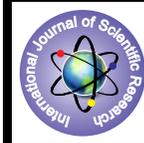


## Effect of Thyroid Hormones on Blood Cell Counts and Blood Cell Indices in Untreated and Treated Sub Clinical Hypothyroidism in Shivamogga Population



### Medical Science

**KEYWORDS :** Subclinical Hypothyroidism, Blood cell counts, Blood cell indices, L-Thyroxine.

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### ABSTRACT

**Background:** Thyroid hormones play an important physiological role in maintaining the metabolic balance of the entire body. Erythrocyte abnormalities are commonly associated with thyroid dysfunction. Thyroid dysfunction induces different effects on blood cell counts and blood cell indices.

**Aims and objectives:** To estimate blood cell counts and blood cell indices in newly diagnosed Subclinical hypothyroid patients and to evaluate the efficacy of the L-thyroxine treatment on the same in Shivamogga population.

**Materials and methods:** We measured Red blood cell count (RBC), White blood cells / Total leukocyte count (TLC), Differential leukocyte count (DLC), platelet (PLT) count, blood cell indices like haemoglobin [Hb] concentration, mean corpuscular volume [MCV], mean corpuscular haemoglobin [MCH], mean corpuscular haemoglobin concentration [MCHC], hematocrit (HCT) / Packed cell Volume (PCV) and Red cell distribution width (RDW) in 100 newly diagnosed subclinical hypothyroid patients & compared it with the euthyroid controls. The same patients were reevaluated after treatment with L-thyroxine at the end of three months. Statistical analysis was done using independent T test. Pearson's correlation coefficient test was done to establish the relationships between the parameters.

**Results:** RBC count was significantly decreased in newly diagnosed Subclinical hypothyroid patients when compared to euthyroid subjects. There was no significant difference in TLC, DLC and Platelet count. Blood cell indices like Hb, MCV, MCH, MCHC and HCT were significantly decreased and RDW was significantly increased when compared with the euthyroid controls. After three months of L-thyroxine treatment, haemoglobin, RBC count, HCT, MCV, MCH, MCHC showed significant increase and there was decrease in RDW which was statistically significant.

**Conclusion:** Thyroid dysfunction induces varied effects on haematological parameters and early intervention with thyroid replacement therapy resulted in reversible change in the haematological parameters.

### Introduction:

Thyroid is one of the largest endocrine glands<sup>1</sup> located immediately below the larynx on either side of the trachea. The principal hormones of thyroid gland are tetra-iodo-L-thyronine or thyroxine (T<sub>4</sub>) and tri-iodo-L-thyronine (T<sub>3</sub>). Thyroid stimulating hormone (TSH) is the anterior pituitary hormone regulating thyroid functions<sup>2</sup>. In normal individuals, the thyroid hormones and TSH have physiological variations according to age<sup>3</sup>, sex<sup>4</sup>, nutrition<sup>5</sup> and race. The thyroid undergoes slight physiological changes with aging, either as a result of its participation in the senescence process or as an effect of changes in other systems<sup>6</sup>. Thyroid hormones are essential for the normal development, differentiation, metabolic balance, and physiological function of virtually all tissues and thyroid function disorders are among the most common endocrine diseases<sup>7</sup>. Hypothyroidism is the most common functional disorder of the thyroid gland. Pathology of the thyroid gland (primary hypothyroidism) accounts for over 99.5% of cases of thyroid gland failure and < 0.5% result from disorders of the pituitary gland or hypothalamus (central hypothyroidism). Overt primary hypothyroidism refers to cases in which the serum thyrotropin (TSH) concentration is elevated and the serum T<sub>3</sub> and T<sub>4</sub> levels are below the reference range, while subclinical hypothyroidism is defined as an elevated serum TSH value associated with a serum T<sub>3</sub> and T<sub>4</sub> that is still within the reference range<sup>8</sup>.

The incidence of overt hypothyroidism has been estimated to be 4.1 cases per 1000 women per year and 0.6 cases per 1000 men per year<sup>9</sup>. The prevalence has been reported to be approximately 1-2% in women and 0.1% in men in large population studies<sup>10-12</sup>. However, the prevalence of subclinical hypothyroidism is approximately 4-8.5%; it can reach to 20% in women aged 60 years or older<sup>13</sup>. In iodine deficient areas such as India, the incidence can reach as high as 10-20 times more than non-iodine areas like U.S.A<sup>10, 14-15</sup>. Subclinical hypothyroidism may progress to overt hypothyroidism in ap-

proximately 2-5% cases annually. All patients with subclinical hypothyroidism with TSH > 10 μ IU/L should be treated<sup>16</sup>. Anaemia is a decrease in number of red blood cells (RBC's) or less than the normal quantity of haemoglobin in the blood. Anaemia can have several reasons, such as, abnormality of the formation<sup>17</sup> and reduction on the half life of the red cells<sup>18</sup>. The size is reflected in mean corpuscular volume (MCV). The prevalence of anaemia in patients with hypothyroidism has been shown to be 20-60%<sup>19</sup>. Thyroid hormone is involved in haemoglobin synthesis in adults and maturation of haemoglobin in foetus<sup>20, 21</sup> and by affecting hematopoietic process; hypothyroidism results in anaemia through slowing the oxygen process<sup>22, 23</sup>.

The present study was therefore undertaken to compare the haematological parameters between Euthyroid normal subjects and untreated subclinical hypothyroid patients and then to compare the haematological parameters between untreated and treated Subclinical hypothyroid patients of Shivamogga district.

### Materials and methods:

With the approval of the Institutional ethics committee and the informed consent of the participants, a total number of 100 Euthyroid individuals and 100 Subclinical hypothyroid patients of ages 30-65 years were chosen for the study. Subclinical hypothyroid patients were treated and after 3 months of therapy, they were evaluated again for the haematological parameters.

**Exclusion criteria:** Patients with cardiovascular, cerebrovascular and neurological diseases, uncontrolled hypertension, Diabetes mellitus, chronic renal failure and pregnant females were excluded from the study. All female patients were asked about their menstrual period duration, frequency, and amount of bleeding. Patients with a menstrual period lasting more than 5 days or more than usual amount of bleeding were excluded from study.

**Sample collection:** About 5-6 ml of venous blood was collected in EDTA Vacutainer [BD Biosciences] from antecubital vein from each patient. EDTA anti coagulated blood samples were processed in Haematology Analyser (cell counter) Erba –Sysmax (XP-100). CBC and Hemogram comprised of RBC count, White blood cells/ Total leukocyte count (TLC), Differential leukocyte count (DLC) which included lymphocyte % neutrophils % and mixed pool %, platelet (PLT) count, Hb concentration, MCV, MCH, MCHC, HCT/PCV and RDW.

Estimation of thyroid profile was done by Lilac kit by using a Chemiluminescence method. The following three parameters were estimated under thyroid profile.

Tri-iodo-L-thyronine (T<sub>3</sub>)

Tetra-iodo-L-thyronine (T<sub>4</sub>)

Thyroid stimulating hormone (TSH).

Diagnosis of Sub clinical hypothyroidism was established based on clinical signs and symptoms and the T<sub>3</sub>, T<sub>4</sub> and TSH estimations.

**Statistical Analysis:**

Data obtained was entered into Microsoft Excel sheet and statistical analysis was performed by SPSS software. Results were reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. Statistical analysis was done using independent T test to evaluate the significance of differences between two groups. P- Value of <0.05 was considered as statistically significant.

**Results:**

**Table-1: Demographic profile of the subjects**

Groups	Healthy controls / Euthyroid		Sub clinical hypothyroid	
	M	F	M	F
Sex				
Number (n)	30	70	24	76
Mean age(Yrs)	53.43	49.33	53.54	50.39

Table-1 shows the demographic profile of the study groups. The mean age & number of the patients in Euthyroid pool and Sub clinical hypothyroid pool was shown in Table-1.

**Table-2: Thyroid profile of the study groups: mean ± SD**

Parameter	Healthy controls / Euthyroid [Mean (SD)]	Untreated Sub clinical hypothyroid	Treated Sub clinical hypothyroid
TSH ( μ IU/ml)	3.267±1.407	11.277±1.599	6.242±0.493
Total T3 (ng/dl)	0.993±0.187	0.992±0.188	0.993±0.187
Total T4 (μg/dl)	8.873±2.021	8.831±2.0045	8.873±2.021

Table-2 shows the Thyroid profile of the study groups. Mean ±SD values of TSH, T<sub>3</sub> & T<sub>4</sub> in euthyroid pool were 3.267±1.407 μ IU/ml, 0.993±0.187 ng/dl and 8.873±2.021μg/dl respectively. Subclinical hypothyroid patients were diagnosed based on clinical signs and symptoms and a raised TSH value. Mean ±SD value of TSH in SCH patients was 11.277±1.599 μ IU/ml and after 3 months of therapy, mean ±SD value of TSH was 6.242±0.493 μ IU/ml respectively and is illustrated in Table-2.

**Table-3: Complete Hemogram of the study groups: mean ± SD**

Parameter	Healthy controls / Euthyroid [Mean (SD)]	Untreated Sub clinical hypothyroid	Treated Sub clinical Hypothyroid
Hb (gm%)	12.083±1.451	10.384±1.095	11.534±1.0084
Total RBC count (10 <sup>6</sup> cells/cumm)	4.249±0.367	3.902±0.315	4.255±0.234
WBC Count / TLC (10 <sup>3</sup> cells/cumm)	8.483±1.879	7.956±1.602	7.869±1.535
Neutrophils (%)	62.41±12.360	61.05±9.462	60.19±8.035
Lymphocytes (%)	32.31±11.284	34.21±9.394	35.23±8.048
Mixed pool (%)	5.30±2.584	4.72±2.118	4.56±2.017
Platelet count (10 <sup>5</sup> cells/cumm)	2.67±6.532	2.68±6.644	2.62±6.006
PCV/Hematocrit (%)	37.254±4.486	31.557±3.089	34.790±3.131
MCV (f l)	87.267±4.262	79.026±2.328	81.610±2.791
MCH (pg)	28.379±1.613	26.520±1.596	27.232±1.088
MCHC (%)	32.699±0.708	32.234±0.923	33.240±0.405
RDW (%)	14.563±1.604	16.155±0.939	15.209±0.843

Table-3 shows the complete Hemogram of the study groups. In untreated subclinical hypothyroid patients, the Mean ±SD values of Blood cell counts were RBC (3.902±0.315 x10<sup>6</sup> cells/cumm), WBC which included Total leukocyte count (7. 956± 1.602 x 10<sup>3</sup> cells/cumm), & Differential leukocyte count like lymphocyte (34.21±9.394) % , neutrophils (61.05±9.462)%, mixed pool (4.72±2.118)% and Platelets (PLT- 2.68±6.644 x10<sup>5</sup> cells/cumm ) and Mean ±SD values of blood cell indices were Hb (10.384±1.095) gm%, MCV (79.026±2.328) fl, MCH (26.520±1.596) pg, MCHC (32.234±0.923)%, HCT/PCV (31.557±3.089)% and RDW (16.155±0.939)% respectively. There was a statistically significant decrease in RBC Count and blood cell indices like Hb, MCV, MCH, MCHC, HCT/PCV and increase in RDW which supports the fact that these patients are at risk of normocytic anaemia. Patients treated with thyroxine therapy show correction in these erythrocyte abnormalities. As compared with patients with the euthyroid status, RDW values showed statistically highly significant difference.

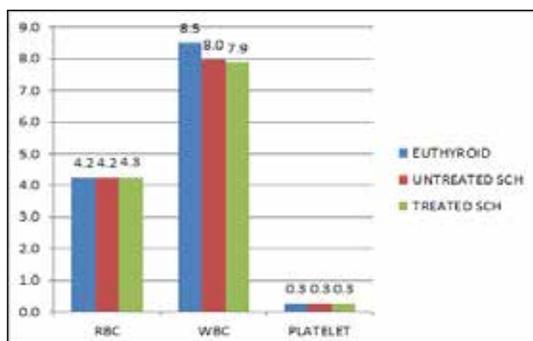
**Table-4: Comparison of the haematological parameters and thyroid hormone levels in Untreated & treated sub-clinical hypothyroid patients with healthy Euthyroid controls.**

Parameter	Healthy controls / Euthyroid [Mean (SD)]	Sub clinical hypothyroid (SCH) Untreated	Sub clinical Hypothyroid Treated	Untreated SCH Vs treated SCH (p-value)
TSH ( μ IU/ml)	3.267±1.407	11.277±1.599 P<0.001, H.S*	6.242±0.493 P<0.001, H.S*	P<0.001, H.S*
Total T3 (ng/dl)	0.993±0.187	0.992±0.188 P=0.955, N.S	0.993±0.187 N.S	P=0.955, N.S
Total T4 (μg/dl)	8.873±2.021	8.831±2.0045 P=0.884, N.S	8.873±2.021 N.S	P=0.884, N.S
Hb (gm%)	12.083±1.451	10.384±1.095 P<0.001, H.S*	11.534±1.0084 P=0.002, H.S*	P<0.001, H.S*
Total RBC count (10 <sup>6</sup> cells/cumm)	4.249±0.367	3.902±0.315 P<0.000, H.S*	4.255±0.234 P=0.896, N.S	P<0.001, H.S*
WBC Count / TC(10 <sup>3</sup> cells/cumm)	8.483±1.87	7.956±1.602 P=0.034, Sig*	7.869±1.535 P=0.012, Sig*	P=0.695, N.S
Neutrophils (%)	62.41±12.360	61.05±9.462 P=0.383, N.S	60.19±8.035 P=0.134, N.S	P=0.489, N.S
Lymphocytes (%)	32.31±11.284	34.21±9.394 P=0.197, N.S	35.23±8.048 P=0.037, Sig*	P=0.411, N.S
Mixed pool(%)	5.30±2.584	4.72±2.118 P=0.084, N.S	4.56±2.017 P=0.025, Sig*	P=0.585, N.S

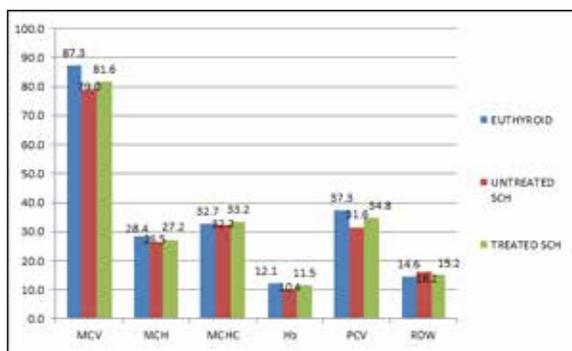
Platelet ((10 <sup>9</sup> cells/cumm)	2.67±6.532	2.68±6.644 p-0.958, N.S	2.62±6.006 P=0.575, N.S	P=0.542, N.S
PCV/Hematocrit (%)	37.254±4.486	31.557±3.089 P<0.001, H.S*	34.790±3.131 P<0.001, H.S*	P<0.001, H.S*
MCV (fl)	87.267±4.262	79.026±2.328 P<0.001, H.S*	81.610±2.791 P<0.001, H.S*	P<0.001, H.S*
MCH (pg)	28.379±1.613	26.520±1.596 P<0.001, H.S*	27.232±1.088 P<0.001, H.S*	P<0.001, H.S*
MCHC (%)	32.699±0.708	32.234±0.923 P<0.001, H.S*	33.240±0.405 P<0.001, H.S*	P<0.001, H.S*
RDW (%)	14.563±1.604	16.155±0.939 P<0.001, H.S*	15.209±0.843 P<0.001, H.S*	P<0.001, H.S*

**Table-4** shows the comparison of the haematological parameters and thyroid hormone levels in Untreated & treated subclinical hypothyroid patients with healthy Euthyroid controls with respect to T<sub>3</sub>, T<sub>4</sub> and TSH and the data was expressed as mean ± SD. The value of P<0.05, denotes that the results were statistically significant. There was no significant difference in WBC and platelet counts between euthyroid and subclinical hypothyroid patients.

**Fig 1: Blood cell counts in Euthyroid, untreated SCH & treated SCH. (RBC Count X 10<sup>6</sup>, WBC Count X 10<sup>3</sup> and Platelet count X 10<sup>5</sup> cells/cumm) - Bar diagram**



**Fig 2: Red blood cell indices in Euthyroid, untreated SCH & treated SCH. (MCV in fl, MCH in pg, MCHC in %, Hb in gm%, HCT/PCV in % AND RDW in %) - Bar diagrams**



**Discussion:**

Thyroid disorders arguably are the commonest endocrine disorder worldwide with India as no exception<sup>24</sup>. Thyroid hormones have crucial effect on erythropoiesis by induction of erythropoietin secretion and also proliferation of erythroid progenitors<sup>25, 26</sup>. They enhance erythropoiesis through hyper proliferation of immature erythroid progenitors and increase secretion of erythropoietin (EPO) by inducing erythropoietin gene expression. Thyroid hormones also augment repletion of hypoxia inducible factor1 (HIF-1) and then motivate growth of erythroid colonies (BFU-E, CFU-E). These hormones also intensify erythrocyte 2, 3 BPG compactness, which enhances the delivery of oxygen to tissues<sup>27</sup>. Generally it seems that hypothyroidism causes hy-

poplasia in all myeloid cell lineages. With regard to lymphocytes, T<sub>3</sub> is as a precursor substance for normal B cell formation in bone marrow through its mediation of pro-B cell proliferation. Therefore, thyroid disorders can induce different effects on various blood cell lineages<sup>28-31</sup>. Subclinical hypothyroidism is a hidden disorder which is detected during investigation of some other causes. Subclinical hypothyroidism [SCH] is associated with serious complications. Substantial number of patients has risk of SCH getting converted into primary hypothyroidism and developing psychological disturbances<sup>8, 32</sup>. There is increasing prevalence of subclinical hypothyroidism and primary hypothyroidism, especially in women. TSH measurement is well recognized sensitive test for detecting subclinical hypothyroidism. It is the first recommended investigation for detection of thyroid disorder<sup>23</sup>. In our study, major population of the groups with subclinical hypothyroidism were females. Previous study has shown similar finding<sup>33</sup>. Thyroid diseases are frequently associated with erythrocyte abnormalities<sup>24</sup>. Anaemia of hypothyroidism has been ascribed to a physiological compensation for the diminished need of tissues for oxygen. The low plasma erythropoietin levels found in hypothyroid anaemia is in accordance with this hypothesis<sup>8</sup>. Patients with hypothyroidism have a decreased erythrocyte mass due to reduction of plasma volume and may be undetectable by routine measurement such as haemoglobin concentration. Alteration in other haematological parameters such as Hb, HCT, MCV, MCH, WBC count and platelet count is associated with thyroid dysfunction<sup>30</sup>, but all changes return to normal if a euthyroid state is obtained. Pancytopenia is a rare side effect of that its cause is not well understood. Treatment of subclinical hypothyroidism with L-thyroxine in patients with anaemia has beneficial effect on blood count, white blood cell differential count, reticulocyte effect and blood cell indices<sup>34</sup>. The determination made by Christ-Crain and colleagues indicated that erythropoietin values were increased as a result of L-thyroxine treatment in women with sub clinical hypothyroidism<sup>35</sup>. It has been shown that in concurrent hypocoagulopathies, hypothyroidism is associated with increased risk of bleeding and hematologic parameters including MCH, MCV, MCHC, HCT and Hb significantly improve in patients with significant response to L-thyroxine suggesting that standard administration of L-thyroxine is able to reduce TSH level and improve concurrent anaemia<sup>36</sup>.

The present study showed decreased Hb, MCV, MCH, MCHC, RBC and HCT values in untreated subclinical hypothyroid subjects and after therapy they were significantly increased to normal range, but no change was seen in WBC and PLT values. Thus, this study clearly indicates that an aggressive line of treatment is required in Subclinical hypothyroid cases with TSH value greater than 10 µ IU/ml as lot of other parameters are affected in these patients. A timely treatment will help in reducing the complications related to Subclinical hypothyroid cases.

In an earlier study done by us, it was seen that anaemia was of greater incidence in primary hypothyroid cases and was more severe. Post treatment, the effect was seen but not sufficient to completely treat the anaemia. But, in Subclinical hypothyroid cases, anaemia was picked up early and treatment had far better final result than primary hypothyroid cases, thus further substantiating the need to treat subclinical hypothyroid cases at the earliest.

**Conclusion:**

Thyroid hormones (T<sub>3</sub>, T<sub>4</sub>) have significant influence on Erythropoiesis. In the present study in 200 subjects, we

found that there is decrease in levels of haematological parameters like Hb, RBC, MCV, MCH, MCHC, HCT, an increase in RDW in patients with thyroid dysfunction and the levels improved on treatment with L-Thyroxine. Further investigation is needed in studying the role of all types of anaemia, erythrocyte abnormalities with increased sample size in thyroid dysfunction patients at district levels of state. Mass screening of thyroid hormone profile should be done and TSH value greater than 10  $\mu$  IU/ml requires intervention and proper follow-up. Substantial numbers of patients have risk of SCH which could be converted into primary hypothyroidism and develop psychiatric problems. These abnormalities should be investigated and corrected and their presence could steer towards thyroid dysfunction allowing its early management. Hence patients with thyroid disorders should be routinely screened for haematological parameters along with biochemical and hormonal profile assay and should be properly treated based on American endocrinologists' guideline. There is no need to fear from this disease as only locally or externally available foods high in iodine mineral are good source and supplements can be provided.

#### Limitation:

There might be some limitation with this study like small sample size. Anaemia in hypothyroidism can be normochromic normocytic, hypochromic microcytic, and macrocytic. The severity of anaemia is associated with the degree of hypothyroidism. Auto immune thyroid disorders can be seen along with other autoimmune disorders. Failure of vitamin B<sub>12</sub> absorption occurs in pernicious anaemia due to intrinsic factor (IF) deficiency and gastric achlorhydria. Folic acid is another vitamin with impaired intestinal absorption and causes macrocytic anaemia in hypothyroidism. Hence different parameters like Anti Tg positivity, Anti TPO positivity, Vitamin B<sub>12</sub>, Folic acid, Iron and Ferritin also could have been included in the study to find out the relationship between anaemia frequency and anaemia types in patients with subclinical and overt hypothyroidism.

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