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CHANGES IN SERUM SELENIUM LEVEL IN THYROID EYE DISEASE PATIENTS – A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Introduction Thyroid Eye disease (TED) is also called as Grave's Orbitopathy (GO). About 20% to 50% of patients with Grave's disease also have Graves orbitopathy (GO), an autoimmune inflammatory disease of the orbit and periorbital tissues. Low selenium level has been associated with a higher incidence of benign thyroid diseases, such as Grave's disease and thyroiditis, according to a number of epidemiological studies. TED has a higher prevalence in women than men. The median age of diagnosis is 43 years for all patients, with a range from 8-88 years. Patients diagnosed over the age of 50 years have a worse prognosis overall. Risk factors for TED include age, gender, ethnicity, and family history. Our objectives were to assess the alterations in serum selenium levels among individuals with thyroid eye disease and to determine any correlations between serum selenium levels and thyroid peroxidase antibodies (TPO) and thyroid related antibodies (TRAb).

Materials and methods: We did a Prospective observational study. Our Study population was Patients diagnosed with thyroid eye disease attending ophthalmology OPD in Saveetha medical college hospital, Thandalam. We conducted this study for a period of 12 months among 47 Thyroid Eye Disease patients. We include patients willing for the study, Naive patients diagnosed with thyroid orbitopathy and patients who are aged 18 years and above**.** We excluded patients who are on previous antithyroid drug treatment, steroid, radioiodine therapy or thyroid surgery, immunomodulator or other medication affecting thyroid function and patients who had severe systemic illness. When the p value is less than 0.005, all statistical tests were deemed statistically significant.

Results and discussion: Among 47 patients, 42.5% were below 40 years, 57.5 % were above 40 years. Females were 61.7% and males were 38.3%. Mean (SD) of the Serum selenium level is 83.59 (27.44) and it ranges from 56.44 -160 mcg/L. The p-value shows significant relationship between serum selenium and thyroid receptor antibody (rho = -0.4362, p-value = 0.0022).

Conclusion: The findings of this study indicate that blood selenium levels are directly correlated with thyroid eye disease, and that serum selenium deficiency is a significant risk factor for TED. There is discernible relationship between serum selenium levels and TRAb or TPO antibody levels. A deficit in selenium is one of the risk factors for TED. As a result, the study comes to the conclusion

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that selenium supplements are crucial for TED patients.
Keywords: Thyroid Eye Disease (TED), Serum selenium, Thyroid Related antibodies (TRAb), Thyroid Peroxidase antibodies (TPO).

INTRODUCTION

Thyroid Eye disease (TED) is also called as Grave's Orbitopathy (GO). About 20% to 50% of patients with Grave's disease also have Graves orbitopathy (GO), an autoimmune inflammatory disease of the orbit and periorbital tissues [1]. Eyelid retraction and swelling, redness, exophthalmos, and diplopia are the hallmarks of GO. If the right treatment is not started in the early stages of the disease, these clinical symptoms may have serious consequences. Although the exact pathophysiology of GO is unknown, orbital fibroblast activation is recognised to be critical to the illness's progression. The metabolism of thyroid hormone and immune system function are two key metabolic pathways that depend on selenium, an important trace mineral. Low selenium level has been associated with a higher incidence of benign thyroid diseases, such as Grave's disease and thyroiditis, according to a number of epidemiological studies [2-4]. As a result, the use of oral selenium supplementation in the medical management of thyroid illness has increased. Selenium supplementation dramatically decreased ocular involvement, enhanced quality of life, and slowed the course of the disease in individuals with mild GO, according to a prospective randomised experiment [5]. In patients with moderate GO of brief duration, the European Thyroid Association/European Group on Graves Orbitopathy recommends a 6-month course of selenium treatment [6]. TED was originally associated to the hyperthyroidism, pretibial myxoedema, and ocular illness known as the Graves triad. In addition to thyroid dysfunction, Hashimoto's thyroiditis has also been linked to TED in more recent times. Even while symptoms are usually bilateral, they can also be asymmetric. Orbital and periorbital odema, eyelid retraction, eyelid lag in downgaze, compressive optic neuropathy, exposure keratopathy, and common feelings of ocular irritation and dryness are the most frequent presenting signs. [7] TED has a higher prevalence in women than men (16 per 100,000 vs. 3 per 100,000, respectively). Both men and women demonstrate a bimodal pattern of age of diagnosis (40-44 and 60-64 years in women; 45-49 and 65-69 years in men). The median age of diagnosis is 43 years for all patients, with a range from 8-88 years. Patients diagnosed over the age of 50 years have a worse prognosis overall. Risk factors for TED include age, gender, ethnicity, and family history. A positive family history of TED is noted in 61% of TED patients.[8] TED is a self-limiting illness that can manifest as either active or quiescent. Active inflammation is present during the active stage, and it can cause swelling of the periocular tissues and eyelids, ocular discomfort, injection and chemosis of the conjunctiva, and expansion of the orbital muscles. This phase, which can extend for months or years, usually entails waxing and diminishing TED symptoms. An antibody-mediated response against the TSH receptor coupled with orbital fibroblast regulation of T-cell cells is considered to represent the underlying pathogenesis. It is thought that T-cell lymphocytes respond to thyroid follicular cells in the retrobulbar region because they share antigenic epitopes. [7] The extraocular muscles experience inflammation, interstitial oedema, and the activation of cytokine networks as a result of the lymphocytic infiltration.[9] One potential significant factor appears to be orbital fibroblasts' excessive production of glycosaminoglycans. The final effect is an increase in the volume of connective tissue, retrobulbar fat, and extraocular muscles.

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The anterior periorbital tissues and eyelids are also affected by similar alterations. The illness affects women more than men, with an annual frequency of about 4/10,000. About 1% of people are impacted at some point in their lives. Recent research has shown that thyroid autoantibodies and immune system genes play a significant role in both predicting the development of ophthalmopathy before it occurs and determining its severity once it does. In cases of ophthalmopathy, anti-TPO antibody and anti-TG positivity rates of 90% and 50%, respectively, have been reported. [10,11] We aimed to evaluate the changes in the serum selenium level in thyroid eye disease patients and also to identify association between Serum selenium levels and thyroid related antibodies (TRAb) and Thyroid peroxidase antibodies (TPO).

MATERIALS AND METHODS

We did a Prospective observational study. Our Study population was patients diagnosed with thyroid eye disease attending ophthalmology OPD in Saveetha medical college hospital, Thandalam. We conducted this study for a period of 12 months among 47 Thyroid Eye Disease patients. Our study population inclusion criteria were patients willing for the study, naive patients diagnosed with thyroid orbitopathy and patients who are aged 18 years and above**.** We excluded patients who are on previous antithyroid drug treatment, steroid, radioiodine therapy or thyroid surgery, immunomodulator or other medication affecting thyroid function and patients who had severe systemic illness.

METHODOLOGY

- Patients diagnosed with TED were assessed for clinical activity score.
- Serum selenium levels by Inductively coupled Plasma Mass Spectrometry (ICPMS),
- Serum TPO and TRAb levels by Automated chemiluminescent technology,
- And Serum T3, T4, TSH levels to determine thyroid status by automated chemiluminescent technology were measured.
- Serum selenium levels were compared with Serum TPO and TRAb levels.

STATISTICAL ANALYSIS

The acquired data is input into a Microsoft Excel document. Analysis were carried out utilising Version 20 of the Statistical Package for the Social Sciences (SPSS). The findings are shown as graphs, counts and percentages, mean, and standard deviation. Initially, the data were summarised using descriptive statistics, which gave a general picture of the patient demographics and preliminary findings. Unpaired t tests were utilised to compare continuous variables, while chi-square tests were utilised to analyse categorical data. When the p value is less than 0.005, all statistical tests were deemed statistically significant.

RESULTS

Total number of patients recruited during the study period were 47 patients in hospital, with previously mentioned inclusion and exclusion criteria applied.

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Age in years:

Table 1: Distribution of study subjects according to Age in years

Age in years	Frequency	%
<40years	20	42.5%
>40years	27	57.5%
Total	**47**	**100%**

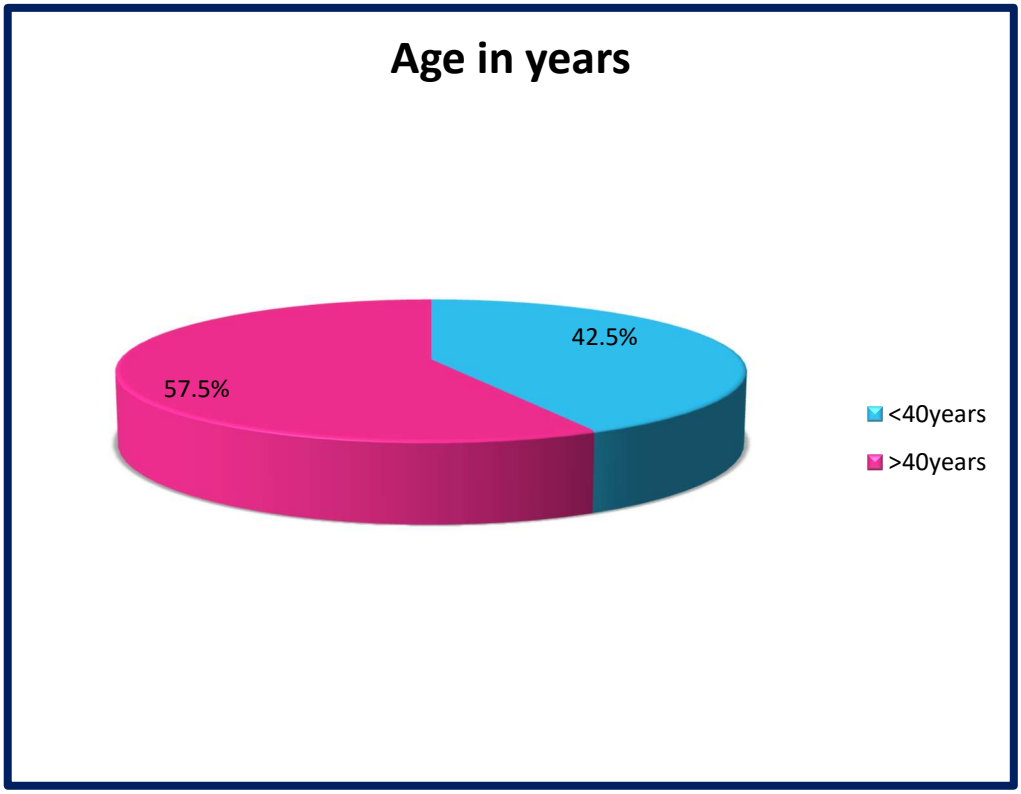

Fig 1: Distribution of study subjects according to Age in years

Gender:

Table 2: Distribution of study subjects according to Gender

Gender	Frequency	%
Male	18	38.3%

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Female	29	61.7%
Total	**47**	**100%**

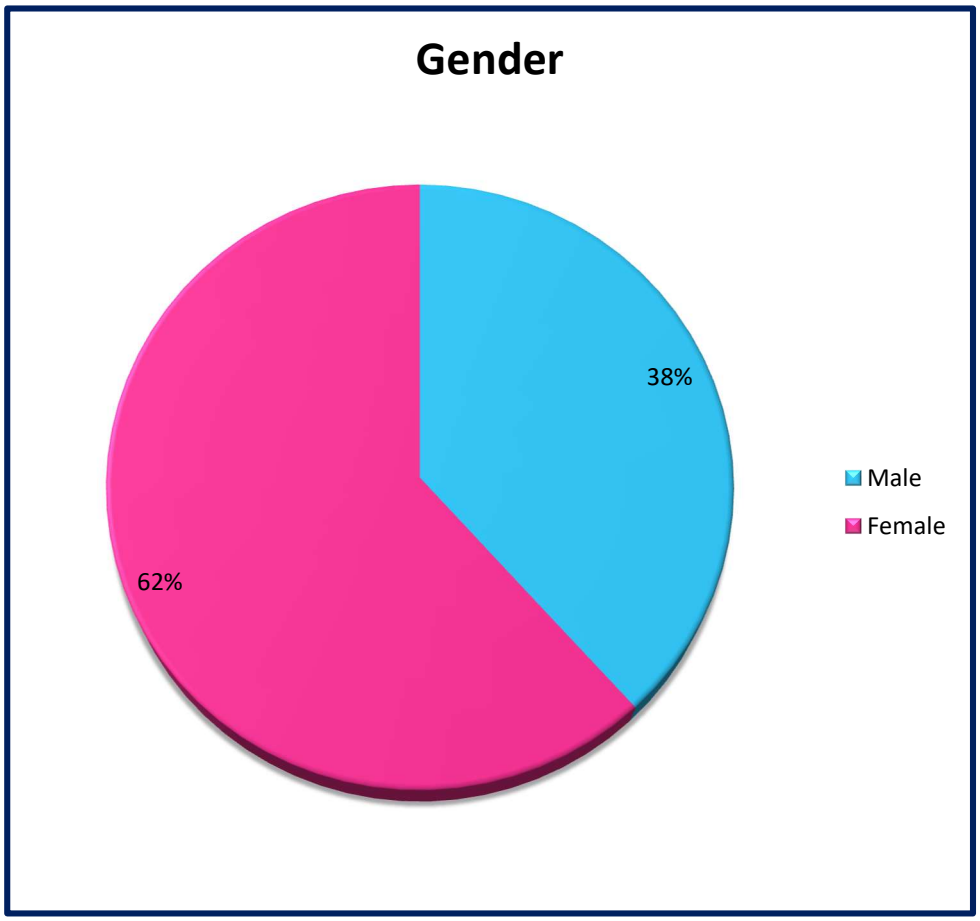

Fig 2: Distribution of study subjects according to Gender

Clinical Activity score:

Table 3: Distribution of study subjects according to Clinical Activity score

Clinical Activity score	Frequency	%
0	21	44.7%
1	15	31.9%
2	7	14.9%

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3	4	8.5%
Total	**47**	**100%**

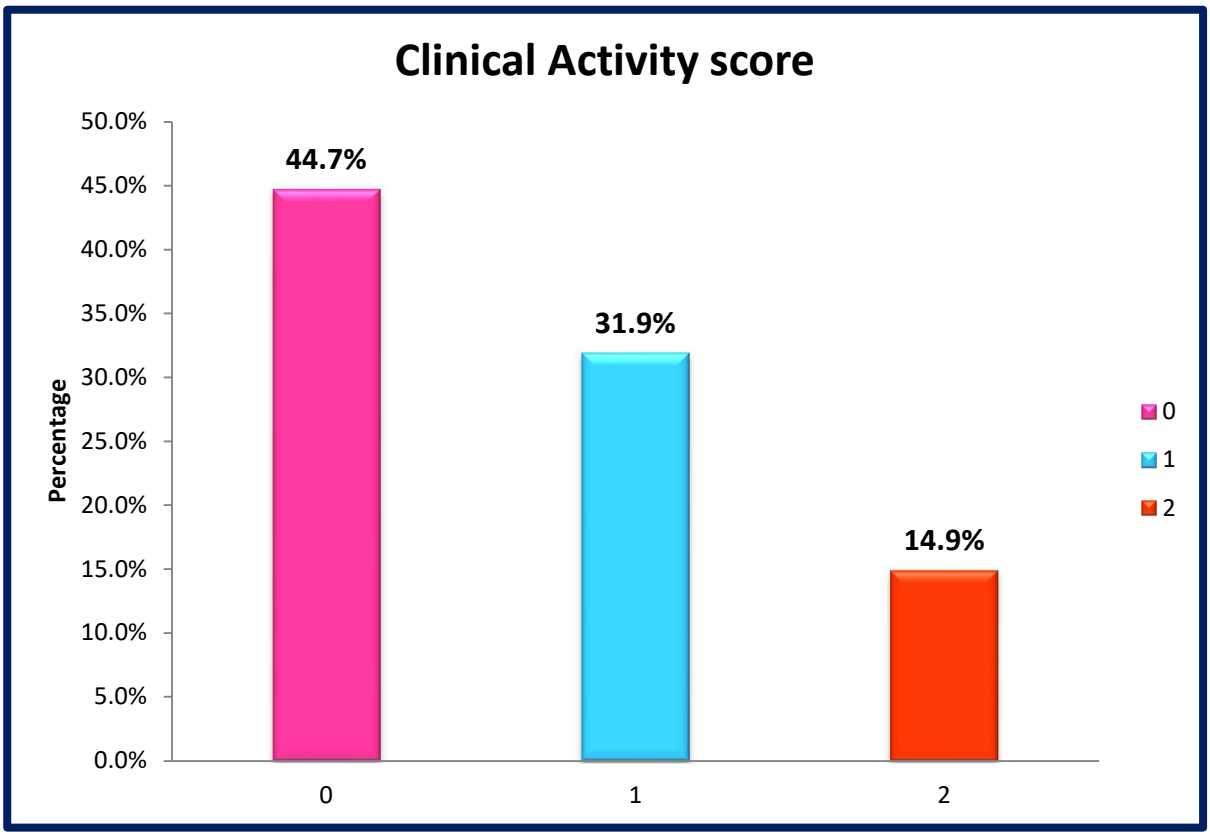

Fig 3: Distribution of study subjects according to Clinical Activity score

selenium:

Table 4: Distribution of study subjects according to serum selenium levels

Serum Selenium (mcg/L)	Frequency	%
50-60	1	2.1%
60-70	26	55.3%
70-80	4	8.5%
80-90	5	10.6%
90-110	1	2.1%
110-130	6	12.8%

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130-160	4	8.5%
Total	**47**	**100%**

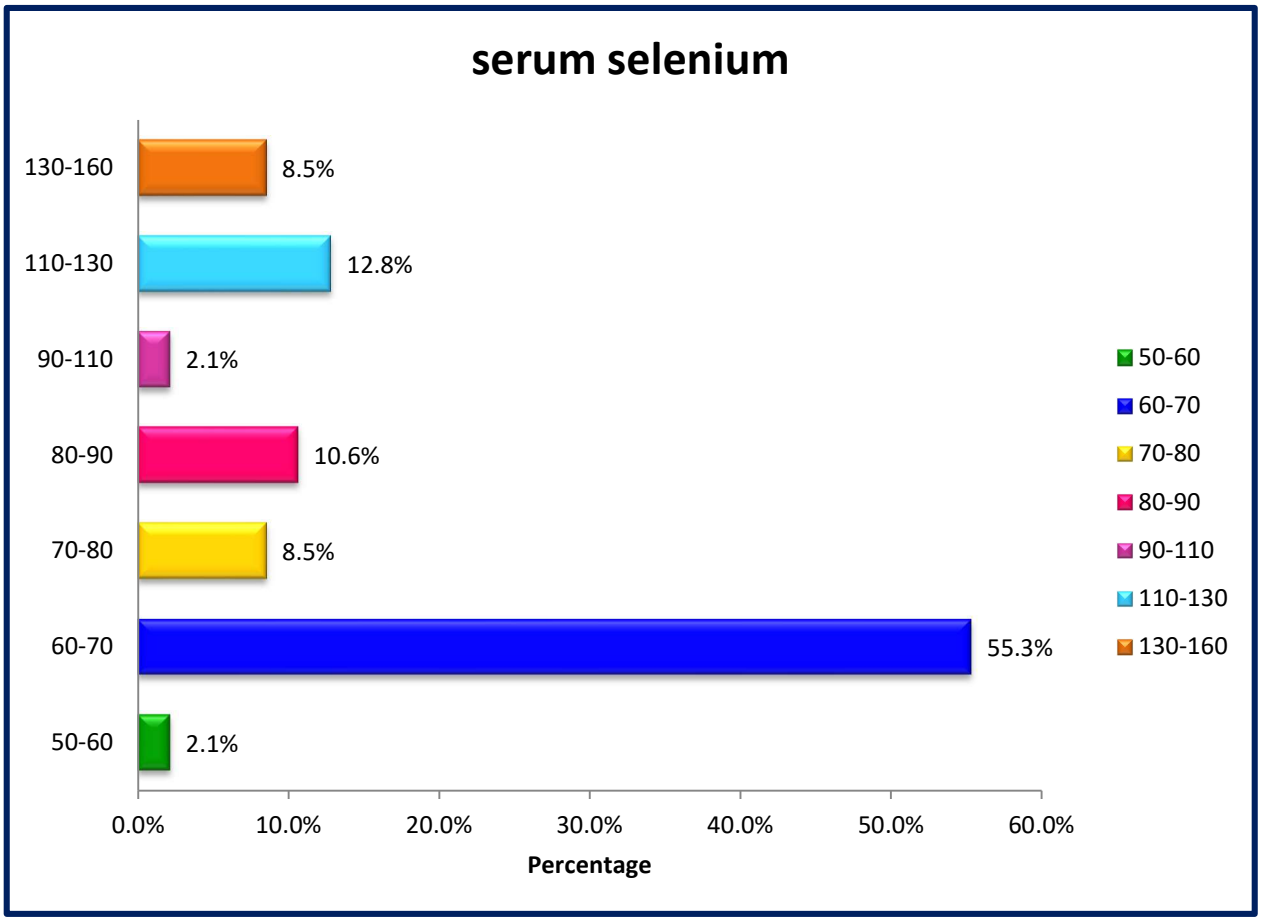

Fig 4: Distribution of study subjects according to serum selenium levels

Table 5: Correlation of serum selenium and TRAb parameters of the study

Parameter	**selenium**		**Results**
	R	**P**	Significant*
TRAb	-0.4362	0.0022*	

*P<0.05 statistically significant

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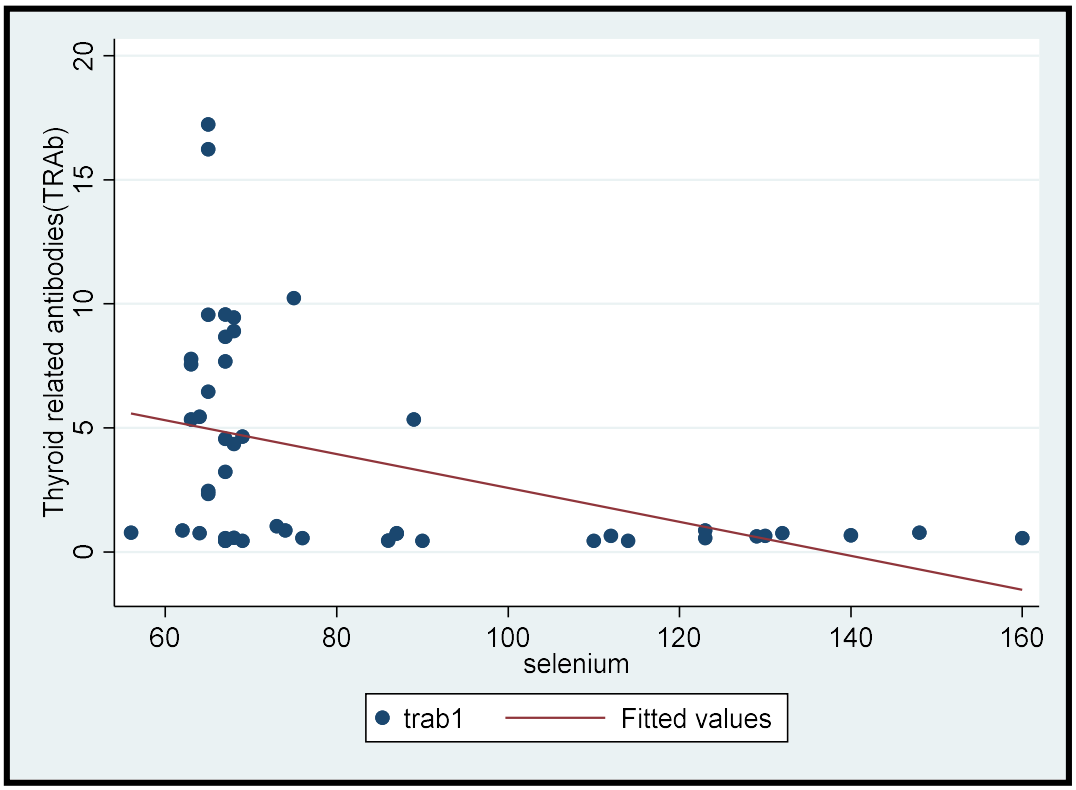

Fig 5: Correlation of selenium and trab parameters of the study

In our study among 47 patients, 42.5% were below 40 years, 57.5 % were above 40 years. Females were 61.7% and males were 38.3%. The mean (SD) value of the BMI is 24.26 (4.42) kg/m2 and it ranges from 17 to 36 kg/m2. Out of 47 patients, 7.9% were vegetarians, 92.1% were non vegetarians. Our study population smokers accounting for 23.7% and non-smokers comprising the rest 76.3%. Family history of thyroid disease which is 13.2% and in 86.8% it was absent. Among the total population 13.2% were having diabetic history and in 86.8% it is negative.

Based on our results clinical activity score, 47% of them had score 0, 31.9% of them had score 1, 14.9% of them had score 2 and 8.5% of them had score 3. According to serum selenium levels in our patients, 21% of them were between 50-60mcg/L, 55.3% of them 60-70 mcg/L, 8.5% of them 70-80mcg/L, 10.6% of them 80-90mcg/L, 2.1% of them 90-110mcg/L, 12.8% of them 110-130mcg/L, 8.5% of them 130-160mcg/L.

Mann-Whitney U test and independent t-test was used to find out the significant difference of clinical activity score and serum selenium level between the age group (≤40 years and >40 years). The p-value using independent t-test shows that there is a significant difference in serum selenium between the age group (≤40 years; Mean (SD) = 98.38 (20.13), p value = 0.051) and >40 years; Mean (SD) = 119.91 (29.19), p-value = 0.013).

Spearman rank order correlation was used to find out the relation between serum selenium level and thyroid receptor antibody, thyroid peroxidase antibody. The p-value shows there is significant relationship between serum selenium and thyroid receptor antibody (rho = -0.436, p-value = 0.0022)

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DISCUSSION

Selenium is a micro nutrient which plays an important role in the function and structure of the thyroid gland. Low selenium levels can lead to thyroid gland abnormalities and dysfunction. Selenium (se) has also been shown to induce inhibition of thyroid cancer cell growth in a number of studies. [12,13] Antioxidant enzymes such thioredoxin reductase, iodothyronine deiodinase, and glutathione peroxidase (GPx) depend on selenium as a component. [14] The most common extra-thyroidal manifestation of thyroid disease, thyroid associated ophthalmopathy (TAO), has been linked to diminished expression of SPs, which suggests that selenium is important for maintaining thyroid hormone homeostasis. [14,15] In our study, a positive correlation between serum selenium and age was found with a p value of 0.013. This is supported by a study in Chinese population by Yang Liu et al [16] where similar correlation has been found. A positive correlation between Clinical activity score and age was also revealed with a p value of 0.051. Selenium can be available in both organic and inorganic form. The organic form selenomethionine and selenocysteine has better absorption hence used in supplementation. Se is incorporated in the body in form of selenomethionine hence it is more preferable. Selenomethione is found in vegetable sources especially cereals, yeast whereas selenocysteine in animal foods mainly. [17] A negative correlation between BMI and serum selenium levels is found in our study. This is in contrast to previous study by Wu et al, [18] which showed a positive association between the both. There was a positive association between CAS and age group with p value found to be 0.051. However, no significant association with regarding to gender, systemic history of diabetes, smoking, BMI was found in our study. Statistical association was found in our study, between selenium levels and Thyroid receptor antibody, Thyroid profile and Clinical Activity score. A study of lack of association between Se status and disease severity and activity in patients with Graves ophthalmopathy by Nora Dehina et al, in 2015. [20] In 2012 Khong et al [21] reported mean Se levels appear to decrease in parallel to increase in severity of GO. Still, the effect of severity of GO on serum selenium is marginal in their study, supporting our notion that severity and activity of GO is not a determinant of serum Se status. Wu et al [18] study also supports no correlation between serum selenium and TSH levels. CAS is also found to be unrelated to the thyroid hormone and TSH levels. Various interventional studies have found a association between Selenium supplementation and reduction in thyroid hormone and antibody levels. Duntas et al [22] in 2003 demonstrated a significant decrease in TPO antibodies of 46% over 3month period and 55.5% at 6month period after Se supplementation. Gartner et al [23] in 2002 also demonstrated a significant reduction in TPO antibodies in selenium supplemented group in comparison to the placebo group in autoimmune thyroiditis patients.

Limitations of our study are

- Inadequate volume of the study
- Shorter study period
- Lack of control group
- Patients from the same geographical area
- Lower number of female patients
- One time analysis

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- Observational study

CONCLUSION

In our study, we conclude that GO activity found to have a direct association with the serum selenium levels in contrast to the previous studies. There is a correlation between serum selenium levels and TRAB, TPO antibody levels. Hence, a randomized controlled trial with a larger sample size eliminating the geographical area as confounding bias is crucial to clarify this issue.

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