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ORIGINAL ARTICLE

Red Blood Cell Indices and Hypothyroidism

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Abstract

Background: Hypothyroidism is a commonly encountered endocrine problem throughout the world which can cause various morphological types of anaemia with various underlying pathogenesis. So the proper evaluation of RBC indices is important to manage the cases of refractory anaemia in patients with thyroid dysfunction. **Aims:** To estimate the mean values of Hemoglobin and RBC indices in hypothyroid and euthyroid status and to determine the significance of association of the RBC indices between hypothyroid group in comparison to euthyroid group. **Materials and Methods:** Total 400 adult non-pregnant patients were included in this hospital based cross sectional study. Blood samples were analysed for Hemoglobin level and RBC indices by 5-part cell counter and TSH level by Electrochemiluminescence method. RBC indices of hypothyroid group was compared with that of the control group (euthyroid) and student t test and Pearson correlation was applied to determine any significant association between these haematological parameters and functional status of thyroid gland.**Results:** 258 (64.5%) patients were categorized as euthyroid group and rest 142 (33.5%) were categorized as hypothyroid group. Hypothyroid group of patients had significantly lower level of Hb with lower MCV, MCH and MCHC compared to euthyroid group ($p<0.05$, unpaired t test) while RDW-CV is higher indicating more anisocytosis in case of hypothyroid group. **Conclusion:** Hypothyroidism is a leading cause of anaemia with decreased level of Hemoglobin and has a significant impact on most of the RBC indices. Hence evaluation of thyroid function is important to evaluate causes of anemia specially with altered RBC indices.

Key Words

Thyroid gland, Thyrotropin, Anemia, Erythrocyte indices

Introduction

Thyroid gland is one of the most important endocrine gland of the body located on the anterior aspect of the neck just below the larynx and is composed of two lobes joined by isthmus. Thyroid gland contains many thyroid follicles lined by cuboidal epithelium. These follicles store thyroid hormones in the form of Thyroglobulin until their secretion is stimulated by Thyroid stimulating hormone (TSH) released from anterior pituitary under regulation of Thyroid releasing hormone (TRH). Two major hormones are secreted by thyroid gland namely 3, 5, 3'-triiodothyronine (T3) and thyroxin also referred to as 3, 5, 3', 5'-tetraiodothyronine (T4). These two hormones play important role in early brain development, somatic growth, bone maturation, protein synthesis and hematopoiesis including haemoglobin (Hb) production in adult and maturation of Hb in fetus. [1-4] Active form of thyroid hormone T3 binds to specific members of the

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nuclear receptors family (TRa and TRB) to function. Thyroid hormone increases erythropoiesis by up regulating the Erythropoietin (EPO) gene expression leading to enhanced secretion of erythropoietin by the kidneys. L-triiodothyronine stimulate the growth of erythroid colonies (BFU-E, CFU-E) and increases 2,3 BPG levels in erythrocytes leading to delivery of oxygen to the tissues. So dysfunction of thyroid hormones leads to different red blood cell (RBC) abnormalities. [5-7] With decreased thyroid hormone kidney produces less amount of EPO resulting in decreased proliferation of erythrocytes leading to anaemia. Hypothyroidism is a commonly encountered endocrine problem throughout the world. Hypothyroidism is more commonly associated with anaemia than hyperthyroidism. Hypothyroidism is associated with reduced proliferation of erythrocytes and can cause various morphological types of anaemia like normocytic-normochromic, microcytic-hypochromic or macrocytic type though the underlying pathogenesis varies in different types of anaemia. Microcytic anaemia is caused by decreased absorption of iron or by menorrhagia as often experienced by patients with hypothyroidism. Macrocytic anaemia is caused by malabsorption of vitamin B12 and folate. In contrast, hyperthyroidism is rarely associated with anaemia, rather it causes hyperproliferation of red blood cells. Anaemia associated with hyperthyroidism is attributed to altered iron metabolism, oxidative stress and haemolysis due to increased osmotic fragility of RBCs. [8] Anaemia in Grave's disease was first described by Charcot in 1881.[9] Incidence of anaemia in subclinical and euthyroid individuals were found be same in different studies.[10, 11] In autoimmune thyroiditis, anaemia is often attributed to associated co morbid conditions like pernicious anaemia, autoimmune haemolytic syndrome, celiac disease and atrophic gastritis.[12] So not only haemoglobin, PCV(Packed cell volume) and life span of erythrocytes are affected in thyroid dysfunction, different RBC indices like MCV, MCH(Mean corpuscular haemoglobin) , MCHC(Mean corpuscular haemoglobin concentration) and RDW(Red cell distribution width) are also affected. So the proper evaluation of RBC parameters is important to manage the cases of refractory anaemia in patients with thyroid dysfunction. Though the prevalence of hypothyroidism is 11% in India, there is scarcity of data to evaluate the changes in haematological parameters with special reference to RBC parameters in patients with thyroid dysfunction in Eastern India which necessitates further study in this geographic location.[13] The present study was conducted to estimate the mean values of Hb and different RBC indices in hypothyroid and euthyroid status and also to determine the significance of association of the RBC indices between hypothyroid group in comparison to euthyroid (control) group.

Materials and Methods

The present study was conducted after obtaining approval from Institutional Ethics Committee (MC/KOL/IEC/NON-SPON/1084/05/2021 dated 28/05/2021) and informed consent from all the participants. It was a hospital based descriptive cross sectional study done over a period of 5 months (from 1st June 2021 to 31st October, 2021) in a tertiary care hospital of Eastern India. All adult non-pregnant patients attending central laboratory for test of Thyroid profile as advised by their concerned physician from out-patient department were included in this study. Patients suffering from haematological malignancy or receiving chemotherapeutic drug or suffering from malignancy of thyroid were excluded from this study. Blood samples were collected both in EDTA anticoagulant vial and in clot activator vial (without any anticoagulant) at OPD blood collection center of central laboratory by single prick method. Blood collected in EDTA vials were analyzed by Sysmex- 6 part automated cell counter for Hb and RBC indices including PCV, MCV, MCH, MCHC and RDW-CV. RBC morphology was further evaluated for correlation by examining the blood films stained by Leishman's stain under light microscope. According to the World Health Organization (WHO) recommendations, anemia was diagnosed with the Hb level < 12.0 g/dL for women and<13.0 g/L for men. Normocytic anemia was defined as a mean corpuscular volume (MCV) between 80 and 100 fl, microcytic anemia was diagnosed as MCV below 80 fl, and macrocytic anemia by an MCV above 100 fl. [14] Again anaemic patients were further subdivided into 3 groups depending on their severity following WHO criteria as mild anaemia (Hb level below normal as per age and sex, but 9.0g/dl or above), moderate anaemia (Hb level 7 to 8.9g/dl) and severe anaemia (Hb level less than 7.0 g/dl). [15] Samples taken in clot activator vial

Table1. Age and sex distribution of study population

Parameter	Euthyroid group (n=258)	Hypothyroid Group (n=142)
No of Male (%)	44 (17.05)	21 (14.78)
No of Female (%)	214 (82.95)	121 (85.22)
Mean Age in years [±SD]	36.27 [±14.6]	32.06 [±11.87]

Table 2. Comparison of study parameters including Hb, MCV, MCH, MCHC and RDW between euthyroid and hypothyroid group by unpaired t test

Study Parameter	Euthyroid group	Hypothyroid Group	P value
Hb (g/dl) [Mean ±SD]	12.01 ±1.83	10.73±1.46	<0.0001
MCV(fl) [Mean ±SD]	84.41±8.94	80.14±9.02	<0.0001
MCH (pg) [Mean ±SD]	27.21±3.25	25.54±2.96	<0.0001
MCHC (g/dl) [Mean ±SD]	32.03±1.55	31.64±1.00	0.0072
RDW-CV (%)[Mean ±SD]	15.02±2.00	16.28±1.91	<0.0001

Table 3. Correlation of Hb, MCV and MCH with TSH level by Pearson correlation test

Study Parameter	r value	P value
Hb (g/dl) [Mean ±SD]	-0.3657	<0.001
MCV(fl) [Mean ±SD]	-0.1122	0.025
MCH (pg) [Mean ±SD]	-0.0984	0.049

Table 4. Comparison of Mean Hb, MCV, MCH, MCHC and RDW-CV of Hypothyroid and Euthyroid group of present study with other studies

RBC parameters	Thyroid status	Present study	Dorgalaleh et al.[1]	Shetty A et al.[18]	Maheshwari et al.[8]	Siddegowda MS et al[20]
Hb%	Hypothyroid	10.73	12.2	11.44	11.5	11.68
	Euthyroid	12.01	13.6	12.58	12.9	12.26
MCV(fl)	Hypothyroid	80.14	84	83.8	86.2	84.64
	Euthyroid	84.41	85	83.06	86.6	82.34
MCH(pg)	Hypothyroid	25.54	27.4	28.06	28.5	30.31
	Euthyroid	27.21	29.3	28.52	28.6	27.96
MCHC(g/dl)	Hypothyroid	31.64	32.5	32.36	32.9	33.69
	Euthyroid	32.03	33.6	33.14	33.1	33.35
RDW-CV(%)	Hypothyroid	16.28	13.7	13.2	13.2	16.33
	Euthyroid	15.02	12.9	12.5	12.5	14.78

Fig 1. Graphical representation of Pearson correlation test between Hb Level and TSH level

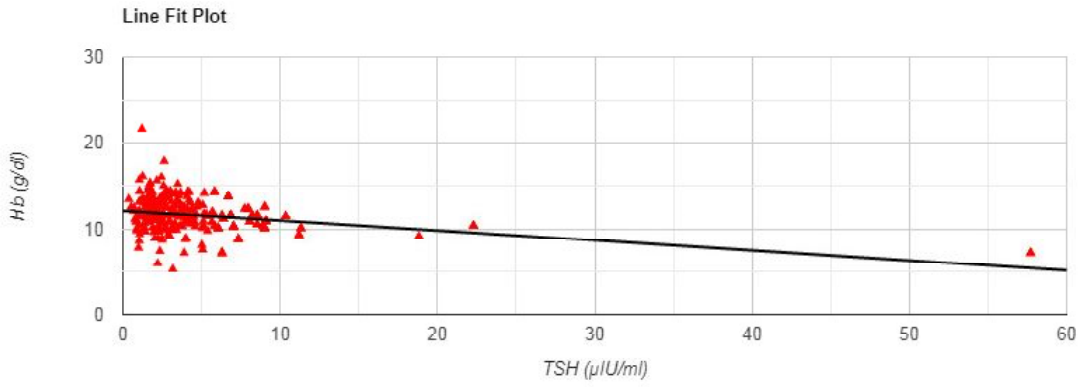
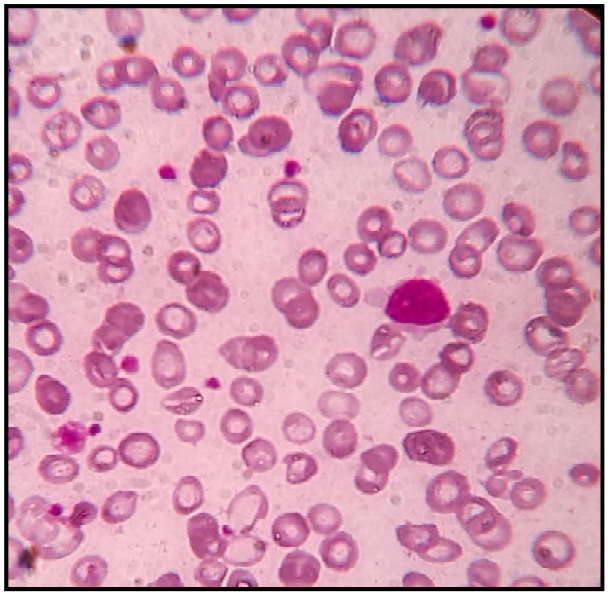


Fig 2. Peripheral blood picture of a microcytic hypochromic anaemia in hypothyroid case



were analyzed for serum TSH level by ECLIA (Electrochemiluminescence) method in Cobas 6000. The quality of results was validated by Internal Quality Control(IQC) procedures. Patients were categorized into hypothyroid and euthyroid based on their TSH level only. TSH >5.50 IU/ml were considered as hypothyroidism while TSH level between 0.35 IU/ml to 5.5 IU/ml were categorized as euthyroid control group.[16] Patients having TSH level <0.35 IU/ml were considered as hyperthyroid group and excluded from further statistical analysis regarding purpose of the study.

Statistical Analysis:

Results were tabulated and data were analyzed in Statistical packages for social sciences (SPSS) software version 11. RBC indices of hypothyroid group was compared with that of the control group (euthyroid) and student t test and Pearson correlation was applied to determine any significant association between these haematological parameters and functional status of thyroid gland.

Results

Out of total 400 cases processed for statistical analysis as per inclusion and exclusion criteria, 258 (64.5%) were categorized as euthyroid group and rest 142 (33.5%) were categorized as hypothyroid group. Female preponderance was noted in both the groups with female: male ratios are 4.86:1 and 5.76:1 in euthyroid and hypothyroid group respectively. Mean age in years were 36.27 (range 5-94) and 32.06 (range 13-65) for euthyroid and hypothyroid group respectively which was considered as statistically significant by unpaired t test with p value of 0.0035 [*Table1*].

Regarding study parameters, Table 2 shows that hypothyroid group of patients had significantly lower level of Hb with lower MCV, MCH and MCHC compared to euthyroid group ($p<0.05$, unpaired t test) while RDW-CV is higher indicating more anisocytosis in case of hypothyroid group. Pearson correlation tests have also been performed regarding TSH level and Hb level. Results indicated that there is a significant small negative relationship between them ($r = -0.3657$, $p<0.001$) which suggests that severity of anaemia has a correlation with level of hypothyroidism [*Fig1*]. Similarly MCV and MCH also have significant negative correlation with TSH level [*Table 3*]. Out of total 142 cases of hypothyroidism, 22 cases (15.5%) have moderate anaemia (Hb level between 7 to 8.9 g/dl) while 101 cases (71%) have mild anemia and rest 19 cases were non-anaemic. Regarding morphology, out of total 123 anaemic cases with hypothyroidism, 67 (54.47%) had microcytic hypochromic anemia [*Fig 2*] and rest were normocytic and normochromic. Compared to this, in euthyroid group only 12% patients were moderately anaemic and 11% have mild anaemia while rest 77% cases were non-anaemic. This anaemia in euthyroid group may be due to other confounding factors including nutritional anaemias.

Discussion

Thyroid gland plays crucial role in regulation of cellular metabolism and erythropoiesis in our body. Deficiency of thyroid hormone is one of the leading causes of anaemia throughout the world. Dysfunction of thyroid gland is associated with reduced proliferation and diminished life span of red blood cells leading to anaemia in patients with thyroid disorders. Hypothyroidism is the most commonly encountered dysfunction of thyroid gland in clinical practice. Hypothyroidism is more commonly associated with anaemia than hyperthyroidism and it leads to different morphological types of anaemia of varying severity. Not only Hb and total RBC count is affected in

deficiency of thyroid hormone, but it also affects different RBC indices like MCV, MCH, MCHC and RDW. [8] So it necessitates detailed evaluation of different RBC parameters in patients with thyroid dysfunction which may help in effective management of anaemia in these patients. As the underlying pathogenesis varies in different morphological types of anaemia in thyroid dysfunction, so the cause of anaemia in thyroid disorder may vary with geographic location with different food habits and genetic predisposition. There is discrepancy in the data as well as limited previous studies are available in Eastern India on this aspect which necessitates further study. With the background of this knowledge the present study was conducted to evaluate the changes in RBC parameters in patients with hypothyroidism and to compare those with euthyroid individuals. Out of total 400 cases evaluated in this study, 142 (33.5%) participants were categorized as hypothyroid based on their TSH level. The prevalence of hypothyroidism was much higher in this study compared to the other study done by Unnikrishnan A G *et al.* in which only 13.3% participants were found to be hypothyroid. [17] In the current study female preponderance was noted among hypothyroid group with a female to male ratio of 5.76:1. This finding was in concordance with the previous studies done by A Dorgalaleh *et al.*[1] and Bashir H *et al.*[17] where incidence of hypothyroidism in females was 62 % and 64.3 % and in males 38 % and 35.7 % respectively. [1,18] Mean age of hypothyroid group was significantly lower than that of the euthyroid group (32.06 years vs 36.27 years respectively) with p value of 0.0035 in this study. Maheshwari KU *et al.*[8] also noted similar age distribution among hypothyroid cases and euthyroid controls in their study with a mean age of 38.5 years and 42.9 years respectively.

In this study anaemia was found to be more common in hypothyroid group compared to euthyroid control group (86.6% vs 33%). The most common morphological pattern was microcytic hypochromic type (54.47%). In the present study statistically significant lower value of Hb, MCV, MCH and MCHC and higher value of RDW was found among hypothyroid group compared to euthyroid group with a p value <0.05. This finding was comparable with the study done by Dorgalaleh A *et al.* who found statistically significant lower value of Hb and MCHC among hypothyroid patients compared to euthyroid controls(p value <0.001). However statistically non significant lower value of MCV and MCH was noted by them among the hypothyroid group. [1] Maheshwari KU *et al.* also found statistically non significant lower value of MCV, MCH and MCHC in hypothyroidism. [8] In the year 2010, Kawa MP and et al recorded lower value of Hb, MCH and MCHC in hypothyroidism compared to controls while MCV was found to be increased in both hypothyroidism and hyperthyroidism. [6] In contrast to present study, Shetty A *et al.* noted a higher value of MCV in hypothyroid cases compared to euthyroid controls (p value <0.001).[18] However study done by Salim E. *et al.* did not found any significant difference in MCV, MCH and MCHC in two groups. [19] In this study we found statistically significant higher value of RDW-CV in hypothyroid group(p value <0.0001) which was in concordance with the previous studies done by Dorgalaleh *et al.*, Shetty A *et al.* and Maheshwari *et al.* [1,18,8] They found non-significant higher value of RDW in hypothyroidism while Siddegowda MS and et al found statistically significant higher value of RDW-CV in hypothyroidism(p value <0.001).[20] Table 4 is depicting the comparison of Mean Hb, MCV, MCH, MCHC and RDW-CV of hypothyroid and euthyroid group of this study with previous studies. To summarize, the present study and previous studies by Dorgalaleh *et al.* and Maheshwari *et al.* observed lower mean values of Hb, MCV, MCH and MCHC in hypothyroid group compared to euthyroid group. In contrast, Siddegowda MS et al found higher mean value of MCV, MCH and MCHC among hypothyroid group. Mean RDW-CV was found to be higher in this study similar to previous studies (*Table 4*). Limitations of the study:It was a hospital based study, hence may not truly represent the problem in general population.

Conclusion

It was concluded from the present study that hypothyroidism is a leading cause of anaemia with decreased level of Hb and a significant impact on most of the RBC indices. Hence evaluation of thyroid function is important to evaluate causes of anemia specially with altered RBC indices.

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Conflicts of Interest
There are no conflicts of interest.

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