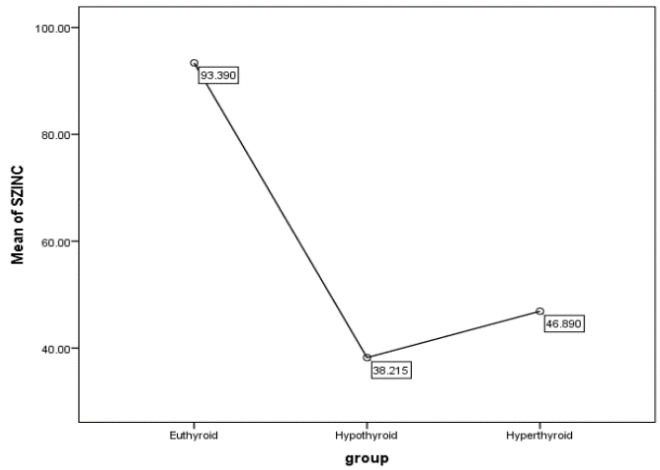

Fig. 1

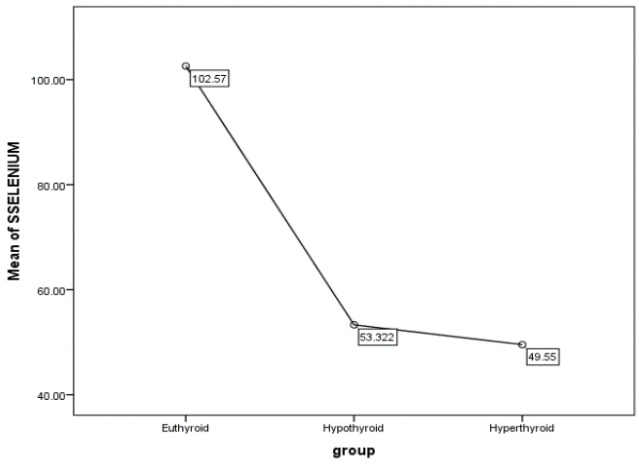

Fig: 2

Table: 3: Post hoc tests for Serum Zinc and Selenium.

Dependent Variable	(I) group	(J) group	Mean Difference (I-J)	Std. Error	P Value
Serum Zinc	Euthyroid	Hypothyroid	55.17500*	1.50386	.000
		Hyperthyroid	46.50023*	1.73651	.000
	Hypothyroid	Euthyroid	-55.17500*	1.50386	.000
		Hyperthyroid	-8.67477*	1.73651	.000
	Hyperthyroid	Euthyroid	-46.50023*	1.73651	.000
		Hypothyroid	8.67477*	1.73651	.000
S Selenium	Euthyroid	Hypothyroid	49.25160*	2.21448	.000
		Hyperthyroid	53.02320*	2.55706	.000
	Hypothyroid	Euthyroid	-49.25160*	2.21448	.000
		Hyperthyroid	3.77160	2.55706	.141
	Hyperthyroid	Euthyroid	-53.02320*	2.55706	.000
		Hypothyroid	-3.77160	2.55706	.141

Std: Standard, Sig: Significance, S Selenium - Serum Selenium, P<0.05 was considered significant: Table is Original.

Table: 4: Pearson Correlation of Variables within Hypothyroid subjects

Hypothyroid		Serum Zinc	S Selenium	FT3	FT4	TSH
Serum Zinc	Pearson Correlation (R)	1	.101	.042	.050	-.044
	P-Value		.319	.675	.624	.664
	Number	100	100	100	100	100
S Selenium	Pearson Correlation (R)	.101	1	-.157	.001	.234*
	P-Value	.319		.119	.994	.019
	Number	100	100	100	100	100

FT3 – Free T3, FT4- Free T4, TSH – Thyroid Stimulating Hormone, S Selenium - Serum Selenium, P<0.05 was considered significant: Table is Original

Table: 5: Pearson Correlation of Variables within Hyperthyroid subjects

Hyperthyroid		Serum Zinc	S Selenium	FT3	FT4	TSH
Serum Zinc	Pearson Correlation (R)	1	-.258*	.241	.047	-.010
	P-Value		.047	.064	.721	.938
	Number	60	60	60	60	60
S Selenium	Pearson Correlation (R)	-.258*	1	-.060	-.080	-.100
	P-Value	.047		.649	.545	.449
	Number	60	60	60	60	60

FT3 – Free T3, FT4- Free T4, TSH – Thyroid Stimulating Hormone, S Selenium - Serum Selenium, P<0.05 was considered significant: Table is Original.

Discussion

Our findings on serum Zinc levels in Hypothyroidism correlated with studies conducted by Pal S et al [7], Arora M et al [8], Shahnaz Khatun et al [9], and Hutheiefa I Y et al [10]. these studies found a statistically significant decrease in Serum Zinc levels in Hypothyroidism. On the contrary, our findings on Zinc levels in Hyperthyroidism correlated with studies conducted by Sinha S et al [11], Khadem-Ansari et al [12], Rezaei M et al [13]. these studies also found statistically significant decreased levels of Serum Zinc levels in Hyperthyroid patients. Our findings of decreased Serum Selenium levels in Hypothyroidism correlated with studies conducted by Ventura M et al [6], Negro R et al [14], and Wu et al [15]. Our findings in Serum Selenium levels in Hyperthyroidism correlated with studies conducted by Ventura M et al [6], Varca V B et al [16], Marcocci C et al [17]. these studies showed lower levels of Serum Selenium in Untreated cases. Patients improved significantly when treatment was given along with Selenium medication.

The reason for this correlation can be explained in the following way. Zinc is required for the function of the enzyme "5'- deiodinase". This enzyme catalyses the peripheral conversion of thyroxine (T4) hormone to its active form triiodothyronine (T3) [5]. This conversion takes place in peripheral blood. The significant positive correlation of Zinc with T3 may be because of decreased activity of hepatic type I 5-deiodinase by 67% during Zn deficiency [18]. Due to the reduced amount of total available T3, there will be Hypothyroidism. Even there will be a compensatory increase in the TSH hormone. Zinc is an essential agent that controls the synthesis of TRH (Thyrotropin-releasing hormone). The thyroid hormone crosses the plasma membrane of the effector cell and binds to the transcription factor. This process is essential for the modulation of gene expression and produces the required protein for the function. It also contains Zinc, which is bound to cysteine residues [19]. So, Zinc is needed for the Gene expression of the Thyroid hormone to produce necessary proteins. T3 receptor on the effector cell where the T3 hormone binds is thought to require Zinc to adopt its biologically active conformation [20].

On the other hand, Hypothyroidism impairs gastrointestinal absorption of Zinc or altered zinc distribution, leading to the sequestration of Zinc in the liver or other tissues. [7]. The thyroid also has an influence on GFR in the kidney in the excretion of this mineral. This sets a cyclical process. Decreased Serum Zinc levels in Hyperthyroidism can be explained in the following way. Serum Zn is mainly bounded to and transported by albumin. Serum albumin level decreases in the hyperthyroid state, and decreased Zn-albumin complex can lead to increased ultrafiltrate serum Zn which accelerates Zn excretion in urine [21]. This can explain a lower Zn level even at the beginning of hyperthyroidism. [22]. In addition, Zn plays an important role in protein metabolism in the human body, so decreasing serum Zn concentrations can impair albumin production, and low serum albumin levels can worsen serum Zn depletion [23].

The thyroid gland is characterized by a high concentration of selenium, which is incorporated into selenoproteins. Some of these selenoproteins have an important antioxidant activity, contributing to the antioxidant defense in the thyroid by removing oxygen free radicals generated during the production of thyroid hormones. Being incorporated into iodothyronine deiodinases, selenium plays also an essential role in the

metabolism of thyroid hormones. it was found that selenium deficiency decreases the synthesis of thyroid hormones, as it decreases the function of selenoproteins, in particular iodothyronine deiodinases (DIOs), which are responsible for the conversion of T4 to T3 [6]. lower levels of Serum Selenium in Hyperthyroidism can also be explained by similar reasons as Zinc. Antibodies produced during Grave's hyperthyroidism affect the synthesis of selenoprotein P, the Transport protein of selenium. It also affects the absorption and storage of selenium in the thyroid gland [6].

Conclusion

In the present study, we concluded that Patients with Clinical Hypothyroidism had statistically significant (P-value <0.0001) lower levels of Serum Zinc and Selenium. The scenario was the same in the case of Grave's Hyperthyroidism patients. Our study found Statistically significant (P-value <0.0001) lower Serum Zinc and Selenium levels in Grave's Hyperthyroidism patients compared to the control. Therefore, Clinicians and Endocrinologists should be advised to test patients with Hypothyroidism and Hyperthyroidism routinely for serum Zinc and Selenium for more effective Thyroid treatment.

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