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ORIGINAL RESEARCH

Comparative analysis of Iron profile and hematological abnormalities in newly diagnosed treatment naive hyperthyroid patients: Tertiary care hospital based study

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ABSTRACT

Background: Thyroid hormones play an important physiological role in hematopoiesis, especially erythropoiesis. Erythrocyte abnormalities are frequently associated with thyroid dysfunction especially hypothyroidism. However, hyperthyroidism are rarely investigated and related to the hematological indices and iron profiling in Kashmiri Patients. **Objectives:** In this study an attempt is made to study hematological parameters and iron profile in hyperthyroidism Patients. **Materials and methods:** This case-control study included 200 subjects**,** among which were untreated hyperthyroidism (n=100) and euthyroid (n=100). This study was carried out at Post Graduate Department of Physiology in collaboration with Department of Endocrinology Government Medical College Srinagar. The hematological parameters, Iron and thyroid profile of the subjects were assessed by the Sysmex(Italy) and Allinityi Abbott (USA) automatic analyzer. **Results:** We evaluated the haematological parameters between untreated hyperthyroidism and euthyroidism in this study group. We discovered that untreated hyperthyroid individuals had considerably lower hematological indices ($p<0.001$) than euthyroid patients, including Hb, MCV, HCV, RBC, and RDW%. Hb (12.3±1.7 g/dl), RBC (4.4±0.89106/µl), MCV (74.34±9.71 fL), HCT (36.4±2.1%), RDW (14.4±1.8 fL), and RBC% (82.7±12.3%) are the values for untreated hyperthyroidism. These patients may be at risk for anemia and other erythrocyte abnormalities based on their Hb (14.8±1.9 g/dl), RBC (4.9±0.95 106/µl), MCV (84.56±3.84 fL), HCT (39.5±3.1%), RDW (13.5±1.2 fL), and RBC% (84.36±10.36 %). Additionally Ferritin and TIBC levels are higher in hyperthyroid individuals than in controls ($p<0.001$). **Conclusion**: **The thyroid dysfunction is frequently associated with anemia in subclinical hyperthyroidism. Erythrocyte abnormalities are associated with predisposition of the disease which further leads to imbalance of thyroid hormones and iron profile.**

Key words: hyperthyroidism, blood count, hemoglobin, red cell distribution, mean corpuscular volume.

INTRODUCTION

The hyperthyroidism is characterized by elevated thyroid hormone synthesis and its release from the thyroid gland [1]. Numerous research have examined the frequency of hyperthyroidism in India. Subclinical and overt hyperthyroidism were found in 1.6% and 1.3% of participants in a community survey [2], respectively, in an epidemiological investigation from Cochin.In a Pondicherry-based study conducted in a hospital, 0.6% and 1.2% of the participants had subclinical and overt hyperthyroidism, respectively [3].The basis for the laboratory diagnosis of hyperthyroidism is serum thyroid-stimulating hormone (TSH), as well as serum hormones (T4) and (T3). While T4 and T3 levels are high, TSH levels are low. [4]. Hyperthyroidism is frequently characterized by tachycardia, restlessness, tremor, weakness, and heat sensitivity in addition to weight loss despite an increase in appetite [5]. Other signs of hyperthyroidism were considered, including agitation and anxiety, sweating, insomnia, and diarrhea [6].Subclinical hyperthyroidism has two types of causes: endogenous

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and external. The thyroid gland's overproduction of thyroid hormone is the most common endogenous cause of endogenous subclinical hyperthyroidism. Exogenous sources include exposure to exogenous iodine and levothyroxine medication [7]. The main cause of this acquired condition is chronic autoimmune thyroiditis (inflammation of the gland).

Hyperthyroidism is a systemic disorder. In addition to the well-known effects of excessive thyroid activity, such as those on the cardiovascular system and bone metabolism, excess thyroid hormone disrupts iron metabolism by raising ferritin and affecting other hematological parameters. Once the patient reaches a euthyroid state, these anomalies disappear temporarily and return to normal. The condition known as hyperthyroidism, which can cause erythrocytosis, does not usually present with anemia. Iron is an essential cofactor in basic metabolic processes, such as the transfer of oxygen. Because elevated iron levels can be harmful, the body's metabolism of iron is strictly managed. A number of proteins are essential to the metabolism of iron. Transferrin-bound iron is moved throughout the plasma and internalized through receptor-mediated endocytosis. The main component in charge of storing and buffering excess iron is intracellular ferritin [8]. Hepcidin is a peptide hormone generated from the liver and one of the key players in iron homeostasis regulation.By down regulatingferroportin 1 (FPN-1), which encourages iron efflux out of cells (enterocytes, hepatocytes, or macrophages), it decreases plasma iron. Hepcidin-25, the bioactive version of the protein, has 25 amino acids [9,10]. Anemia in hyperthyroidism can be due to altered iron metabolism, oxidative stress and hemolysis due to increased osmotic fragility. Anemia is a prevalent clinical condition, with a general In certain regions of the world, the population may reach up to 10%, with women of childbearing age and the elderly making up the majority population. Anemia is characterized by a decrease in hemoglobin (Hb) or red blood cells (RBC), which lowers the blood's capacity to deliver oxygen to bodily tissues. The World Health Organisation (WHO) recommends that anaemia be diagnosed when the Hb level is less than or equal to 12.0 g/dL for women and less than or equal to 13.0 g/L for males. Mean corpuscular volume (MCV) between 80 and 100 fl is considered normocytic anemia; MCV below 80 fl indicates microcytic anaemia; and MCV beyond 100 fl indicates macrocytic anemia[11-13].

Thyroid hormones influence blood parameters directly through their stimulation of erythrocyte precursors and indirectly through their enhancement of erythropoietin synthesis [13]. anemia can also be caused by bone marrow suppression and other associated comorbid diseases [14]. Patients with thyroid abnormalities may also have low iron levels, which can affect hemoglobin levels. Additionally, they may have reduced levels of both folate and B12, which have been detected in up to 25% of patients. Lack of literature on hyperthyroidism and hematologicalabnormalities lead us to attempt to investigate the role of hematological indices and iron profile in hyperthyroidism in Kashmiri patients.

MATERIALS METHODS

Subjects and recruitment process

This cross sectional-hospital based study was conducted at the Post graduate Department of Physiology, in collaboration with Department of Endocrinology Government Medical College Srinagar from April 2022 to February 2024. All patients were referred from Out-Patient Department (OPD) and Inpatient Department (IPD) of Government Medical College Srinagar and its associated Shri-Maharaja Hari Singh Hospital (SMHS) hospital, a major referral hospital of Kashmir valley (North-India), to the diagnostic Biochemistry and Hematology laboratory of Government Medical College Srinagar for the evaluation of thyroid function test, Iron profiling, and analysis of blood count (CBC). The study was approved by Institutional ethical committee of Government Medical College (GMC) Srinagar. Individuals who fulfilled exclusion criteria for hyperthyroidism diseases and gave consent to participate in the study were recruited as normal. All the Subjects' information was kept confidential. Patients and normal subjects recruited for study were age matched and gender matched. A total of 200 subjects were selected for the study. These included the hyperthyroid untreated (n=100), and normal-controls (n=100).

Exclusion criteria: Patients with ischemic heart disease, cerebrovascular and neurological diseases, diabetes mellitus, chronic renal impairment, known psychological illnesses, previous history of thyroid disease or previous thyroxine therapy, asthma and pregnancy.

Inclusion criteria: Hyperthyroid patients, Kashmiri ethnicity, normal patient.

Blood Sample collection

About 5-6 ml of venous blood was collected, 3 ml blood was taken in EDTA vials and remaining 3 ml was centrifuged to separate serum from the cells as soon as the clot was formed.

Measurement of Hematological parameters

The 3ml peripheral venous blood was taken in sterilized EDTA vials. The complete blood count and haemogram comprised of (Hb, TLC, DLC, RBC, PLT, MHC, MCV, MCHC, PDW, RDCV, LYM%, GRA%, HB%, RBC%, Color Index, ESR). Blood samples were processed manually for various hematological indices mainly hemoglobin (Hb), total erythrocyte counts (TEC), total leukocyte count (TLC), mean corpuscular value (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular

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hemoglobin concentration (MCHC), Red cell width distribution(RDW). The CBC and haemogram were assayed in Sysmex (Italy) haemocytometer analyzer. The Erythrocyte sedimentation rate (ESR) was determined by Wintrobe's method. The Hb%, RBC% and Color Index were determined by the formulae *(*Godkar *et al*., 2020*).*

Hb%=100*Hb value/14.5
RBC%=100* RBC Count/5.0
Color Index=Hb%/RBC%

Measurement of thyroid hormone profile

Serum aliquots were stored at 4ºC to be run in batches. The samples were allowed to thaw prior to assay, mixed thoroughly. Hemolysed and lipemic samples were rejected. Bi level i.e. high and low control was run with each batch .Iron Profile and Thyroid function test (TFT) comprising of FT3, FT4, T3, T4 and TSH levels was carried out by chemiluminescence **I**mmuno**a**ssay method using fully automatic analyzer Allinity i(Abbott, USA).

Statistical Analysis

Data were extracted and analysed by GraphPad Prism 12.0. The results were expressed as mean ± standard deviation (SD).Qualitative data were expressed as frequency and percentage. To equate proportions between two qualitative variables, the Chi-square (X2) test of significance was used.The differences were considered to be significant at $p<0.05$or $p<0.01$.

RESULTS

In this study, the total 200 subjects participated in the research among which 57% were females and 43% were males, in the age group between 25-60. There were 100 euthyroid (normal) and 100 hyperthyroid (untreated). Median + Standard deviation values of Hb, RBC,WBC, MCV, RDW, Hct, Lym%, Hb% and RBC% with respect to Fe-PI, TRF, TIBC, FT3, FT4 T3, T4 and TSH were assessed and data are presented as P-value. The value of $P<0.05$, denotes results are stastically significant and have association in the thyroid disorder and iron imbalance.The general characteristics of hundred hyperthyroid patients (n=100) were discussed in Table 1. Mean age of the hyperthyroid patients was 39.9 ± 12.3 years and among 100 hyperthyroid patients males were (n = 43) and females (n=57). The prevalence and etiology of hyperthyroidism patients of our study was Graves disease (80%), toxic multinodular goiter (18%), toxic adenoma (1%), and subacute thyroiditis (1%). In our observation and clinical symptoms reported by hyperthyroidism patients includepalpitation (40%), exertional dyspnea (50%), and atypical chest pain (10%). The Anthropometric and socio-demographic characteristics like BMI, Residence and duration within one year shows statically significant ($p<0.005$) (Table 1). There was no relationship of familial history with disease. Gender wise distribution of hyperthyroidism patients is shown as Pie-chart (Figure 1).

Table 1. General characteristics of the hyperthyroid patients in study subjects.

Parameters	Hyperthyroid patients N=100	P Value
Age (Years)	**39.9±12.3**	**0.851**
Gender (n%) **Male** **Female**	 **43 (43%)** **57 (57%)**	**0.565**
BMI (kg/m2) **(18.5-24.9 Kg/m2)**	**27.4±2.6**	**<0.005**
Residence (n%) **Rural** **Urban**	 **62 (62%)** **28 (28%)**	**<0.005**
TSH **(0.35 to 5.0 uIU/ml)**	**0.005±0.1**	**<0.001**
Duration **< 6 months** **>6 months**	 **70 (70%)** **30 (30%)**	**<0.005**
Familial History **Yes** **No**	 **10 (10%)** **90 (90%)**	**0.741**
Types of Hyperthyroidism ✓ **Graves Disease** ✓ **Toxic multi nodular goitre** ✓ **Toxic adenoma** ✓ **Subacute hyper thyroiditis**	 **80 (80%)** **18 (18%)** **1 (1%)** **1 (1%)**	**<0.005**
Symptoms (n%) **Palpitation** **Exertionaldyspnea** **Atypical Chest Pain**	 **40 (40%)** **50 (50%)** **10 (10%)**	**<0.005**

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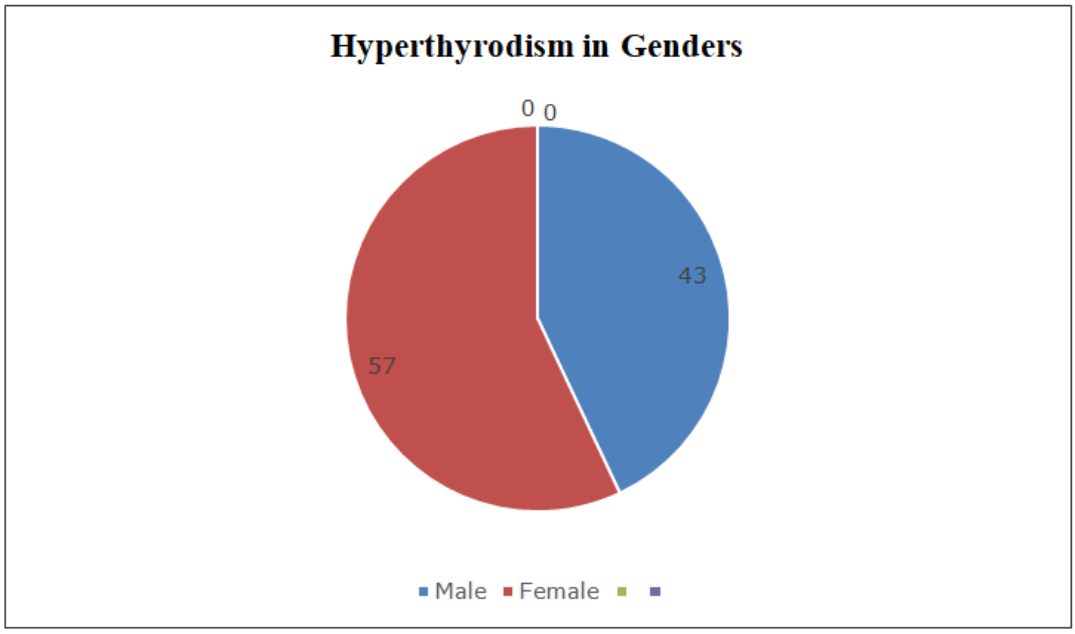

Figure 1: Pie chart Diagram showing distribution of hyperthyroidism in both Genders.

Table 2. Comparison of Thyroid profile and Iron Profile parameters between hyperthyroidism and normal.

Parameters	Control N=100	Hyperthyroidism N=100	P Value
T3 (0.6-1.6 ng/ml)	4.1 ± 1.5	5.5 ± 0.75	<0.001
T4 (4.8-11.72 ug/dl)	17.3 ± 2.5	22.3 ± 3.5	<0.001
TSH (0.35 to 5.0 uIU/ml)	0.09 ± 0.03	0.01 ± 0.1	<0.001
FT3 (1.7-3.7 pg/ml)	4.8±0.5	5.2±0.4	<0.001
FT4 (0.7-1.48 ng/dl)	2.5±0.1	3.2±0.5	<0.001
Anti-TPO (0.00-5.61 IU/ml)	157.46±50.5	215±45.5	<0.001
Iron-Protein 50-70 µg/dl	57.5±5.5	48.5±5.5	<0.001
Ferritin M=22-274 µg/dl F=10-204 µg/dl	95.5±25.5	172.5±24.5	<0.001
TRF 170-370 mg/dl	350±45.5	305±25.5	0.004
TIBC 70-310 µg/dl	275±25.5	330±15.5	<0.001

(Abbreviations:- T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid Stimulating Hormone, FT3: Free triiodothyronine, FT4: Free Thyroxine, Anti-TPO's: Anti-Thyroid Peroxidase, TRF: Transferrin, TIBC: Tissue Iron Binding Capacity).

Summarized in Table 2: In the group I (Euthyroid/ Controls), the levels of thyroid profile parameters are as: T3 : 4.1 ± 1.5, T4: 17.3 ± 2.5,TSH: 0.09 ± 0.03, FT3: 4.8±0.5, FT4: 2.5±0.1, Anti-TPO: 157.46±50.5, Fe-Pi: 57.5±5.5, Ferritin: 95.5±2.5, TRF:350±4.5, TIBC: 275±25.5 Whereas, in group II (Hyperthyroidism), thyroid profile parameters are as: T3: 5.5 ± 0.75, T4: 22.3 ± 3.5, TSH: 0.01 ± 0.1, FT3: 5.2±0.4, FT4: 3.2±0.5, Anti-TPO: 215±45.5, Fe-Pi: 48.5±5.5, Ferritin: 12.5±4.5, TRF:305±25.5, TIBC: 330±15.5 Across the groups all thyroid profile and Iron profile parameters are stastically significant ($p<0.001$).

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Table 3: Comparison of WBC's Count in hyperthyroid cases and controls.

White Blood Cell Count Indices	Hyperthyroid cases N=100	Controls N=100	P-Value
TLC (10^3/µl)	8.2±2.1	7.4±1.91	0.186
Neutrophil (10^3/µl)	5.15±1.65	4.21±1.0	0.097
Lymphocytes (10^3/µl)	2.5±0.97	2.6±0.91	0.340
Monocytes (10^3/µl)	0.5±0.1	0.4±0.2	0.829
Eosinophil (10^3/µl)	0.2±0.2	0.2±0.2	0.791
Basophil (10^3/µl)	0.019±0.05	0.01±0.03	0.499

As shown in table 3, no statistically significant difference was noted between the studied groups regarding TLC, neutrophil, lymphocytes, monocytes, eosinophil, and basophil (P-value > 0.05)

Table 4: Comparison of Hb, RBC and Platelet count in hyperthyroid cases and controls.

Haematological indices	Hyperthyroid cases N=100	Controls N=100	P-Value
Hb(g/dl)	12.3±1.77	14.8±1.93	<0.001
RBC(10^6/µl)	4.4±0.89	4.9±0.95	0.084
HCT(%)	36.4±2.1	39.5±3.1	0.005
MCV(fL)	74.34±9.71	84.56±3.84	<0.001
RBC (%)	82.71±12.3	84.36±13.2	0.008
MCHC (g/dl)	33.8±1.9	35.0±1.85	0.065
MCH (pg/cell)	28.6±2.8	29.5±1.5	<0.001
RDW (%)	14.4±1.8	13.5±1.2	0.001
Platelets x10^3/µl)	285.3±84.0	271.4±79.0	0.749

Table 4 summarizes that, HCT and Hb were significantly lower in the hyperthyroidism groups than in the normal group (p-value < 0.05). RDW was significantly higher in hyperthyroidism than in the normal group (p-value < 0.05). Hb, MCV and MCH were significantly lower in the hyperthyroidism groups than the normal group (p-value < 0.001). No significant differences were reported between the study groups regarding RBCs, MCHC, and platelets (P-values > 0.05).

DISCUSSION

Our goal in the current study was to evaluate the Iron Profile in hyperthyroidism and the daily routine blood cell characteristics. One hundred patients with hyperthyroidism participated in this study. One hundred euthyroid people have been selected to serve as the control group. The age and sex of the control participants were chosen to match that of the patients. Regarding the demographic information, the mean age of the hyperthyroid patients was 39.9 ± 12.3 years, with n = 43 males and n = 57 females among the 100 hyperthyroid patients. An essential endocrine gland in our body, the thyroid controls lipid metabolism, protein synthesis, glucose metabolism, and appropriate growth and development. It also controls our body's hematopoiesis. Anaemia can range in severity and type depending on the thyroid gland's health issues. Thrombocytopenia, leukopenia, pancytopenia, and abnormalities in blood indices such as PCV, MCV, MCHC, RDW, and Hb have all been linked to hypothyroidism. HCT and Hb were substantially lower in the hyperthyroidism groups than in the normal group (p-value < 0.05), according to our study's findings in both the hyperthyroidism and control participants. RDW was much greater in the hyperthyroid group compared to the normal group (p-value < 0.05). The groups with hyperthyroidism had considerably lower levels of Hb, MCV, and MCH compared to the normal group (p-value < 0.001). Regarding RBCs, MCHC, and platelets, no significant changes were found across the research groups (P-values > 0.05). The study concurs with the findings of Kawa et al. (2010)[15]. In a different study, Carmen S.P. Lima et al. (2006) presented their findings about four patients of pancytopenia with grave's disease. They determined that in order to rule out the causes of pancytopenia , a thyroid evaluation is necessary [16].The results of our investigation compared the characteristics of the thyroid and iron profiles in patients and controls. The thyroid profile parameters in group I (Euthyroid/Controls) are as follows: Anti-TPO: 157.46±50.5, Fe-Pi: 57.5±5.5, Ferritin: 95.5±2.5, TRF: 350±4.5, TIBC: 275±25.5, T3: 4.1 ± 1.5, T4: 17.3 ± 2.5, TSH: 0.09 ± 0.03, FT3: 4.8±0.5, FT4: 2.5±0.1 In contrast, the thyroid profile values for group II (hyperthyroidism) are as follows: T3: 5.5 ± 0.75, T4: 22.3 ± 3.5, TSH: 0.01 ± 0.1, FT3: 5.2±0.4, FT4: 3.2±0.5, Anti-TPO: 215±45.5, Fe-Pi: 48.5±5.5, Ferritin: 12.5±4.5, TRF: 305±25.5, TIBC: 330±15.5. Every measure related to the thyroid and iron profiles is statistically significant (p<0.001) across all groups. The study is consistent with prior research conducted on various populations.According to a study by AbdollahJafarzadeh et al., patients with abnormal thyroid function had significantly lower MCVs than those with euthyroid status. This finding is consistent with our own research, which found that patients with

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hyperthyroidism had lower MCVs than normal individuals (P <0.001) [17].

Red cell distribution width (RDW), which measures the extent of RBC anisocytosis, is elevated in individuals with iron-deficiency anaemia, vitamin B12 and folate deficiencies, and thyroid function abnormalities. We found a strong relationship (P value 0.001) between thyroid dysfunction, iron insufficiency, and RDW in our investigation [18, 19]. The most prevalent kind of anaemia in people with thyroid dysfunction is microcytic anaemia, and studies have shown that MCV is lower in these patients than in people with normal thyroid function. In our investigation, we discovered a highly significant relationship (P <0.001) between MCV and Hb, respectively, and thyroid malfunction (hyperthyroidism) [20]. Ferritin and TIBC levels were higher in hyperthyroidism in our study than in controls (p<0.001), which is consistent with research by Kuboto K et al. (1993) [21]. Additionally, they stated that four anaemic patients had serum ferritin levels that were noticeably greater than those of nine nonanemicindividualsThus, it may be inferred that the direct effect of thyroid hormones on the synthesis of serum ferritin may account for the increase in levels observed in patients with hyperthyroidism; in certain situations, however, reduced iron utilisation by erythropoietic cells may also play a role. Numerous studies have indicated that the condition of thyroid function has less of an impact on platelets. This may be because platelets are non-nucleated and have a short lifespan with continuous rapid turnover (p=0.749) [22].

CONCLUSION

The study found that while erythrocyte irregularities affect all blood parameters and that hyperthyroidism patients are more prone to iron deficiency anaemia, platelets are less affected than other parameters (such as WBC count), suggesting that thyroid hormones play a critical role in blood formation. Thyroid hormone imbalance must be controlled with appropriate drug therapy in order to improve patients' quality of life.

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