A study of hematological parameters and their correlation with thyroid hormone status in non-pregnant women of childbearing age

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Abstract

Introduction: Thyroid imbalances and anaemia due to their high prevalence and close interrelationship constitute a good proportion of problems encountered by practitioners, especially in the female reproductive age group. In a developing country it becomes all the more important to study the relationship between the same as correction of the hormonal imbalance may restore the deranged haematological parameters to normal.

Aims and Objectives: To compare the haematological parameters among the various thyroid hormonal statuses (euthyroid hypothyroid and hyperthyroid) in non-pregnant females.

Materials and Methods: 50 non pregnant females between ages of 18–45 years newly diagnosed with hypothyroidism and hyperthyroidism were taken up for the study. 50 normal age matched females with normal thyroid hormonal levels were taken as controls. The haematological parameters of the three categories were further compared with a p value of <0.05 taken as significant.

Results: There was significant variation in the haematological parameters like Haemoglobin, RBC count, total count highest between the hyper and hypothyroid groups. RDW and AEC was significantly more in hypothyroid groups though within normal limits. No significant variation was seen for MCV indicating the type of anaemia in the hypothyroid group to be of the normocytic type.

Conclusion: Thyroid dysfunction has effect on haematological parameters. Evaluation of anaemia in females must include screening for thyroid dysfunction.

Keywords: Anaemia, Hypothyroid, Hyperthyroid, Haematological parameters, Euthyroid.

Introduction

Thyroid hormones play a vital role in the normal development, differentiation, metabolic balance, and physiological functioning of tissues in the human body. Thyroid disorders constitute a major category of endocrine disorders in day to day practice. A relationship between thyroid hormones and haematological abnormalities has been postulated by many authors.[1] Anaemia is often associated with hypothyroidism, while erythrocytosis has been associated with Grave's disease. Females being more prone to anaemia and thyroid hormonal imbalances specially during the reproductive age group, making it all the more important to study the relationship between thyroid hormones and basic haematological parameters for early intervention and treatment.[2,3] To support these facts it has been observed that bringing back a euthyroid state restores the abnormal haematological parameters to normal in women. The present study aims to explore the relationship of the thyroid hormone levels (both normal and abnormal) with basic haematological parameters in non-pregnant females of the reproductive age group, as no previous study has been done in this part of our country till date.

Materials and Methods

In total, 100 non pregnant female patients, aged 40 to 65 years, with thyroid diseases, who were admitted to our hospital under various clinical departments were taken up for this study. Patients were classified, as having hyperthyroidism (n=50) or hypothyroidism (n=50). The diagnosis of hyperthyroidism was made on the basis of clinical features such as diffuse thyroid swelling exophthalmos, tachycardia, tremor, palpitations and sweating, with supporting laboratory data of reduced levels of serum TSH and elevated levels of serum T3 and T4 (T3>3.6 nmol/L; T4>160 nmol/L TSH<0.35 mIU/L). The existence of symptoms and signs of hypothyroidism like weight gain, dry skin, with laboratory data showing low levels of T3 and T4 and elevation levels of TSH were taken as criteria in diagnosing of hypothyroidism. (T3<1.6 nmol/L; T4<60 nmol/L; TSH>3.5 mIU/L). Only patients who had all T3, T4 and TSH tested were taken up for categorization as hypo and hypothyroid.

A third sex- and age-matched group consisted of 50 females who had normal thyroid functional tests and were thus registered as a euthyroid control group. These were the category of patients who were suspected to have thyroid disorders but were found to be serologically normal as per the serum thyroid hormonal values. (T3:1.8-3.6 nmol/L; T4:60-160 nmol/L; TSH:0.35-3.5 mIU/L).

Inclusion Criteria: Females between 18 – 45 years of age.

Exclusion Criteria: Known cases of hypo or hypothyroidism on treatment. Other exclusion criteria included malignancy, surgery and major trauma within the previous six months, chronic diseases, pregnant ladies, history of bleeding diathesis.

Peripheral blood (2-4 mL) was collected from the 150 subjects and the serum separated and stored at -20^0C. Serum concentrations of T3, T4 and TSH were measured using Electro Chemiluminescence in COBAS C411 auto

analyser. The minimal detectable limits were 0.5 nmol/L for T3, 5 nmol/L for T4 and 0.05 MIU/L for TSH.

Total and differential leukocyte counts were carried on samples obtained from peripheral blood using EDTA samples. Total cell counts were generated from Sysmex XN550 six part haematology analyzer. These parameters (Haemoglobin – Hb, Total Count – TC, RBC count and, red cell indices, RDW and Platelet count) were standardized by routine external and internal quality control checks. Leishman stain was used for peripheral smears.

Statistical Analysis

The results were expressed as mean ± SD. The Statistical software namely SPSS V.20 and R environment ver.3.2.2 were used for the analysis of the data. Microsoft word and Excel were used to generate graphs, and tables. Independent T test was used to find difference between means. P value less than 0.05 considered as significant. The study was approved by the institutional ethical committee.

Results

The thyroid profile of the three study groups were as follows.

Table 1: Distribution of thyroid hormone levels in the three groups

Hormone	Hypothyroid subjects N= 50	Euthyroid subjects N= 50	Hyperthyroid subjects N= 50
T3 (nmol/L)	1.3 ± 0.38	3.11 ± 0.374	3.99 ± 1.63
T4(nmol/L)	52.64 ± 38.24	138.22 ± 143	212.05 ± 15.2
TSH (m IU/L)	142 ± 189.85	1.8 ± 0.6	0.05 ± 0.02

In the present study 50 newly diagnosed cases of hyperthyroidism and hypothyroidism were taken as per criteria mentioned in the methods and 50 cases were randomly selected as controls. All females were taken up for the study as incidence of thyroid dysfunction in male is of relatively low prevalence.

Table 2: Comparison of haematological parameters between hypo and euthyroid subjects

	Hypothyroid subjects N=50	Euthyroid subjects N= 50	p-value
Hb (g/dl)	11.44±1.264	12.58±9.50	0.001*
RBC $x10^6$ µl	4.1 ± 0.32	4.6 ± 0.41	0.001*
MCV (fl)	83.80±6.624	83.06±4.967	0.529
MCH (pg)	28.06±1.114	28.52±1.092	0.04
MCHC (g/dl)	32.36±1.208	33.14±1.050	0.001*
TLC $x10^3$/µl	5992.0±1434.109	7032.0±1275.265	0.001*
PLT $x10^3$ µl	2.50±0.678	2.76±0.687	0.60
RDW %	14.50±1.249	13.02±1.270	0.001*
AEC	400±149.216	260±82.065	0.001*

Hb – Haemoglobin, TLC- Total Leukocyte Count, PLT- Platelet count RBC- Red Blood Cell Count MCV- Mean cell volume, MCH Mean Cell Haemoglobin, MCHC- Mean cell haemoglobin concentration RDW- Red cell distribution width, AEC- Absolute Eosinophil count *- Significant P value

Among the parameters assessed the highest significant P value was found for Haemoglobin, MCHC and RBC count and total leukocyte count between the groups. Haemoglobin was significantly lower with a mean of 11.4 g % indicating the prevalence of anaemia in hypothyroid females. However the cells in both hypothyroid and euthyroid categories were normocytic as evident by the MCV. Although the Total Leucocyte count was significantly lower in the hypothyroid group, it did not go below the normal reference ranges to be categorized as leucopenia. MCH did not show any significant variation in between the two groups

The RDW and AEC was found to be significantly more in hypothyroid subjects. AEC though increased was still within the normal range.

Table 3: Comparison of haematological parameters between hyper and euthyroid subjects

	Hyperthyroid subjects N = 50	Euthyroid subjects N = 50	p-value
Hb (g/dl)	12.82±0.873	12.58±9.50	0.191
RBC $x10^6$ µl	4.8±0.23	4.6 ± 0.41	0.740
MCV (fl)	83.34±5.837	83.06±4.967	0.797
MCH (pg)	28.50±1.111	28.52±1.092	0.928
MCHC (g/dl)	33.14±1.069	33.14±1.050	1.000
TLC $x10^3$/µl	7048±1274.593	7032.0±1275.265	0.950
PLT $x10^3$ µl	2.96±0.755	2.76±0.687	0.169
RDW	13.40±1.370	13.02±1.270	0.154
AEC	228.80±68.947	260±82.065	0.052

Hb – Haemoglobin, TLC- Total Leucocyte Count, PLT- Platelet count RBC- Red Blood Cell Count MCV- Mean cell volume, MCH Mean Cell Haemoglobin, MCHC- Mean cell haemoglobin concentration RDW- Red cell distribution width, AEC- Absolute Eosinophil count * Significant P value

There was no significant relationship between the above mentioned haematological parameters between the hyperthyroid and the euthyroid groups. The AEC in the euthyroid group of females was found to be little higher however not statistically significant so compared to the hypothyroid group.

Table 4: Comparison of haematological parameters between hypo and hyperthyroid subjects

	Hypothyroid subjects N=50	**Hyperthyroid subjects N=50**	**P value**
Hb (g/dl)	11.44±1.264	12.82±0.873	0.000*
RBC $x10^6$ µl	4.1 ± 0.32	4.8±0.23	0.0018
MCV (fl)	83.80±6.624	83.34±5.837	0.713
MCH (pg)	28.06±1.114	28.50±1.111	0.051
MCHC	32.36±1.208	33.14±1.069	0.008*
TLC $x10^3$/µl	5992.0±1434.109	7048±1274.593	0.000*
PLT $x10^3$ µl	2.50±0.678	2.96±0.755	0.002*
RDW %	14.50±1.249	13.40±1.370	0.000*
AEC	400±149.216	228.80±68.947	0.000*

Hb – Haemoglobin, TLC- Total Leucocyte Count, PLT- Platelet count RBC- Red Blood Cell Count MCV- Mean cell volume, MCH Mean Cell Haemoglobin, MCHC- Mean cell haemoglobin concentration RDW- Red cell distribution width, AEC- Absolute Eosinophil count * Significant P value

From the above table it is clear that all the haematological indices are reduced in hypothyroid patients as compared to hyperthyroid cases. However there is no significant difference in the MCV and MCH indicating that the cells are normocytic in both groups. RDW and AEC are also raised significantly within the hypothyroid group, though within the normal range.

Discussion

Thyroid hormones are known to play an important role in maintaining the metabolic balance of the human body. Thyroid hormone imbalances are one of the commonest endocrine disorders prevalent worldwide at an estimated frequency of 2- 5% worldwide.[2,4] They are of all the more importance in females during the reproductive phase at it is essential for the normal growth of the foetus. These hormones are also known to play a crucial role in the process of erythropoesis by contributing to the proliferation of the erythroid progenitors in the bone marrow.[1,2] Thyroid hormones also increase the delivery of oxygen to the tissues by increasing the levels of 2-3 Diphosphoglycerate (2,3 DPG).[5]

According to the WHO a haemoglobin level of less than 12 g/dl in a female is considered to be anaemia. In the present study it was found that haemoglobin was comparatively lower in the hypothyroid group. The presence of thyroid hormone receptor has been demonstrated on the surface of erythropoetic progenitor cells, thereby emphasising their crucial role in the production of the RBCs. To support the same fact, the RBC count was also low in the hypothyroid group as compared to the control.[6] Anaemia is also commoner in developing country like ours due to various factors, one of the causes of which may be hypothyroidism. The prevalence of anaemia in patients with hypothyroidism is found to be between 20 5 and 65%.[7] A study by Das et al[8] in eastern India concluded that the most common anaemia was normocytic normochromic followed by microcytic hypochromic anaemia due to iron deficiency type in the hypothyroid cases. It has been documented that the efficacy and absorption of oral iron in women with subclinical hypothyroidism has shown improvement after administering levothyroxine treatment.[9] Another similar study by Ravanbod et al[10] has shown that a combination therapy of levothyroxine and iron supplements was more effective in treating subclinical hypothyroidism than receiving monotherapy with iron or levothyroxine alone.[10] Microcytic anaemia has also shown to be associated with subclinical hypothyroidism in a study by Khan et al.[11] A study by Geetha and Srikrishna have shown the MCV to be raised and anaemia to be of the macrocytic type in hypothyroidism.[12] In our study the anaemia was predominantly of the normocytic normochromic type as evidenced by the normal Mean cell volume in the hypothyroid group. The RBCs in the hyper and euthyroid category were within normal limits in our study. The proposed theories for anaemia in hypothyroid group are – lack of stimulation of erythroid colony development by thyroid hormones, reduction in oxygen distribution to tissues and reduction in erythropoietin levels in the absence of the stimulation by thyroid hormones.[13] However, treating anaemic hypothyroid patients with erythropoesis stimulating agents has been found to be unsatisfactory if the patients are on dialysis due to chronic renal failure.[14]

Fein showed that Grave's disease is associated with anaemia.[15] A large cohort study by Omar et al reported a very high incidence of microcytosis (87.7%) among patients with hyperthyroidism, regardless of the haemoglobin

status.[16] However, the present study showed normal Hb levels in hyperthyroid cases. Very few reports have also documented the association of Pancytopenia with Grave's disease and the same has been shown to resolve dramatically after treatment of the latter. The pancytopenia in Grave's is postulated to be due to increased destruction or sequestration of the blood cells by an immune mediated mechanism.[17] Studies have shown reduction in other haematological parameters like MCV, MCH, MCHC in hypothyroid states similar to our study, and have also proven that the same improves after the patient is started on Levothyroxine therapy.[7,18] Conflicting studies have also shown no significant changes in MCV among hypo and hyper thyroid groups[18] leaving a gap for a thorough understanding of the same.

As far as white blood cells are concerned, thyroid hormones play an important role in the regulation of human hematopoesis as evident by previous studies.[19] With regard to white blood cells, T3 has been shown to contribute towards normal production of B cells in the marrow by regulating the Pro B cell proliferation.[15] The total leukocyte counts are also influenced by thyroid hormonal imbalances. The lowest counts in our study were found in the hypothyroid group, the counts being significantly lower than the hyperthyroid group and not significantly lower when compared to the euthyroid groups. A study by Jafarzadeh et al[6] however showed no statistical variation in the leukocyte count between the three groups.

Platelet counts have also been assessed in thyroid disorders. Some studies have shown no significant change in platelet counts[6,18] while few studies have shown low platelet counts in hypothyroid states[15,20] In our study the platelets though within the normal range were found to be significantly lower in the hypothyroid group compared to the hyper and euthyroid groups. An interesting study has shown the eosinophil count to be higher in hypothyroid group though not of statistical significance when compared with other groups.[6] In the present study also the absolute eosinophil count was found to be the highest in the hypothyroid group, the same being statistically significant when compared to the hyperthyroid group. Serum IgE levels are also an indicator of the immunopathogenesis of allergic disorders reflected by absolute eosinophil counts in the peripheral blood. It has been shown that serum IgE levels are higher in hypo and hyperthyroid states suggesting a link between immune responses involving the cytokine releasing Th2 cells and thyroid hormones. To support the same it has been shown that the absolute number of pro – B, pre- B and B cells in the marrow of hypothyroid mice are significantly reduced.[6] The same may be a subject for further detailed investigation and a subject of potential research in humans.

RDW – refers to the red cell distribution width, increase in which indicates RBCs of varying sizes. The study by Geetha and Srikrishna[12] showed increased RDW in both hyper and hypothyroid subjects as compared to the euthyroid category, suggesting that the thyroid hormonal imbalance may influence the sizes of the RBCs. In our study the highest RDW was found in the hypothyroid group, similar to study by Montagnana et al[21] and Aktas et al[22] but was statistically not significant when compared to the hyper and euthyroid groups.[12] Studies have also shown that in patients with increased RDW, but without iron deficiency, thyroid function must be evaluated together with folate and Vitamin B12 levels.

Small sample size, unrevealed confounding factors present at the time of testing, associated undetected medical conditions if any are some of the limitations of the present study.

Conclusion

Thyroid hormones in more than one way play a crucial role in regulating the various haematological parameters. Though concurrent medical conditions may also contribute to the same it is important not to ignore the evaluation of thyroid hormones in cases of unexplained anaemias in the female reproductive age group. Treating the thyroid hormonal imbalance may help to restore the deranged haematological parameters back to normal thereby avoiding subjecting the patients to unnecessary investigations and therapies for anaemia. In view of confounding factors always present at any point of time, more large scale studies would contribute more to an understating of the play between haematological parameters and thyroid hormones.

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