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Association Of Subclinical And Overt Hypothyroidism On Red Blood Cell Indices Together With Reticulocyte Counts.

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ABSTRACT

Thyroid diseases are arguably the most common endocrine disorder worldwide. Thyroid hormones play an important role in haematopoiesis and erythropoiesis. Both anemia and thyroid diseases due to their high prevalence and close relation, are significant clinical problems often encountered during treatment. Hemoglobin concentration was reported to be significantly lower in both patients with increased and decreased thyroid stimulating hormone. Observational cross-sectional study for 2 years among patients were recruited from endocrinology OPD and general medicine OPD. 125 samples processed Patients were grouped in to subclinical and overt hypothyroidism based on their thyroid status. 2 mL of the sample was collected in serum tube and 2 mL in K_2 EDTA tube Complete thyroid profile including TSH, FT4, FT3, T3 &T4 was assessed with fully automated Electro chemiluminescence immunoassay (ECLIA) from Cobas e411 Roche diagnostics which is a closed system. The data was analysed using SPSS (Statistical Package for Social Science) Version16.01. Continuous variables were presented as mean ± SD (standard deviation) and categorical variables were represented as frequencies and percentages. Non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. Spearman Correlation and scatterplot were used to explore the correlation between the two variables, as at least one of the variables. There was a significant difference observed in TSH concentration between gender and age among subclinical and overt hypothyroidism

Keywords: Anaemia, overt hypothyroidism, red blood cell indices, subclinical hypothyroidism, thyroid profile

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INTRODUCTION

Thyroid diseases are arguably the most common endocrine disorder worldwide [1]. According to various studies conducted it has been estimated that nearly 42 million Indian populations is suffering from thyroid diseases. Among them primary hypothyroidism is the most prevalent disorder [2]. Hypothyroidism causes a protracted course of illness varies from asymptomatic to severe myxoedema coma. Hypothyroidism causes a metabolic deceleration affecting all organ system. Hematopoietic system is the primary among these affected organ system [3]. Thyroid hormones play an important role in haematopoiesis and erythropoiesis. It exerts a direct stimulating effect on the proliferation of erythrocyte precursors, also it promotes erythropoiesis by increasing erythropoietin gene expression and erythropoietin production in the kidneys [4].

Both anemia and thyroid diseases due to their high prevalence and close relation, are significant clinical problems often encountered during treatment. Hemoglobin concentration was reported to be significantly lower in both patients with increased and decreased thyroid stimulating hormone [5]. Hence, the severity of anemia is proportional to the degree of hypothyroidism. Anemia in hypothyroidism can be normochromic normocytic, hypochromic microcytic and macrocytic. Present study done to evaluate following things.

To evaluate association of hypothyroidism and anemia by comparing thyroid function test and red blood cell indices including Hb, MCV, MCH and reticulocyte count

MATERIALS AND METHODS

The study protocol was approved by the Institutional Ethics committee.

Informed consent

Was obtained from all the participants in the study before their enrolment in to the study.

Study design: Observational cross-sectional study

Study duration: 1 Year.

Sample size: 125 Samples

Sample size estimated using the formula:

$$\text{Sample size} = z2xpxq/r2$$

Z=1.96, p= 43.3 %, q=56.7%, r=8.66

Study period: 1 year

Source of study population:

All the patients were recruited from endocrinology OPD and general medicine OPD.

Study group

Patients were grouped in to subclinical and overt hypothyroidism based on their thyroid status.

Group 1: total number of cases of primary subclinical hypothyroidism is 100

Primary subclinical hypothyroidism defined as elevated thyroid stimulating hormone (TSH) above the reference range (0.4 to 4.2mIU/ml). with normal free T4 levels with no specific symptoms of hypothyroidism.

Patient will be recruited after fulfilling the inclusion and exclusion criteria

Group 2: Total number of cases of primary overt hypothyroidism is 25 cases.

Primary overt hypothyroidism, Defined as elevated TSH above 10 mIU/ml with decreased levels of free T4 with or without obvious symptoms of hypothyroidism.

Inclusion criteria

- Patients with primary subclinical hypothyroidism.
- Patients with primary overt hypothyroidism with or without obvious classical symptoms of hypothyroidism.
- Both male and female patients
- Age above 18 years.

Exclusion criteria

- Patients with acute illness and critically ill
- Patients with malignancy
- Female patients with pregnancy
- Patients on antithyroid medication and steroids
- Patients with history of gastro-intestinal bleeding
- Patients on iron supplement therapy
- Patients with chronic kidney diseases
- Patients with chronic liver disease
- Patient with history of gastrointestinal surgery affecting iron absorption (i.e gastrectomy, bowel loop surgery)
- Patient with history of thyroid surgery
- Patients with hemoglobinopathies.
- Patients with connective tissue disorders
- Patients with hemorrhoids.

Sample Collection

Morning random blood sample was collected from all subjects. 2 mL of the sample was collected in serum tube and 2 mL in K_2 EDTA tube. After adequate clotting achieved, serum tube is centrifuged for 10 minutes at room temperature at 3500 rpm, further the aliquoted serum sample was used for the estimation of thyroid profile and Hemoglobin along with red blood cell indices.

Assay

Complete thyroid profile including TSH, FT4, FT3, T3 &T4 was assessed with fully automated Electro chemiluminescence immunoassay (ECLIA) from Cobas e411 Roche diagnostics which is a closed system. ALL the assay was performed as per the manufacture's specifications. A two-level QC was regularly run before testing patient's samples to eliminate bias and imprecision.

Statistical analysis

The data was analysed using SPSS (Statistical Package for Social Science) Version16.01. The data collected was tabulated in excel sheet and analysed. Continuous variables were presented as mean ± SD (standard deviation) and categorical variables were represented as frequencies and percentages. For the non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. Median and inter quartile ranges were applied among different groups for gender differentiation, and Spearman Correlation and scatterplot were used to explore the correlation between the two variables, as at least one of the variables.

Age, gender, TSH, Total T3 and T4, free t3 and t4, complete blood counts were compared between the study groups. All the Statistical results were considered to be significant at P value ≤0.05.

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RESULTS

Continuous variables were presented as mean ± SD (standard deviation) and categorical variables were represented as frequencies and percentages.

Non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. Median and inter quartile ranges were applied among different groups gender differentiation

Spearman Correlation and scatterplot were used to explore the correlation between the two variables, as at least one of the variables.

There was a significant difference observed in TSH concentration between gender and age among subclinical and overt hypothyroidism.

Table I: Comparison of the 2 Subgroups of the Variable Gender in Terms of TSH (mIU/L) in (Hypothyroidism: Subclinical) (n = 100)

TSH (mIU/L)	Gender		t-test	
	Male	Female	t	p value
Mean (SD)	7.74 (1.76)	7.23 (1.35)	1.115	0.279
Median (IQR)	8.45 (6.25-9.12)	7.4 (6.35-8)		
Range	4.7 – 10	4.8 – 12		

There was no significant difference between the groups in terms of TSH (mIU/L) (t = 1.115, p = 0.279).

The Box-and-Whisker plot below depicts the distribution of TSH (mIU/L) in the 2 groups. The middle horizontal line represents the median TSH (mIU/L), the upper and lower bounds of the box represent the 75th and the 25th centile of TSH (mIU/L) respectively, and the upper and lower extent of the whiskers represent the Tukey limits for TSH (mIU/L) in each of the groups.

Graph I Association between gender and TSH

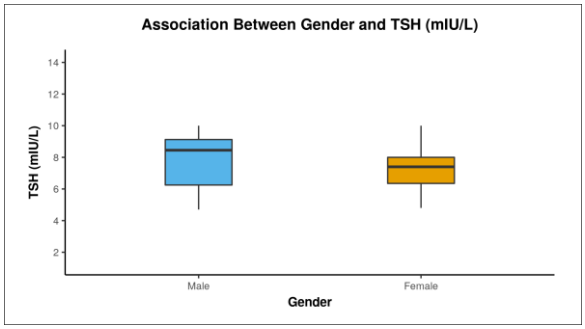

Table II: Comparison of the 2 Subgroups of the Variable Gender in Terms of TSH (mIU/L) in (Hypothyroidism: Overt) (n = 25)

TSH (mIU/L)	Gender		Wilcoxon-Mann-Whitney U Test	
	Male	Female	W	p value
Mean (SD)	21.06 (2.48)	26.44 (7.65)	30.000	0.185
Median (IQR)	22 (19-22.3)	25.75 (19.85-32.25)		
Range	18 - 24	15 – 40		

There was no significant difference between the groups in terms of TSH (mIU/L) (W = 30.000, p = 0.185).

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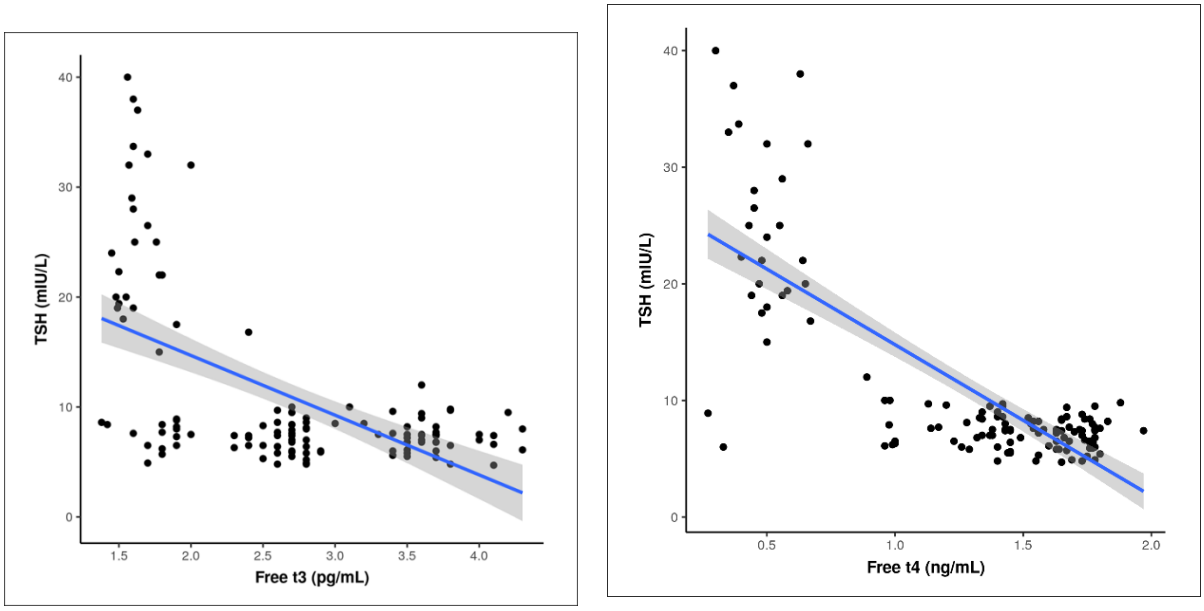
The Box-and-Whisker plot below depicts the distribution of TSH (mIU/L) in the 2 groups. The middle horizontal line represents the median TSH (mIU/L), the upper and lower bounds of the box represent the 75th and the 25th centile of TSH (mIU/L) respectively, and the upper and lower extent of the whiskers represent the Tukey limits for TSH (mIU/L) in each of the groups.

Correlation between Free t3 (pg/mL) and TSH (mIU/L) (n = 125)

Correlation between Free t4 (ng/mL) and TSH (mIU/L) (n = 125)



Graph II: Correlation between TSH concentration and Thyroid hormones.

Graph III: Correlation between Hemoglobin (g/dL) and TSH (mIU/L)

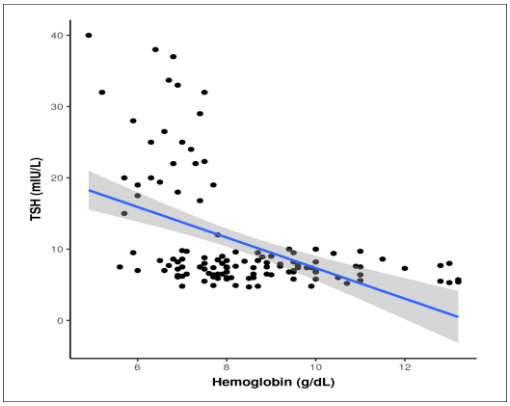


Table III: Correlation between Hemoglobin (g/dL) and TSH (mIU/L)

Correlation	Spearman Correlation Coefficient	P Value
Hemoglobin (g/dL) vs TSH (mIU/L)	-0.5	<0.001

There was a moderate negative correlation between Hemoglobin (g/dL) and TSH (mIU/L), and this correlation was statistically significant (rho = -0.46, p = <0.001).

For every 1-unit increase in Hemoglobin (g/dL), the TSH (mIU/L) decreases by 2.14 units.

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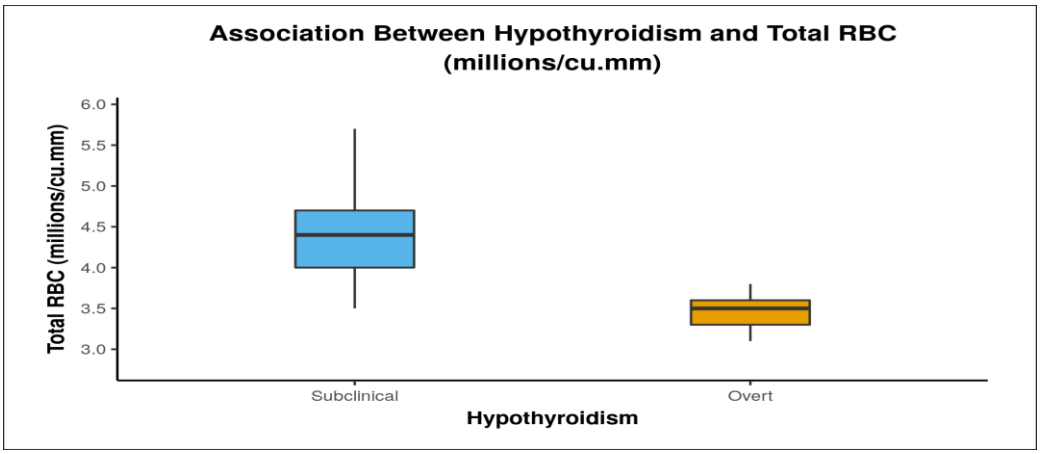
Conversely, for every 1-unit increase in TSH (mIU/L), the Hemoglobin (g/dL) decreases by 0.11 units.

Table IV: Comparison of the 2 Subgroups of the Variable Hypothyroidism in Terms of Total RBC (millions/cu.mm) (n = 125)

Total RBC (millions/cu.mm)	Hypothyroidism		Wilcoxon-Mann-Whitney U Test	
	Subclinical	Overt	W	p value
Mean (SD)	4.35 (0.43)	3.46 (0.18)	2449.500	<0.001
Median (IQR)	4.4 (4-4.7)	3.5 (3.3-3.6)		
Range	3.5 - 5.7	3.1 - 3.8		

There was a significant difference between the 2 groups in terms of Total RBC (millions/cu.mm) (W = 2449.500, p = <0.001), with the median Total RBC (millions/cu.mm) being highest in the Hypothyroidism: Subclinical group.

The Box-and-Whisker plot below depicts the distribution of Total RBC (millions/cu.mm) in the 2 groups. The middle horizontal line represents the median Total RBC (millions/cu.mm), the upper and lower bounds of the box represent the 75th and the 25th centile of Total RBC (millions/cu.mm) respectively, and the upper and lower extent of the whiskers represent the Tukey limits for Total RBC (millions/cu.mm) in each of the groups.



Graph V: Correlation between Total RBC (millions/cu.mm) and TSH (mIU/L) in (Hypothyroidism: n = 125

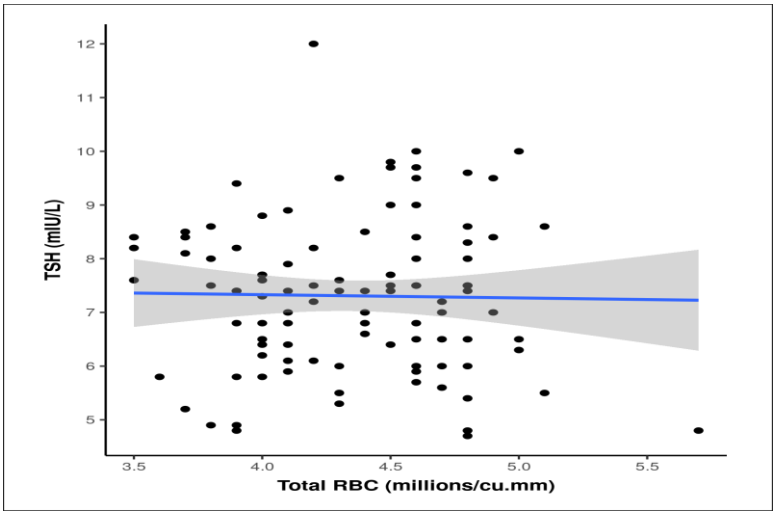


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Table V: Correlation between Total RBC (millions/cu.mm) and TSH

Correlation	Spearman Correlation Coefficient	P Value
Total RBC (millions/cu.mm) vs TSH (mIU/L)	-0.0	0.905

There was a weak negative correlation between Total RBC (millions/cu.mm) and TSH (mIU/L), and this correlation was not statistically significant (rho = -0.01, p = 0.905).

Graph VI: Correlation between MCV (fL) and TSH (mIU/L) in (Hypothyroidism: n = 125)

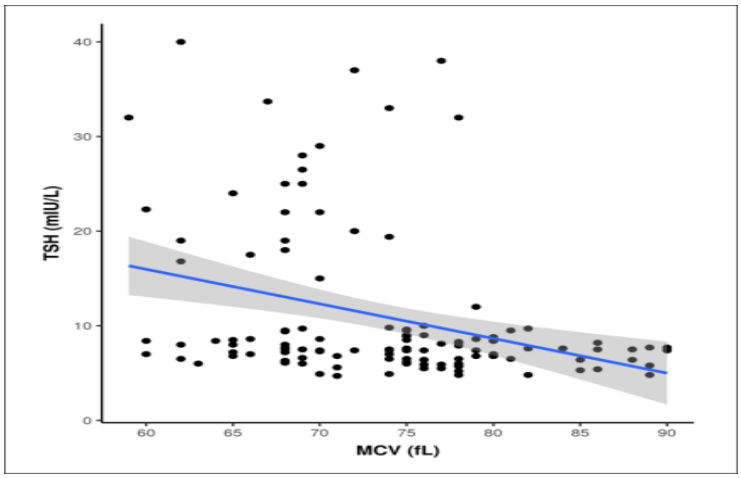

Table VI: Correlation between MCV (fL) and TSH (mIU/L)

Correlation	Spearman Correlation Coefficient	P Value
MCV (fL) vs TSH (mIU/L)	-0.3	<0.001

There was a moderate negative correlation between MCV (fL) and TSH (mIU/L), and this correlation was statistically significant (rho = -0.31, p = <0.001).

For every 1-unit increase in MCV (fL), the TSH (mIU/L) decreases by 0.37 units.

Conversely, for every 1-unit increase in TSH (mIU/L), the MCV (fL) decreases by 0.30 units.

Graph VII: Correlation between MCH (pg) and TSH (mIU/L) in (Hypothyroidism: Subclinical) (n = 100)

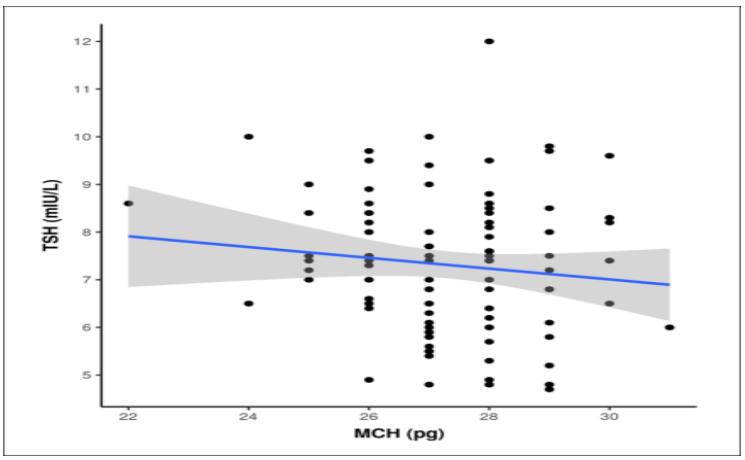

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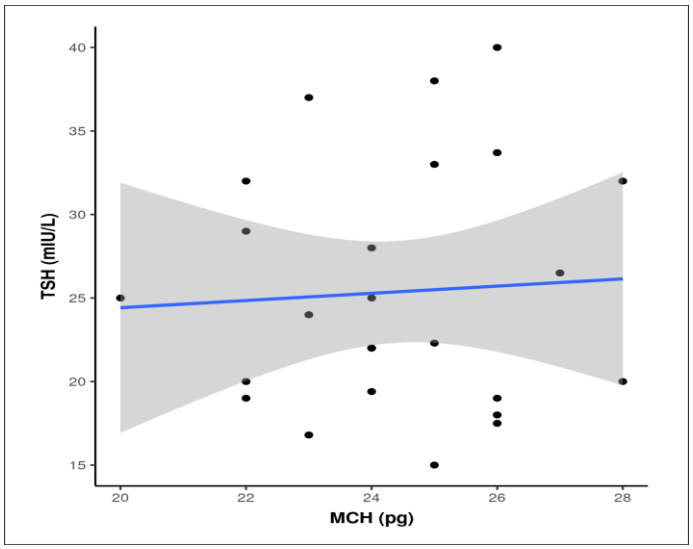
Table VII: Correlation between MCH (pg) and TSH (mIU/L) in (Hypothyroidism: Sub clinic

Correlation	Spearman Correlation Coefficient	P Value
MCH (pg) vs TSH (mIU/L)	0.0	0.902

The above scatterplot depicts the correlation between MCH (pg) and TSH (mIU/L). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.

Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

There was a weak negative correlation between MCH (pg) and TSH (mIU/L), and this correlation was not statistically significant (rho = -0.1, p = 0.316).



Graph VIII: Correlation between MCH (pg) and TSH (mIU/L) in (Hypothyroidism: Overt) (n = 25)

The above scatterplot depicts the correlation between MCH (pg) and TSH (mIU/L). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.

Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

There was a weak positive correlation between MCH (pg) and TSH (mIU/L), and this correlation was not statistically significant (rho = 0.03, p = 0.902).

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Graph IX: Correlation between Reticulocyte Count (%) and TSH (mIU/L) in (Hypothyroidism: Subclinical) (n = 100)

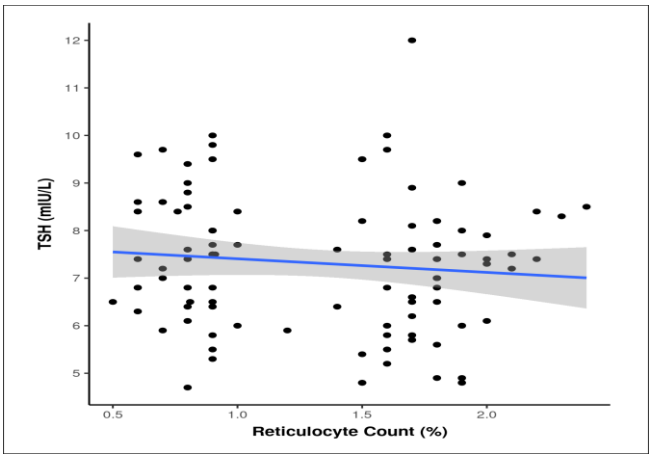

Table VIII: Correlation between Reticulocyte Count (%) and TSH (mIU/L) in (Hypothyroidism: Subclinical) (n = 100).

Correlation	Spearman Correlation Coefficient	P Value
Reticulocyte Count (%) vs TSH (mIU/L)	-0.1	0.247

The above scatterplot depicts the correlation between Reticulocyte Count (%) and TSH (mIU/L). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline. Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

There was a weak negative correlation between Reticulocyte Count (%) and TSH (mIU/L), and this correlation was not statistically significant (rho = -0.12, p = 0.247).

Graph X: Correlation between Reticulocyte Count (%) and TSH (mIU/L) in (Hypothyroidism: Overt) (n = 25)

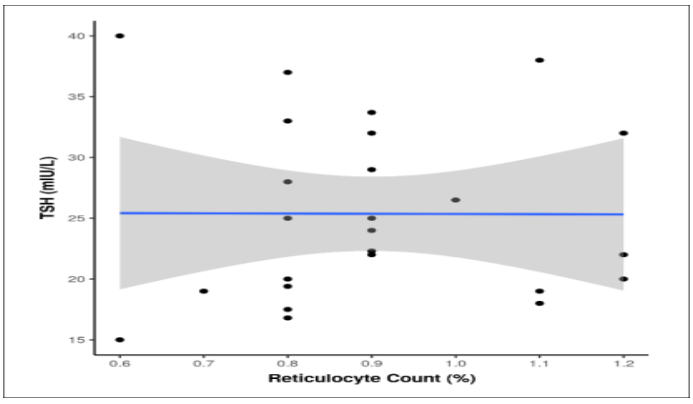

Table IX: Correlation between Reticulocyte Count (%) and TSH (mIU/L) in (Hypothyroidism: Overt) (n = 25)

Correlation	Spearman Correlation Coefficient	P Value
Reticulocyte Count (%) vs TSH (mIU/L)	0.1	0.639

The above scatterplot depicts the correlation between Reticulocyte Count (%) and TSH (mIU/L). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline.

Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

There was a weak positive correlation between Reticulocyte Count (%) and TSH (mIU/L), and this correlation was not statistically significant (rho = 0.1, p = 0.639).

DISCUSSION

Thyroid hormones play crucial role in normal development, differentiation, metabolic balance, and physiological function of virtually all tissues and thyroid function [6-10].

Presence of anaemia in hypothyroidism is because of bone marrow depression, decreased erythropoietin production, comorbid diseases, or concomitant iron, vitamin B12, or folate deficiency. Another cause of anaemia in hypothyroidism is Altered iron metabolism and oxidative stress. The coexistence of anaemia and thyroid disease constitutes a very important clinical problem [11=13].

Thyroid hormones stimulate erythropoiesis and also increase erythrocyte 2,3-DPG concentrations, which ultimately enhance the delivery of oxygen to tissues [14]. Low level of thyroid hormones cause anaemia and may be normocytic, hypochromic-microcytic, or macrocytic [15]. Anemia is not common finding in hyperthyroidism but when present may be morphologically similar to that observed in hypothyroidism. Continued attention to hematologic profile is very crucial in the management of patients with thyroid disorder [16, 17].

In this study the overall patients presented with hypothyroidism were divided in to two sub groups including subclinical and overt hypothyroidism which indicates mildly elevated TSH level with normal thyroid hormone in peripheral blood and the latter being elevated TSH with low ft4 levels respectively.

The present study shows that there is a significant association between anaemia and hypothyroidism, also the severity of anaemia increases substantially with increase in TSH concentration. Gender and age distribution of hypothyroidism was unequally distributed in overall cases of hypothyroidism in which females are affected significantly more than males in both the groups of subclinical and overt hypothyroidism with 84 % and 80% respectively.

Reported cases of overt hypothyroidism were found in younger age group than the older age groups, likewise the average age groups of patients with subclinical hypothyroidism were 43 years which is proportionately higher in comparison to overt hypothyroidism, our findings are similar to previous epidemiological study where the highest prevalence was noted in age group of 45.85 (14.68) [18]. Overall prevalence of hypothyroidism in India is higher in compared to western population which is presumably due to partially corrected iodine deficiency in rural regions of the country [19]. Thyroid hormone levels were significantly lower in all age groups and gender with a compensatory increase in TSH concentration as a feedback response (Graph II) illustrate the negative correlation physiological response between TSH and thyroid hormones.

In this study there was a significant negative correlation between thyrotropin, hemoglobin and MCV levels which is represented in the scatterplot with a p value <0.001 9 (graph III & VI), similar observation was reported by several authors previously [20, 21], however there are few other studies reported contradictory and inconsistent findings where the changes in RBC indices in thyroid dysfunction exhibit coarse uniformity requiring more profound studies to evaluate further.

On the other hand, decrease in RBC mass also strictly one of the reasons for the cause of anemia in our study patients with subclinical hypothyroidism had RBC within limits yet there was a notable decrease in RBC mass in patients with over hypothyroidism this may indicates that the progression of

hypothyroidism might play a role in erythropoiesis or which may affect synthesis of erythropoietin hormone [22-25].

There was varying findings described in individual case control and observational studies in which thyroid dysfunction was associated with anemia and abnormal RBC indices however mechanism by which changes in thyroid hormone status leads to anemia is not fully understood [26].

In a prospective cohort study reported that subclinical hypothyroidism is not associated with anemia however the coexisting conditions like chronic inflammatory disorders which might influence and probably could over estimate anemia in thyroid dysfunction was not eliminated in the same study [27].

Further in this present study we report that hypothyroidism is not associated with other RBC including MCH and reticulocytes our finding markedly differs from recent observational studies where many authors reported significant association between hypothyroidism and other battery of tests accommodated in RBC indices apart from RBC mass and HB concentration were HCT, MCH, MCHC, RDW the possible explanation could be that the effect of clinical hypothyroidism on the hematopoietic cells in its initial stages of the disease is apparently weaker with varying degrees of severity.

The major limitations of the study are confounding by indication and the population selection as all the patients recruited in this study are all referred to a tertiary care hospital which may not reflect a true prevalence of disease present in the population also concerning the financial constraint and logistical reasons the sample size was optimised, recruitment of larger population in this descriptive observational study might have been a significant advantage. Nonetheless in this present study we able to demonstrate the effect of hypothyroidism on RBC parameters which needs to be evaluated further and in addition the association and effect of physiologically active free thyroid hormone on erythropoiesis per se needed additional studies.

CONCLUSION

In this present study we report a significant difference observed in TSH concentration between gender and age among subclinical and overt hypothyroidism groups, also we describe the significant association between hypothyroidism and reduction in haemoglobin concentration and MCV, yet another evidence that anemia is a coexisting disorder in patients with hypothyroidism.

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