IJPRP

Indian Journal of Pathology: Research and Practice
Volume 9 Number 2 (Part II), May – August 2020
DOI: http://dx.doi.org/10.21088/ijprp.2278.148X.9220.31

Original Research Article

Alterations in Indices of RBC and Iron Metabolism in Hypothyroidism - A Cross-Sectional Study

Mousumi Sharma[1], Dilutpal Sharma[2], Debadyuti Sahu[3], Prabhat[4], Madhusmita Sahu[5]

[1]Associate Professor, Department of Pathology, Integral Institute of Medical Science and Research, Lucknow, Uttar Pradesh 226026, India, [2]Associate Professor, [3]PhD Scholar cum Senior Resident, Department of Biochemistry, King George Medical University, Lucknow, Uttar Pradesh 226003, India, [4]Assistant Professor Department of Biochemistry, All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh 273008, India, [5]Demonstrator, Department of Periodontics, HiTech Dental College, Bhubaneswar, Odisha 751025, India.

Corresponding Author:

Debadyuti Sahu, PhD Scholar cum Senior Resident, Department of Biochemistry, King George Medical University, Lucknow, Uttar Pradesh 226003, India.

E-mail: mousumi@iul.ac.in

How to cite this article:

Mousumi Sharma, Dilutpal Sharma, Debadyuti Sahu, Prabhat, Madhusmita Sahu. Alterations in Indices of RBC and Iron Metabolism in Hypothyroidism - A Cross-Sectional Study. Indian J Pathol Res Pract 2020;9(2 Part II):197–205.

Abstract

Background: Thyroid hormones regulate metabolic rate and stimulate hematopoiesis via multiple mechanisms. Alterations in various hematological parameters have been reported in various thyroid disorders. Hypothyroidism is the most common thyroid disease.

Objectives: To evaluate various erythrocyte indices and indices of iron metabolism in (subclinical and overt) hypothyroid cases and compare with control (euthyroid) group.

Materials and Methods: Laboratory data and medical records of patients were retrieved. Patients were grouped as 'overt hypothyroid' (TSH >5.5 µIU/ml and reduced serum T4 and/or T3); 'subclinical hypothyroid' (TSH 4.0-5.5 µIU/ml with normal thyroxin) and euthyroid (control) group (TSH 0.03-4.0 µIU/ml with normal serum THs). Complete blood count (CBC) and iron indices data of these cases were compiled. Statistical analysis was carried out using IBM SPSS version 25.0 statistical software.

Result: 158 euthyroid, 56 subclinical hypothyroid and 28 overt hypothyroid cases were included.>70% of hypothyroid and ~60% of control group was anemic. Normocytic anemia was reported in 80% (overt) and 60% (subclinical) hypothyroid anemics, rest were microcytic. Reduced levels of TIBC;all erythroid markers {hemoglobin, TRBC, color index (CI), MCV, MCH, MCHC and PCV}, and significant increase in serum iron were observed in both subclinical and overt hypothyroid cases compared to euthyroid. Reduction of Hb, PCV, MCH and CI were statistically significant. These four parameters exhibited significant negative correlation with serum TSH whereas serum iron showed a significant positive correlation.

Conclusion: Anemia cases (particularly treatment resistant ones) should be screened for thyroid abnormality. CBC should be carried out in all overt and subclinical hypothyroid cases.

Keywords: Color Index (CI); Mean Corpuscular Hemoglobin Concentration (MCHC); Subclinical Hypothyroidism (SCH); Total Iron Binding Capacity (TIBC); Thyroid stimulating hormone (TSH).

Introduction

The thyroid is the largest endocrine gland of human body. Microscopically, thyroid gland consists of number of spherical follicles, lined by follicular cells which may be low cuboidal to tall columnar in shape according to their degree of metabolic activity.[1,2] Functionally, it has two types of cells: thyroid follicular cells (producing thyroid hormones or THs) and parafollicular (or C-cells) (secrete calcitonin)[3] Thyroglobulin inside thyroid follicles (rich in amino acid tyrosine residues) store iodine as mono-iodo tyrosine (MIT) and di-iodo tyrosine (DIT), the inactive precursors of THs. Substitution of a second phenol moiety in place of phenolic hydrogen in tyrosine produces thyronine. Differential iodination at meta positions of two phenyl rings of thyronine leads to production of various thyroid hormones: the active form T3 (3, 5, 3′-triiodothyronine), major form thyroxine or T4 (3, 5, 3′, 5′-tetraiodothyronine) and biologically inactive form reverse-T3 (3, 3′, 5′-triiodothyronine).[1,4] THs actas transcription factors via their nuclear receptors (TRa and TRb) mediating expression of various genes. Thus THs help in normal development, growth, differentiation and physiological functioning of most tissues. They also regulate the metabolic rate of various tissues, including hematopoietic tissues.[4-6] THs are involved in hemoglobin production in adults as well as fetal hemoglobin maturation.[7-9]

Thyroid function tests include measurement of serum levels of THs (T3 and T4) and TSH. Accordingly patients are classified into euthyroid (both TSH and THs in normal reference range), hyperthyroid (low TSH and higher THs) and hypothyroid (higher TSH and lower THs).[10-12] Hypothyroidism is the most prevalent functional derangement of thyroid, caused chiefly by thyroid pathology (primary hypothyroidism >99.5%) and rarely (<5%) due to pituitary or hypothalamic pathology (secondary or central hypothyroidism). Hypothyroid cases also has been categorized as overt hypothyroid (TSH higher than 5.5 mIU/L and lower THs) and subclinical hypothyroid (TSH>4.0 mIU/L with THs, particularly thyroxine within normal reference range).[3,5] Worldwide annual incidence of hypothyroidism has been estimated to be approximately 0.6 cases per men and 4.1 cases per 1000 women.[13] Hypothyroidism prevalence is roughly 0.1% in males and 1-2% in females.[14-16] Interestingly, subclinical hypothyroidism prevalence is much higher (4-10%) and more so among elderly (18%).[17-20]

Thyroid hormones are being implicated to erythropoiesis via various mechanisms. THs induce erythropoietin (EPO) gene expression hence indirectly enhance erythropoiesis.[21-24] Under the direct mechanism, THs increase hypoxia inducible factor1 (HIF-1) repletion thus motivating various erythroid colonies (BFU-E, CFU-E) growth. This leads to hyper proliferation of immature erythroid progenitors thus enhancing erythropoiesis. THs augment RBC 2,3-DPG compactness, hence enhancing tissue oxygen delivery.[4,6,25-33]

Anemia is generally defined as a reduction in either the number of red blood cells (RBC) and/or hemoglobin (Hb), resulting in reduced in blood oxygen carrying capacity.[34,35] It is very much prevalent in all parts of world, in many a places up to 10% of population being affected. Reproductive age group females and elderly are more prone to develop anemia.[35] As per World Health Organization (WHO) guidelines, Hb level <13.0 g/dL for men and is <12.0 g/dL for women is considered as diagnostic criteria foranemia.[35] According to red cell size/volume, anemia is classified into: normocytic anemia (mean corpuscular volume or MCV in the range of 80 to 100 fl or femtoliter), microcytic anemia (MCV <80 fl) and macrocytic anemia (MCV >100 fl).[27,36,37] Most common cause for anemia is iron deficiency (microcytic hypochromic anemia) in developing countries flowed by folate and/or cobalamine deficiency (macrocytic/megaloblstic/pernicious anemia), which is major cause in developed nations.[38,39]

The associations of various types of thyroid disorders with hematological abnormalities have been reported since long.[40] The association of anemia with Grave's disease has already been demonstrated since 1979.[41] Subclinical hypothyroid cases usually present with various hematological parameters abnormalities, particularly anemia[22] Reduced total RBC count in thyroidectomy cases was first reported by Horton et. al.[42] All myeloid cell lines show hyperplasia in hyperthyroidism and hypoplasia in hypothyroidism.[43-47] But anemia is not so commonly seen in hyperthyroidism as is erythrocytosis.[41,48] Hypothyroidism has been reported to be associated with either anemia (in most cases) or immature erythroid progenitor proliferation.[42] Among hypothyroid cases, anemia prevalence has been estimated to be ranging from 20% to 60%.[49] Though many varieties of anemia (normocytic, microcyticand macrocytic) are reported in hypothyroids; microcytic hypochromic (mimicking iron deficiency) anemia is the most common presentation.[27,42,50] This phenomenon can

be attributed to the prevalence of low levels of iron, folate and/or vitamin B12 in the population(and so among hypothyroid cases).[42,51] Pancytopenia is a rare immunologic presentation among hypothyroids, caused by decreased life span of thrombocytes and erythrocytes.[52] All hematological abnormalities are reversible and normal levels of blood parameters are restored once euthyroid state isreachieved.[4,53]

Iron is bound to pyrrole rings in number of hemoproteins. Some hemoproteins like hemoglobin and myoglobin act as oxygen carrier and many others like cytochrome oxidase, cytochrome P450s, electron transport proteins, catalase, peroxidase, etc. function as molecular oxygen activator. Total Iron Binding Capacity (TIBC) is the measure of iron reserve deficiency in the body.[54,55] Ferritin is storage form of iron, mostly intracellular and sparsely found in plasma (20-270 ng/ml).[56] It is a reliable marker of total body iron.[44] Its blood levels raise in conditions of rapid RBC turnover.[57,58] Iron deficiency (ID) has been reported to reduce plasma THs by attenuating hepatic deiodinase activity, thus hampering peripheral T4 to T3 conversion.[43] Positive correlation of serum ferritin with plasma reverse-T3 concentration and T4/T3 ratio has been observed.[31,41] Significant negative correlation of hemoglobin and serum TSH levels has been reported in Nepal.[59,60] ID has been proved to reduce TRH induced TSH response[43] and TPO activity.[61] Subjects with moderate to severe ID with(out) anemia have demonstrated upto 10% reduction in THs levels.[62-65]

Many studies have been conducted for accessing associations of various hematological parameters in various thyroid diseases. Most of these studies were conducted either in developed countries or in middle-east nations, very few in Africa and India. Thus we considered for looking into association of various indices of iron metabolism and erythrocyte associated parameters in (both subclinical and overt) hypothyroids in comparison to their normal counterparts.

Abbreviations

THs: Thyroid Hormones
TRH: Thyroid Releasing Hormone
EPO: Erythropoietin
TIBC: Total Iron Binding Capacity
RBC: Red Blood Cell
TRBC: Total RBC Count
WBC: White Blood Cell
TLC: Total Leukocyte Count
Hb: Hemoglobin
DC: Differential Count
ID: Iron deficiency
TPC: Total Platelet Count
MCV: Mean Corpuscular Volume
PCV: Packed Cell Volume
MCH: Mean Corpuscular Hemoglobin
MCHC: Mean Corpuscular Hemoglobin Concentration.

Materials and Methods

This is a retrospective cross-sectional study. Laboratory data of study participants were collected from laboratory data in Pathology department. Patient data of Thyroid Function Tests [serum free T3 (NR 3.1-5.9 pMol/L), free T4 (NR 0.7-2.7 ng/dl) and TSH (NR 0.35-5.50 mIU/L)]; Hematological parameters [Hemoglobin, Total RBC count (TRBC: NR 4.32-5.72 million cells/microLiter), Total Leukocyte count (TLC: NR 3000-10500million cells/microLiter), Total Platelet count (TPC: NR 1.5-4.0L/microLiter), Differential WBC Count(DC), Hematocrit, Mean Corpuscular Volume (MCV: NR 80-100 femtoLiter/RBC), Mean Corpuscular Hemoglobin (MCH: NR 27.5-33.2pg/RBC), Mean Corpuscular Hemoglobin Concentration (MCHC: NR 32-36 gm/dl)] alongside indices for iron metabolism [serum iron (NR35-15 µg/dl), serum ferritin (NR 20-270 ng/ml) and TIBC(NR 252-479 µg/dl)]were collected. Those patients' medical records were also accessed retrospectively. Color Index (CI) was calculated as {(%Hb)/(%RBC)} where [%Hb=(Hb*100)/14.5] and [%RBC= (TRBC*100)/5.0] [7]. [*NR: Normal Range]

All the hematological parameters and TIBC were measured in whole blood while rest of parameters was estimated in serum samples. TFT was performed by electrochemiluminescence immunoassay (eCLIA) technology. CBC was carried out using automated cell counter. The TSH reference range was considered as 0.03-5.5 µIU/ml. Thus patients with TSH level >5.5 µIU/ml alongside reduced serum T4 and/or T3 level were considered as (overt) hypothyroid. Patients with TSH ≤4.0 µIU/ml (and ≥0.03 µIU/ml) with normal serum THs were designated as euthyroid. Those patients with TSH >4.0 µIU/ml (and <5.5 µIU/ml) with normal thyroxin levels were considered as subclinical hypothyroid cases.

Exclusion Criteria

Patients with known thyroid or hematological

Table 1: Prevalence of Different Types of Anemia in Various Thyroid Disorders.

Thyroid_Disorder/ Anemia_Type	Microcytic	Normocytic	No_Anemia	Total
Euthyroid	20 (12.66%)	76 (48.10%)	62 (39.24%)	158 (100%)
Subclinical Hypothyroid	16 (28.57%)	24 (42.86%)	16 (28.57%)	56 (100%)
Overt Hypothyroid	4 (14.29%)	16 (57.14%)	8 (28.57%)	100%)

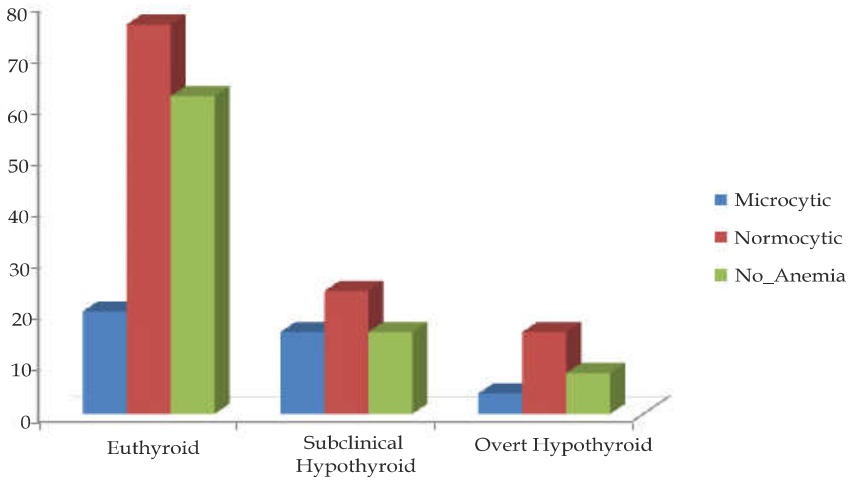

Fig. 1: Prevalence of Different Types of Anemia in Various Thyroid Disorders.

malignancy; or any other type of chronic disease were excluded.

Statistical Analysis

Kolmogorov-Smirnov test (N=242) was used to assess normality of parameters concerned. All the study parameters except serum iron, serum ferritin and TLC (Total Leukocyte Count) followed Gaussian distribution; thus was expressed as Mean± SD; compared by using Student's t-test (two groups) and one-way ANOVA (more than two groups); and correlation assessed by Pearson's correlation. Other three parameters, not following normal distribution, were expressed as Median (IQR); compared by using Mann-Whitney U test (two groups) and Kruskal Wallis test (more than two groups); and correlation assessed by Spearman Rank correlation. Chi Square test was employed for assessing comparison among proportions. IBM SPSS version 25.0 was used to carry out all statistical analyses.

Result

In this study, we considered register data of a particular time frame. Thus among 242 cases included (as per inclusion and exclusion criteria) 158 were euthyroid, 56 were subclinical hypothyroid and 28 were overt hypothyroid cases. All three groups were age-matched (p-value: 0.360) (Table 2). Serum iron, ferritin, TLC, neutrophil and lymphocyte were not following Gaussian distribution, thus compared using Kruskal Wallis test and correlation with other parameters accessed by Spearman Rank Correlation. Other parameters were following normal distribution, thus comparison among groups carried out using one-way analysis of variance (ANOVA) and correlation by Pearson's correlation.

Prevalence of various types of anemia in study population was analysed in-accordance with thyroid profile status. It was observed that ~71.5% of patients in both subclinical and overt hypothyroid groups were anemic compared to ~60% of euthyroid (control) group. Among anemic patients, 20% presented with microcytic anemia and 80% were normocytic in both overt hypothyroidism and control groups. But in subclinical hypothyroid group anemic patients, 40% were microcytic and 60% were normocytic. The comparison of different types of anemia prevalence in different study groups was compared using Chi Square test, which showed that the differences were not statistically significant. (Fig. 1, Table 1)

Table 2: Comparison Among Three Groups.

Parameters	Euthyroid (158) (A)	Subclinical (B) hypothyroid (56)	Overt (C) (28) hypothyroid	One-way ANOVA/KW test	
				F/ KWH	p-value
Age	23.9 ± 3.5	25 ± 3.4	25.43 ± 4.68	1.032	0.360
fT3	2.56 ± 0.63	2.31 ± 0.98	2.29 ± 1.02	1.079	0.344
fT4	0.96 ± 0.32	1.02 ± 0.17	1.02 ± 0.48	0.303	0.739
Serum Iron	78.23 ± 36.24	99.5 (74.5-152.7)	87 (64-100)	7.112	0.029
TIBC	494.33 ± 68.29	490.29 ± 62	491.86 ± 51.18	0.025	0.976
Serum Ferritin	25 (17.4-53)	19.85 (12.4-25.9)	28 (16.2-58.2)	2.088	0.352
Hb	11.54 ± 1.38	10.5 ± 2.11	9.71 ± 1.21	6.924	0.002
TRBC	4.17 ± 0.51	4.01 ± 0.71	3.93 ± 0.24	1.140	0.324
CI	1.03 ± 0.12	0.97 ± 0.09	0.917 ± 0.115	3.859	0.024
MCV	84.77 ± 6.12	81.8 ± 6.45	80.5 ± 5.35	2.643	0.076
MCH	27.78 ± 2.42	26.17 ± 2.59	25.64 ± 1.74	4.657	0.012
MCHC	32.64 ± 1.54	32.06 ± 1.67	31.91 ± 1.62	1.356	0.263
PCV	35.62 ± 3.78	32.68 ± 5.22	31 ± 2.94	6.864	0.002
TLC	10.1 (8.8-11.5)	8.9 (7.52-10.5)	10.3 (9.4-13.1)	4.654	0.098
N	77 (73-82)	72.5 (68-77)	78 (72-81)	5.357	0.069
L	19 (14-23)	22 (18.5-25.2)	17 (13-24)	4.522	0.104
M	2.78 ± 1.42	3.71 ± 1.26	3.57 ± 1.39	3.319	0.040
TPC	196.33 ± 69.93	226.36 ± 84.1	232.57 ± 46.24	1.723	0.184

CI: Color Index, Sig. (2-tailed): p-value [Column Width]

Bonferroni post-hoc:

Hb: AandB=0.056, BandC=0.775, CandA=0.008, CI: AandB=0.270, BandC=1.000, CandA=0.060, MCH: AandB=0.071, BandC=1.000, CandA=0.081, PCV: AandB=0.036,BandC=1.000, CandA=0.012, M: AandB=0.072, BandC=1.000, CandA=0.472.

Table 3: Correlation Among Parameters:

Pearson's Correlation	Correlation Coefficient	p-value	Pearson's Correlation	Correlation Coefficient	p-value
TSH and fT3	-.117	.245	TSH and TIBC	.002	.986
TSH and fT4	-.011	.914	TSH and MCV	-.191	.057
TSH and Hb	-.319	.001	TSH and MCH	-.291	.003
TSH and TRBC	-.114	.257	TSH and MCHC	-.115	.253
TSH and PCV	-.296	.003	TSH and CI	-.270	.007
TSH and TPC	.135	.181			
Spearman Correlation	ρ	p-value	Spearman Correlation	ρ	p-value
TSH and s_iron	.364	<.001	TSH and s_ferritin	.108	.284
TSH and TLC	-.142	.159			

[Spearman ρ (serum iron, serum ferritin, TLC)] [Pearson's Correlation Coefficient: (Rest)] [Column Width]

Study parameters were compared across three groups (euthyroid, subclinical hypothyroid and overt hypothyroid). Serum iron (KWH: 7.112, p=0.029); Hemoglobin (F: 6.924, p=0.002); CI (F: 3.859, p=0.024); MCH (F: 4.657, p=0.012); PCV (F: 6.864, p=0.002) and Monocyte count (F: 3.319, p=0.040) were found to statistically significantly differ among three groups. Bonferroni post-hoc analysis (carried out with ANOVA) has shown statistically significant reduction of hemoglobin and PCV in overt hypothyroid cases compared to euthyroid. But only PCV had exhibited statistically significant reduction in subclinical hypothyroid group in comparison to euthyroid group. (Table 2)

Serum TSH level exhibited a significant positive correlation with serum iron level. In contrast significant negative correlation of serum TSH was observed with hemoglobin, PCV, MCH and color index. (Table 3)

Discussion

Thyroid, the largest endocrine organ, is perhaps the most important endocrine gland in human as per functional perspectives.[4] Thyroid hormones regulate the metabolic rate of various tissues, hematopoietic tissues inclusive.[4-6] These hormones augment erythropoiesis both via direct and indirect (erythropoietin gene expression) mechanisms.[21-24,26-33] Hypothyroidism is the most common thyroid dysfunction where blood levels of THs are reduced. Subclinical hypothyroidism is more prevalent than overt hypothyroidism.[5] Subclinical hypothyroidism is associated with more complications and most of the patient progress to overt hypothyroidism in due course.[5]

Hypothyroidism has been reported to be associated with either anemia (mostly) or immature erythroid progenitor proliferation.[42] Anemia prevalence among hypothyroids has been estimated to be falling between 20% and 60%.[49] According to our finding, >70% patients in both subclinical and overt hypothyroid groups were anemic compared to ~60% of euthyroid (control) group. Since Northern India is in the goiter belt and thus soil iodine deficiency may be the major contributing factor for higher prevalence. Also our study participant selection was by convenient sampling and may not be random enough and/ or sufficient sample size to represent the true population.

Though normocytic, microcytic and macrocytic anemia, all types are reported in hypothyroids; microcytic hypochromic (mimicking iron deficiency) anemia is the most common presentation.[27,35,50,66] But studies also reported preponderance of macrocytic anemia in hypothyroid cases.[33,42,67] as well as both normo- and macrocytic anemia in hypothyroids.[5] Our findings were majority of normocytic anemia (80% in overt and 60% in subclinical hypothyroids) with microcytic anemia in minority. None of macrocytic anemia cases reported in hypothyroids of our study. This indicates coexistence of iron deficiency in the population.

In hypothyroid cases, reduced levels of erythropoietin[5], hemoglobin, TRBC, MCH and MCHC and raised MCV and PCV were reported.[4,33] Other study reported only MCV increased and no difference in Hb or PCV in hypothyroids compared to controls.[68] One study also shows no significant difference in all these hematological parameters in hypothyroid cases.[69] In our study, we report reduced levels of all erythroid markers {hemoglobin, TRBC, color index (CI), MCV, MCH, MCHC and PCV} and TIBC where as significant increase in serum iron. Among reduced parameters, reduction of Hb, PCV, MCH and CI were statistically significant. Prevalence of anemia in hypothyroids may be a physiological adaptation to the decrease in tissue oxygen requirement owing to lower metabolic rate in absence of sufficient THs.[5] All these alterations in hematological parameters normalize once appropriate hormonal replacement is instituted.[70] We also report significant negative correlation of serum TSH with Hb, CI, PCV and MCH and significant positive correlation of serum TSH and serum iron.

Conclusion

Both subclinical and overt hypothyroidisms have direct effects on all red cell indices. Thus all patients with hypothyroid state should be screened at regular interval for development of hematological (particularly erythroid indices) abnormality, hence appropriate correction in treatment regime can be instituted at an earlier stage. All cases of anemia (particularly treatment resistant ones) should be screened for thyroid abnormality as subclinical conditions are very much prevalent in our population.

Conflict of Interest: The authors declare no conflict of interest.

Acknowledgement: We thank our patients and acknowledge staffs for their support.

Funding: Being a retrospective study based on previous records, no fund was utilized.

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