Original Research Article

A study of anemia in primary hypothyroidism

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ABSTRACT

Background: The association between anemia and hypothyroidism has been recognized, although the prevalence of anemia in hypothyroid patients varies widely between studies. The main objectives were to study the prevalence, type, etiology of anemia in primary hypothyroidism and to correlate severity of anemia with severity of hypothyroidism.

Methods: A case control study was carried out in a tertiary care hospital. Newly diagnosed 60 overt primary hypothyroid patients and 180 euthyroid controls were evaluated for anemia. Morphological types of anemia, their etiology were studied. Severity of anemia was correlated with that of hypothyroidism.

Results: Anemia was observed in 45 patients with hypothyroidism. Symptoms due to anemia were significantly higher in cases than in the anemic controls. RBC morphology showed normocytic normochromic in 39, microcytic hypochromic in 14 and macrocytic in 7 cases. Serum iron was significantly lower in the cases than in the controls. Serum anti-TPO positivity was 63.33% in cases as compared to 10% in controls. Anemia was severe in cases with high TSH.

Conclusions: The prevalence of anemia was 75% which was higher than that seen in the euthyroid controls. Hypothyroid patients were more symptomatic for anemia than the controls. Normocytic normochromic type of anemia was the most common type in our study. Autoimmunity in the form of anti-TPO positivity was detected in 69% of anemic cases. Iron deficiency was observed in the cases more than in the controls. There was a statistically significant negative correlation between TSH and hemoglobin.

Keywords: Anemia, Anti TPO, Primary hypothyroidism, TSH

INTRODUCTION

Hypothyroidism is a common disease with varying frequency between countries. A decreased thyroid hormone adversely affects erythropoiesis; anemia develops in hypothyroidism.[1] Abnormalities in hematological parameters have been noted in patients with thyroid diseases. Nevertheless, the exact mechanism of thyroid hormones action on human hematopoiesis is exactly not clear.[2] According to the data of WHO, anemia prevalence is 24.8% throughout the world and it is seen more frequently in underdeveloped countries.[3]

Prevalence of anemia in subclinical and overt hypothyroid groups was 26.6 % and 73.2 %, respectively. Thus, the frequency of anemia in subclinical hypothyroidism is higher than in general population (non-hypothyroid). Therefore, presence of hypothyroidism is a risk factor for anemia. Normocytic anemia, which is the most frequent type of anemia in hypothyroid patients is caused by lack of stimulation of erythroid colony development, reduction in oxygen distribution to tissues and diminution of erythropoietin level.[4] The second most common type of anemia is microcytic anemia due to iron deficiency (43.2%) which is one of the most frequently

seen diseases all over the world. Larson found that 52% (13 out of 25) of his patients of hypothyroidism had iron deficiency anemia, based on the finding of a low determination of serum iron.[5] Iron deficiency anemia is largely due to menorrhagia occurring as a result of various hormonal instability and malabsorption observed in hypothyroidism.

Prevalence of vitamin B12 deficiency increases along with the age and the prevalence was observed as 1.6% to 10% in Europe.[6] Vitamin B12 deficiency mostly occurs as a result of malabsorption due to pernicious anemia accompanying hypothyroidism. Antiparietal cell antibody was present in 3 patients (4.8%) out of the 6 patients with macrocytic anemia. Most common cause of anemia in hypothyroidism is normocytic normochromic and replacement of levothyroxine corrects this type of anemia.

The association between anemia and hypothyroidism has been recognized, although the prevalence of anemia in hypothyroid patients varies widely between studies.1 Present study was carried out to investigate and explore primary hypothyroid patients, to know prevalence, types and severity of anemia in them as compared with controls.

Aims of the study were to study prevalence of anemia in primary hypothyroidism, to study types and etiology of anemia in primary hypothyroidism, to correlate severity of anemia with primary hypothyroidism.

METHODS

Patients attending Endocrinology and Medicine out-patient department of a tertiary care hospital were the source of the data.

Inclusion criteria

- Laboratory confirmation of primary overt hypothyroid patients (TSH >10 IU/ml)
- Age > 18 years
- Patients willing to give written informed consent.

Exclusion criteria

- Other comorbidities (connective tissue disorders, haemoglobinopathies, bleeding disorders) causing anemia
- Secondary hypothyroid patients
- Patients on anti-thyroid drugs (carbimazole, amiodarone, radio-iodine, propylthiouracil and others)
- Patients on hematinic
- Post-thyroidectomy hypothyroid patients
- Obesity (BMI>35).

Criteria for selection of controls - age, sex, socio-economically matched euthyroid individuals who were

not relatives of the patients and were without family history of hypothyroidism.

Methodology

It was a case control study which was carried out in a tertiary care hospital after obtaining approval from the institutional Ethics committee. Newly diagnosed 60 overt primary hypothyroid patients and 180 euthyroid controls were included in the study. A detailed history was taken, a thorough clinical examination was done and investigations were done for evaluation of anemia. Complete blood count (CBC) and peripheral smear examination were the basic investigations for anemia. Based on the RBC morphology they were divided into the following groups and the specific investigations were carried out to determine the etiology of anemia.

Normocytic normochromic: coombs test (to rule out autoimmune etiology)

Microcytic hypochromic: stool OB, upper GI scopy (wherever indicated), iron study (to rule out iron deficiency)

Macrocytic: Vitamin B12 levels (to rule out vitamin B12 deficiency). Test for anti-parietal cell antibodies was not done due to financial constraints.

Anemia was classified as[7]

- Mild - Hb 10 to 12 gm%
- Moderate - Hb 8 to 10 gm%
- Severe - Hb< 8 gm%.

Estimation of serum anti-TPO antibodies in addition to the thyroid function test (T3, T4, and TSH) was carried out in both the groups.

The collected data was analyzed by applying appropriate statistical tests- chi square test, (with continuity correction for all tables (2 by 2) and fisher exact test (for all 2 by 2 tables where p-value of chi-square test is not valid due to small counts), unpaired t-test (if data passes normality test), mann-whitney test (if data fails normality tests)

RESULTS

The mean age was 34.60±11.27 years in the cases and 35.01±11.13 years in the control group. On comparing it was found that age of the two groups in the study was comparable.

Amongst the cases, males were 8.33% and females were 91.67%. Controls had 9.33% males and 91.67% females. Thus both the groups were comparable regarding the sex distribution. The mean socioeconomic status of both the groups was comparable with predominance of the poor class. In the cases, 57% patients had complaints of

fatigue while in the control group none of the participants had complaints of fatigue. On comparing it was found that fatigue occurs significantly higher in the cases than in the controls. Dyspnea on exertion was present in 13.33% cases and none of the controls. On comparing it was observed that the dyspnea on exertion is significantly higher in the cases than in the controls. Generalized weakness was present in the 88.33% cases and none of the controls. On comparing it was found that the generalized weakness is significantly higher in the cases as compared to the controls. History of weight gain was observed in 5% cases and none of the controls. On comparing it was observed that the weight gain was significantly higher in the cases as compared to the controls (Table 1).

History of blood transfusion was present in 1.67% cases and none of the controls. On comparing it was found that the history of blood transfusion of the two groups is comparable to each other. Family history of hypothyroidism was present in 1.67% cases and none of the controls.

The pulse rate in the cases and controls was 77.75±9.84 and 80.43±5.94 per minute respectively. On comparing it was found that the pulse is significantly lower in the cases as compared to the controls. The systolic blood pressure in the cases and controls was 112.53±8.85 and 115.67±11.83 mmHg, respectively. On comparing it was found that the systolic blood pressure of the two groups was comparable to each other. The diastolic blood pressure of the cases and controls was 72.70±7.87 and 78.26±9.45 mmHg, respectively. On comparing it was found that the diastolic blood pressure was significantly lower in the cases as compared to the controls.

Among the cases, 50% had pallor of grade 1+ and 20% had pallor of grade 2+ while 30% had no evidence of pallor. Among the controls, 16.11% had pallor of grade 1+ and 4.44% had pallor of grade 2+ while 79.44% had no evidence of pallor. On comparing it was found that pallor is significantly higher in the cases as compared to the controls.

Table 1: Symptoms.

Parameters	Case (60)	Control (180)	Statistical test	P value and its interpretation
Fatigue	Y: 57 (95%) N: 3 (5%)	Y: 0 N: 180 (100%)	Fisher's exact test	<0.0001. Fatigue is significantly higher in the cases as compared to the controls
Dyspnea on exertion	Y: 8 (13.33%) N: 52 (86.67%)	Y: 0 N: 180 (100%)	Fisher's exact test	<0.0001. Dyspnea on exertion is significantly higher in the cases as compared to the controls
Generalized weakness	Y: 53 (88.33%) N: 7 (11.67%)	Y: 0 N: 180 (100%)	Fisher's exact test	<0.0001. Generalized weakness is significantly higher in the cases as compared to the controls
Weight gain	Y: 3 (5%) N: 57 (95%)	Y: 0 N: 180 (100%)	Fisher's exact test	0.015. Weight gain is significantly higher in the cases as compared to the controls

Table 2: Hemoglobin.

Parameter	Case (60)	Control (180)	Statistical test	P value and its interpretation
Hb (g/dL)	9.94±2.03	12±2.19	Mann Whitney test	<0.0001. Hb is significantly lower in the cases as compared to the controls

Icterus was absent in both cases and controls. Edema was not observed in both the groups. The nutrition was average in both cases and controls. The respiratory and cardiovascular system findings were normal in both cases and controls. Splenomegaly was absent in both cases and controls.Reflexes of grade 1+ were present in 2.33% cases and none of the controls. The reflexes of grade 2+ were present in 96.67% cases and all controls. On comparing it was found that the grades were comparable to each other in the two groups.

The hemoglobin level (gm/dl) in the cases and controls was 9.94±2.03 and 12±2.19 respectively. On comparing it was observed that the hemoglobin was significantly lower in the cases as compared to the controls. (Table 2)

The mean corpuscular volume (MCV) in the cases and controls was 82.3±11.17 and 84.11±5.26 FL respectively. On comparing it was found that the MCV of the two groups was comparable with each other. The mean corpuscular hemoglobin (MCH) of the cases and controls was 30.91±4.64 and 31.98±2.97 pg respectively. On comparing it was found that the MCH was significantly lower in the cases as compared to the controls.

Of the 60 cases included in the study, 65.9% patients RBC morphology was normocytic normochromic. Microcytic hypochromic morphology was observed in 22.72% patients had and 11.36% had macrocytic morphology (Figure 1).

Table 3: Serum TSH levels.

Parameter	Case (60)	Control (180)	Statistical test	P value and its interpretation
TSH	45.49±46.11	3.81±0.76	Mann Whitney test	<0.0001. TSH is significantly higher in the cases as compared to the controls

Table 4: Serum iron.

Parameter	Case (60)	Control (180)	Statistical test	P value and its interpretation
S. Iron	69.07±31.46 Count: 38	74.102±23.57 Count: 39	Unpaired T test	<0.0001. S. iron is significantly lower in the cases as compared to the controls

Table 5: Anti TPO.

Parameter	Case (60)	Control (180)	Statistical test	P value and its interpretation
Anti TPO	Positive: 38 (63.33%) Negative: 22 (36.67%)	Positive: 18 (10%) Negative: 162 (90%)	Fisher's exact test	<0.0001. The incidence of positive anti-TPO is significantly higher in the cases as compared to the controls

Table 6: Anti TPO in cases and controls with anemia.

	Cases with anemia	Controls with anemia	Total
Anti TPO positive	31	3	34
Anti TPO negative	14	56	70
Total	**45**	**59**	**104**

Of the 180 controls, approximately 94.44% of them had normocytic normochromic RBC morphology, 5% had microcytic hypochromic RBC morphology and only 1 patient had Macrocytic normochromic RBC morphology. (Figure 2). The serum T3 level (ng/dl) in the cases and controls was 66.28±48.89 and 77.29±37.47 respectively. On comparing it was observed that the serum T3 level in the two groups was comparable to each other. The serum T4 level (ng/dl) in the cases and controls was 6.64±13.42 and 4.36±2.42 respectively. On comparing it was found that the serum T4 level of the two groups was comparable to each other. The serum TSH level (mIU/mL) in the cases and controls was 45.49±46.11 and 3.81±0.76, respectively. On comparing it was found that the serum TSH level was significantly higher in the cases as compared to the controls (Table 3).

Correlation between TSH and Hb in cases

Applying Pearson's correlation analysis between TSH and Hb level, there was a negative correlation between these two factors in cases. Pearson's correlation coefficient was -0.34 (95% CI: -0.54 to -0.09). This was statistically significant with a P value of 0.0078 (Figure 3).

Correlation between TSH and hemoglobin in controls

Applying Pearson's correlation analysis between TSH and Hb level, there was no correlation between these two factors in controls. Pearson's correlation coefficient was

0.005 (95% CI: -0.14 to 0.15). This was statistically non-significant with a P value of 0.94.
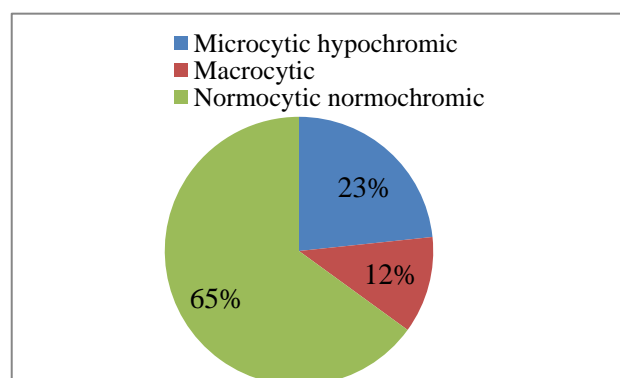
Figure 1: RBC morphology in cases.

Vitamin B12 level (pg/ml) in 5 cases was 150.8±43.37 while it was 111pg/ml in one control. Serum iron level (µg/dl) in the cases and controls was 69.07±31.46 and 74.102±23.57 respectively. On comparing, serum iron was significantly lower in the cases as compared to the controls (Table 4).

The total iron binding capacity (TIBC) (µg/dl) in cases and controls was 381.66±88.82 and 394.85±80.17 respectively. On comparing it was observed that the TIBC level of the two groups was comparable to each

other. The Direct and Indirect Coomb's test was positive in 1.67% cases and none of the controls.
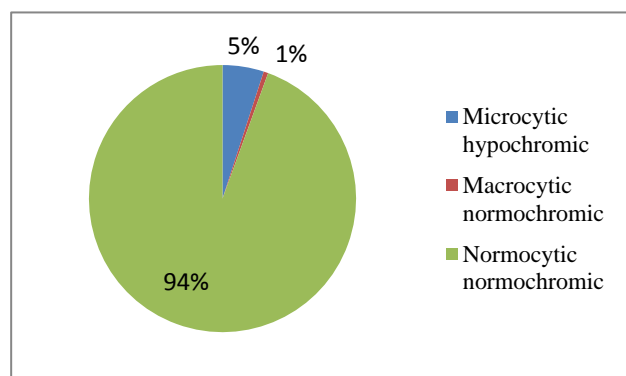

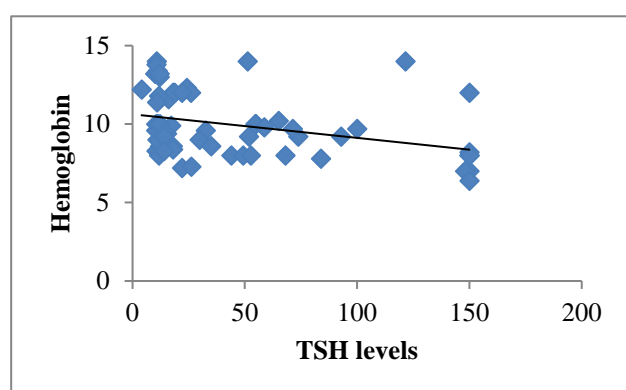**Figure 2: RBC morphology in controls.**

Figure 3: Correlation between hemoglobin and TSH levels in cases.

The thyroid peroxidase antibodies were found in 63.33% cases and 10% controls. On comparing it was found that the incidence of positive anti-TPO is significantly higher in the cases as compared to the controls (Table 5). The anti TPO antibody serum levels in the hypothyroid cases in our study were 429.89±564.16 IU/L.

Total number of cases with hypothyroidism is 60 in our study. Of these 45 (75%) patients had anemia as defined by Hemoglobin <12 g/dl. Of these 45 patients, 31 patients (69%) had anti-TPO positive antibodies while 14 patients (31%) were not positive for anti-TPO antibodies.

Total number of controls in the present study was 180. Of these 59 (32.77%) patients had anemia as defined by Hemoglobin <12 g/dl. Of these 59 patients, 3 patients (5%) had anti-TPO antibodies while 56 patients were negative for anti-TPO antibodies (Table 6).

DISCUSSION

According to WHO (2008) anemia affects 1.62 billion worldwide, this is roughly 25% of the global population. The lowest prevalence was seen in men. WHO reported that the problem of anemia was severe in India.[7]

According to the study by Das C et al among the anemic patients with hypothyroidism in Eastern India, 51.6% had normocytic anemia, 43.2% had iron deficiency microcytic anemia, 4.8% had pernicious anemia while 6% had vitamin B12 deficiency anemia. Among the anemic patients in this study, 51.6% of the hypothyroid patients had mild anemia, 25% had moderate while 20% of the hypothyroid patients had severe anaemia.[8] This study was lacking in its comparison with the general population.

As mentioned by Hess SY et al, the iron deficiency anemia causes abnormality in the thyroid function by decreasing the plasma T4 and T3 levels, reducing the peripheral conversion of T4 to T3 and also may cause an increase in the circulating TSH.[9] The age of hypothyroid subjects in our study was lower, comparable and higher than the age in a study by Mehmet E et al, Das C et al8 and Dorgalaleh A et al respectively.[10,11]

In a study by Mehmet E et al, it was found that the mean age of the subjects in the hypothyroid and control groups was 44.5 and 45.3 years, respectively and the ages of the two groups were comparable.[10] According to a study by Das C et al in hypothyroid subjects with anemia, the mean age of the patients was 36.5 years.[8] In the study by Dorgalaleh A et al the mean age of the patients in the hypothyroid and control groups was 14.1 and 15.2 years respectively.[11]

Of the hypothyroid cases in the current study, it was observed that majority of the cases (68.33%) belonged to the poor class while 31.67% belonged to middle class. However, this might be reflected due to greater access of poor population to the government institutions.

Gender wise distribution in our study was similar in both the groups. These findings are similar to the Mehmet E et al study. In a study by Mehmet E et al sex distribution revealed that the proportion of males and females in the hypothyroid group was 12% and 88% respectively while in the control group the proportion was 16% and 84% respectively. According to the study by Das C et al it was found that 70% of the subjects were females.[8] The proportion of males in the study by Dorgalaleh A et al was 38% and 39% in the hypothyroid and control groups, respectively while the proportion of females was 62% and 61% respectively.[11] In accordance with the previous studies it can be concluded that the prevalence of anemia in hypothyroid patients is higher in the female population compared to males. This can be multifactorial mainly caused by monthly menstrual blood loss in the females. The complaints of fatigue, tiredness, dyspnea on exertion and generalized are occur more frequent in the hypothyroid patients compared to the controls in our study.

The prevalence of family history of hypothyroidism in the cases and controls in our study was not significantly different. History of blood transfusion and iron

supplementation was negligible in the participants in our study.

The general condition was moderate in 98.33% of the hypothyroid patients. This was higher compared to the controls in our study. The pulse rate of the hypothyroid subjects in our study was 77.75 per minute and of controls was 80.43 per minute. The pulse rate was lower in the patients of hypothyroidism.

In our study pallor in the hypothyroid patients was seen in 70% cases, compared to controls in which pallor was seen in 20.55%. Fifty percent of cases had mild pallor and 20% had moderate to severe pallor while 16.11% had mild pallor and 4.44% had moderate to severe pallor in controls.

The hemoglobin levels in the hypothyroid patients was lower (9.94 gm %) compared to the controls (12 gm%) in our study. The hypothyroid patients are at a greater risk of having lower hemoglobin values compared to the general population. In a study by Mehmet E et al it was found that the hemoglobin level in the hypothyroid subjects and control groups was 11.9 and 12.8 gm% respectively and it was lower in the hypothyroid subjects.[10] The mean hemoglobin levels of the hypothyroid and control groups was 12.2 and 13.6 gm% in the Dorgalaleh A et al study.[11]

In our study the MCV in the cases and controls was 82.3 and 84.11 FL respectively and was comparable in the two groups. This finding was similar to the findings in the study by Mehmet E et al and Dorgalaleh A et al study. In study by Mehmet E et al the MCV was 84.4 and 84.5 FL in the hypothyroid and control subjects respectively and it was comparable in the two groups.[10] The MCV of the hypothyroid and control group was 84 and 85 FL, respectively in the Dorgalaleh A et al study.[11] In our study it was found that the MCH in the hypothyroid patients (30.91 pg) was lower than that in general population (31.98 pg).The MCH in the hypothyroid and control groups in the Dorgalaleh A et al study was 27.4 and 29.3 pg respectively.[11]

The study of RBC morphology in our study revealed that the 70% of cases and 94.44% of controls were having normocytic normochromic RBCs. Microcytic hypochromic RBCs were greater in the hypothyroid patients (20%) than in the controls (5%). Thus, study of RBC morphology revealed greater abnormalities in the hypothyroid population.

The mean serum TSH levels in our study were 45.49 mIU/ml in cases and 3.81 mIU/ml in the controls. The serum TSH levels were significantly higher in the hypothyroid patients compared to the controls. These findings were comparable to findings of the study by Mehmet E et al. In a study by Mehmet E et al it was found that the mean serum TSH levels in the hypothyroid group and control group was 43.1 and 1.7 mIU/mL,

respectively and the serum TSH levels were higher in the hypothyroid group compared to the control group.10 In the study by Dorgalaleh A et al the mean serum TSH levels were 4.97 and 2.6 mIU/ml, respectively in the hypothyroid and control groups respectively.[11] In our study there was negative correlation between TSH levels and hemoglobin levels in cases. Such findings were also seen in a study conducted by Dorgaleleh et al where a decreased level of hemoglobin was seen in hypothyroid population with raised TSH as compared to the total population.[11]

The bilirubin (total and direct) levels of both the groups in our study were found to be comparable. The liver enzymes (SGOT and SGPT) in the hypothyroid patients were found to be higher compared to the controls; however, they were within the normal range. The association of hypothyroidism with increase in liver enzymes needs to be studied in further detail.

In our study Vitamin B12 levels were found to be deficient in 8.33% of the hypothyroid subjects with a mean level was 150.8pg/ml. In the study by Das C et al, vitamin B12 deficiency was present in 10% cases.8 According to study by Mehmet E et al, it was found that the mean Vitamin B12 levels in the hypothyroid and control subjects was 400.2 and 299.1pg/ml respectively and vitamin B12 levels were higher in the hypothyroid group.[10]

In our study the serum iron levels in the hypothyroid and general population was 69.07 and 74.10 mcg/dl and the serum iron levels were lower in the cases compared to the controls. Our study showed for the first time that hypothyroidism was associated with lower serum iron levels. This was not observed in the study by Mehmet E et al even though the levels of serum iron of the two groups were similar to findings in our study. In study by Mehmet E et al serum iron level was 69.6 and 75.5 mcg/dl in the hypothyroid and control subjects respectively and it was comparable in both groups.[10]

The results of the direct and indirect Coomb's test were similar in the hypothyroid and control subjects in our study. In our study, TPO antibodies were positive in the 63.33% of the cases and 10% of the controls and incidence in the hypothyroid cases was higher than in the controls. These findings were similar to the studies by Mehmet E et al and Das C et al. In a study by Mehmet E et al, TPO antibody positivity was observed in 100% hypothyroid subjects and 22.5% controls.[10] In the study by Das C et al, TPO antibody was positive in 58.3% cases.8 Thus, presence of TPO antibodies should be evaluated in the patients with a risk for development of hypothyroidism.

It was found that higher incidence of anti-TPO antibodies was in anemic cases compared to the anemic controls. Previous studies have not shown association of TPO antibodies with that of anemia among the hypothyroid

patients. This is a significant finding in our study which will help predict the risk of anemia in hypothyroid patients with anti-TPO antibodies.

CONCLUSION

The prevalence of anemia in hypothyroid patients was 75%. It was quite higher than the prevalence of 32.77% seen in the general population, RBC morphology in hypothyroid patients was- (A) Normocytic normochromic-65.9% (most common) (B) Microcytic hypochromic-22.72% (second most common) (C) Macrocytic anemia -11.36%, symptoms of anemia occurred more frequently in hypothyroid population than in general population, iron deficiency anemia was quiet common in hypothyroid population as compared to general population, among anemic hypothyroid patients, 68.88 % had anti-TPO positivity, hypothyroid patients with higher TSH levels had higher prevalence of moderate to severe anemia. This correlation between the severity of hypothyroidism and of anemia was statistically significant.

REFERENCES

1. Crosby WH. Certain things physician do red cell indices. Arch Intern Med. 1979;139(1):23-4.
2. Carmel R. Macrocytosis, mild anemia, and delay in the diagnosis of pernicious anemia. Arch Intern Med. 1979;139(1):47-5.
3. Benoist B, Mclean E, Egli I, Cogswell M. Global database on anemia. Geneva: WHO. Worldwide prevalence of anemia. 1993-2005; 2008:1-2.
4. Erdogan M, Kosenli A, Sencer G, Kulaksizoglu M. Characteristics of anemia in subclinical and overt hypothyroid patients. Endocr J. 2012;59:213-20.
5. Larson SO. Anemia and iron metabolism in hypothyroidism. Acta Med Scand. 1957;157:339-63.
6. Mclean E, Benoist B, Allen LH. Review of the magnitude of folate and vitamin B12 deficiencies worldwide. Food Nutr Bull. 2008;29(2):38-51.
7. Benoist B, Mclean E, Egli I, Cogswell M. Global database on anemia. Geneva: WHO. 2008;7-21.
8. Das C, Sahana PK, Sengupta N, Giri D, Roy M. Etiology of anemia in primary hypothyroid subjects in a tertiary care center in Eastern India. Indian J Endocrinol Metab. 2012;16(2):361-3.
9. Hess SY, Zimmermann MB, Arnold M, Langhans W, Hurrell RF. Iron deficiency anemia reduces thyroid peroxidase activity in rats. J Nutrition. 2002;132(7):1951-5.
10. Mehmet E, Aybike K, Ganidagli S, Mustafa K. Characteristics of anemia in subclinical and overt hypothyroid patients. Endocrine Journal. 2012;59(3):213-20.
11. Dorgalaleh A, Mahmoodi M, Varmaghani B, Node FK, et al. Effect of thyroid dysfunctions on blood cell count and red blood cell indices. Iran J Ped Haematol Oncol. 2013;3(2):73-7.