ISSN: 0975-1556

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2021; 13(6); 307-314
Original Research Article

The Relationship Between Haematological Parameters and Thyroid Hormone Levels in Non-pregnant Women of Reproductive Age

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Received: 05-06-2021 / Revised: 12-07-2021 / Accepted: 28-08-2021
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Conflict of interest: Nil

Abstract

Aim: Study of hematological parameters and their correlation with thyroid hormone status in non-pregnant women of childbearing age.

Methods: This comparative study was conducted in a tertiary care centre, Shahjahanpur, Uttar Pardesh, India. In total, 120 non pregnant female patients, aged 18 to 50 years, with thyroid diseases, were taken up. Patients were classified, as having hyperthyroidism (n=60) or hypothyroidism (n=60). Only patients who had all T3, T4 and TSH serum levels tested were taken up for categorization as hypothyriod or hyperthyroid.

Results: Among the parameters assessed the highest significant P value was found for Haemoglobin, MCHC and RBC count and Total Leucocyte Count (TLC) between the groups. Haemoglobin was significantly lower with a mean of 11.5 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 were found to be significantly more in hypothyroid subjects. AEC though increased was still within the normal range. There was no significant relationship between the above mentioned haematological parameters and the hyperthyroid and the euthyroid groups.

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 but it is important not to ignore the evaluation of thyroid hormones in cases of unexplained anaemia in the female reproductive age group.

Keywords: thyroid hormones, reproductive age group, hematological parameters

Introduction

Stress of pregnancy may result in clinical or sub clinical hypothyroidism in women with limited reserve. Reference ranges of TSH or free thyroxine (FT4) obtained from non-pregnant populations change in pregnant women because of the physiological changes in thyroid function in pregnancy. Physiological and hormonal changes in pregnancy result in increased production of thyroxine (T4) and triiodothyronine (T3) by up to 50%, leading to an increase in a woman's daily iodine requirement, while thyroid-stimulating hormone (TSH) levels decrease, especially in the first trimester.[1] As Human Chorionic Gonadotrophin (HCG) is thyrotrophic ,its high level

specially in 1st trimester result in low TSH values and thus cut offs become less. In women with low thyroid reserves ,stress of pregnancy manifests as overt disease.[2] In an iodide sufficient area, thyroid adaptations are well tolerated, as stored inner thyroid iodine is adequate; however, in iodide deficient areas, these physiological adaptations lead to significant changes in pregnancy.[3] Hypothyroidism is widely prevalent in pregnant women and the rate of detection, especially in a developing country like India, has not kept pace with the magnitude of the problem. Since hypothyroidism is easily treated, timely detection and treatment of the dysfunction could reduce the burden of adverse fetal and maternal outcomes in pregnancy which is commonly encountered. Prevalence of overt thyroid dysfunction is 2–3% in pregnant women, subclinical dysfunction is 10%, while rate of autoimmunity is 5–10%.[4,5]

Maternal complications include miscarriage, anaemia, preeclampsia, gestational hypertension, placental abruption, preterm delivery, increased rate of caesarean section, and postpartum hemorrhage. The mode of delivery may have adverse impacts on fetal-pituitary-thyroid axis. Fetal outcomes resulting from thyroid dysfunction are preterm birth, neonatal respiratory distress syndrome, low birth weight (LBW), perinatal morbidity and mortality, increased NICU admission; and neuropsychological and cognitive impairment. Thyroid hormone is critical for brain development in the developing fetus. Children born with congenital hypothyroidism have severe cognitive, neurological and development abnormalities if the condition is not recognized and treated promptly. A study demonstrated that children born to pregnant women with hypothyroidism had lower intelligence quotient (IQ) scores compared to children born to pregnant women without hypothyroidism.[6]

Material and methods

This comparative study was conducted in a tertiary care centre.

Inclusion Criteria: Females between 18 – 50 years of age.

Exclusion Criteria: Known cases of hypothyroid 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.

Methodology

In total, 120 non pregnant female patients, aged 18 to 50 years, with thyroid diseases, were taken up for this study. Patients were classified, as having hyperthyroidism (n=60) or hypothyroidism (n=60). 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 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 hypothyroid or hyperthyroid.

A third sex- and age-matched group consisting of 60 females with normal thyroid function tests, and were

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).

Peripheral blood (2-4 mL) was collected from the 180 subjects and the serum was separated and stored at -20^0C. Serum concentrations of T3, T4 and TSH were measured. 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 done on the blood samples. Total cell counts were obtained. 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.21.0 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.

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= 60	Euthyroid subjects N= 60	Hyperthyroid subjects N= 60
T3 (nmol/L)	1.4 ± 0.28	3.21 ± 0.27	3.89 ± 1.53
T4(nmol/L)	53.64 ± 37.24	139.22 ± 14	213.05 ± 14.2
TSH (m IU/L)	143 ± 188.85	1.9 ± 0.50	0.06 ± 0.01

In the present study 60 newly diagnosed cases of hyperthyroidism and hypothyroidism were taken ,60 cases per group as per criteria mentioned in the methods and 60 cases were randomly selected as controls. All females were taken for the study.

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

	Hypothyroid subjects N=60	Euthyroid subjects N= 60	p-value
Hb (g/dl)	11.54±1.25	12.68±9.40	0.001*
RBC $x10^6$ µl	4.2 ± 0.42	4.7 ± 0.51	0.001*
MCV (fl)	84.70±6.52	84.06±4.95	0.57
MCH (pg)	29.06±1.10	29.52±1.11	0.05
MCHC (g/dl)	33.36±1.21	34.14±1.11	0.001*
TLC $x10^3$/µl	5988.0±1411.11	7052.0±1255.27	0.001*
PLT $x10^3$ µl	2.52±0.68	2.86±0.69	0.58
RDW %	14.70±1.25	13.12±1.28	0.001*
AEC	401±148.22	261±82.10	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 11.5 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 hyperthyoid and euthyroid subjects

	Hyperthyroid subjects N = 60	**Euthyroid subjects N = 60**	**p-value**
Hb (g/dl)	12.92±0.88	12.68±9.60	0.17
RBC $x10^6$ µl	4.9±0.21	4.7 ± 0.42	0.71
MCV (fl)	82.34±5.77	84.06±5.22	0.87
MCH (pg)	29.50±1.22	29.52±1.23	0.88
MCHC (g/dl)	34.14±1.10	34.14±1.12	1.01
TLC $x10^3$/µl	7058±1284.57	7042.0±1287.27	0.87
PLT $x10^3$ µl	2.86±0.88	2.86±0.67	0.17
RDW	13.60±1.38	13.12±1.28	0.16
AEC	229.80±67.74	261±80.11	0.057

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 as compared to the hypothyroid group.

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

	Hypothyroid subjects N=60	**Hyperthyroid subjects N=60**	**P value**
Hb (g/dl)	11.54±1.264	12.92±0.873	0.000*
RBC $x10^6$ µl	4.2 ± 0.32	4.7±0.23	0.0017
MCV (fl)	84.80±6.624	84.34±5.837	0.62
MCH (pg)	27.06±1.114	29.50±1.111	0.057
MCHC	31.36±1.208	32.14±1.069	0.007*
TLC $x10^3$/µl	5972.0±1434.109	7058±1274.593	0.0001*
PLT $x10^3$ µl	2.60±0.678	2.86±0.755	0.003*
RDW %	14.60±1.249	13.50±1.370	0.0001*
AEC	401±149.216	228.74±67.947	0.0001*

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 imbalance is one of the commonest endocrine disorder prevalent worldwide at an estimated frequency of 2-5% worldwide.[7,8] 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 proliferation of the erythroid progenitors in the bone marrow.[7] Thyroid hormones also increase the delivery of oxygen to the tissues by increasing the levels of 2-3 Diphosphoglycerate (2,3 DPG).[9]

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. Presence of thyroid hormone receptor has been demonstrated on the surface of erythropoetic progenitor cells, thereby emphasising it's 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.[10] Anaemia is also common in a developing country like ours due to various factors- one of which may be hypothyroidism. The prevalence of anaemia in patients with hypothyroidism is found to be between 20 5 and 65%.[11] A study by Das et al[12] 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.[13] Another similar study by Ravanbod et al[14] 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.[14] Microcytic anaemia has also shown to be associated with subclinical hypothyroidism in a study by Khan et al.[15] A study by Geetha and Srikrishna have shown , MCV to be raised and anaemia to be of the macrocytic type in hypothyroidism.[16] 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 hyperthyroid and euthyroid categories 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.[17] 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.[18]

Fein showed that Grave's disease is associated with anaemia.[19] 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.[20] 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 disease has been due to increased destruction or sequestration of the blood cells by an immune mediated mechanism.[21] 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 parameters improve after the patient is started on Levothyroxine therapy.[22] Conflicting studies have also shown no significant changes in MCV among hypothyroid and hyper thyroid groups 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.[23] 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.[19] The Total Leukocyte Counts are also influenced by thyroid hormone imbalance. 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[10] 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[10,22] while few studies have shown low platelet counts in hypothyroid states[20,24] 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 hypothyroid 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.[10] 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[16] 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[25] and Aktas et al[26] but was statistically not significant when compared to the hyper and euthyroid groups.[16] 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 anaemia

in female reproductive age group. Treating the thyroid hormonal imbalance may help to restore the deranged haematological parameters to normal and can save the patients from unnecessary investigations and therapies for anaemia.

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