

Original Research Article

A study of prevalence of anemia among hypothyroidism patients and relationship between types of anemia and 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: This research was conducted as a case-control study. Patients with newly diagnosed overt primary hypothyroidism and euthyroid controls totaling 170 in total were included in the study. The morphological subtypes of anemia and the causes of each were investigated. There was a correlation between the severity of anemia and that of hypothyroidism.

Results: Anemia was highly prevalent among cases, as it was present in 110 (64.7%) of patients with hypothyroidism and in 60 (35.3%) of patients who did not have hypothyroidism in the control group. In cases, 100 (58.8%) of serum samples tested positive for anti-TPO, while just 20 (11.8%) of control samples did so. In these cases, with elevated TSH, the anemia was severe.

Conclusions: Our study concluded that a statistically significant high anaemia prevalence was found among the patients with primary hypothyroidism. In comparison to the controls, it was shown that cases had a significantly higher incidence of certain types of, as well as anti-TPO positive and iron insufficiency. The TSH level and hemoglobin level were shown to have a statistically significant inverse association with one another.

Keywords: Anti-TPO, Hypothyroidism, Prevalence of anaemia, 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 the general population (nonhypothyroid). 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

Type of study

It was a hospital-based case control study.

Study place

Department of medicine in SRG Hospital of Jhalawar medical college and hospital, Jhalawar

Sampling technique

Simple random sampling was used as sampling technique.

Inclusion criteria

Laboratory confirmation of newly diagnosed primary overt and uncontrolled hypothyroidism on treatment overt hypothyroid patients (TSH>10 IU/ml), age >18 years, patients willing to give written informed consent.

Exclusion criteria

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

Criteria for selection of controls- age, sex, socioeconomically 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 110 overt (primary and uncontrolled on hypothyroidism treatment) hypothyroid patients and 60 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 in newly diagnosed hypothyroidism (overt and uncontrolled hypothyroidism on hypothyroidism treatment). 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 (according to WHO grading): mild - Hb 9.5 to 10.9 gm%, moderate- Hb 8 to 9.4 gm%, severe- Hb <8 gm%

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

Data analysis

The collected data was analysed 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 was 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 32.40±11.27 years in the cases and 34.01±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 10.91% (12) and females were 89.09% (98). Controls had 6.66% (4) males and 93.34% (56) 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, 63.63% (70) patients had complaints of fatigue while in the control group none of the participants had

complaints of fatigue. On comparison it was found that fatigue occurs significantly higher in the cases than in the controls. Dyspnea on exertion was present in 16.36% (18) cases and 5% (3) 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 87.27% (96) 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 10% (11) 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).

Table 1: Symptoms.

Parameters	Case (110)	Control (60)	Statistical test	P value and its interpretation
Fatigue	Y: 70 (63.63%) N:40 (36.37%)	Y: 0 (0%) N: 60 (100%)	Fisher's exact test	<0.0001. Fatigue is significantly higher in the cases as compared to the controls
Dyspnea on exertion	Y:18 (16.36%) N:92 (83.64%)	Y:3 (5%) N:57 (95%)	Fisher's exact test	<0.0001. Dyspnea on exertion is significantly higher in the cases as compared to the controls
Generalized weakness	Y:96 (87.27%) N:14 (12.73%)	Y: 0 (0%) N: 60 (100%)	Fisher's exact test	<0.0001. Generalized weakness is significantly higher in the cases as compared to the controls
Weight gain	Y: 11 (10%) N:99 (90%)	Y: 0 (0%) N: 60 (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 (110)	Control (60)	Statistical test	P value and its interpretation
Hb (gm/dl)	9.86±2.12	12±2.20	Mann Whitney test	<0.0001. Hb is significantly lower in the cases as compared to the controls

History of blood transfusion was present in 3.63% (4) 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 2.27% cases and none of the controls.

The pulse rate in the cases and controls was 70.75±9.84 and 79.43±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±9.83 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 70.70±6.87 and 76.26±8.45 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% (55) had pallor of grade 1+ and 20% (22) had pallor of grade 2+ while 30% (33) had no evidence of pallor. Among the controls, 13.33% (8) had pallor of grade 1+ and 6.66% (4) had pallor of grade 2+ while 80% (48) had no evidence of pallor. On comparing it was found that pallor is significantly higher 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.

The hemoglobin level (gm/dl) in the cases and controls was 9.86±2.12 and 12±2.20 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 83.3±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).

Of the 60 controls, approximately 93.33% (56) of them had normocytic normochromic RBC morphology, 5% (3) had microcytic hypochromic RBC morphology and only 1 patient had macrocytic normochromic RBC morphology (Figure 2).

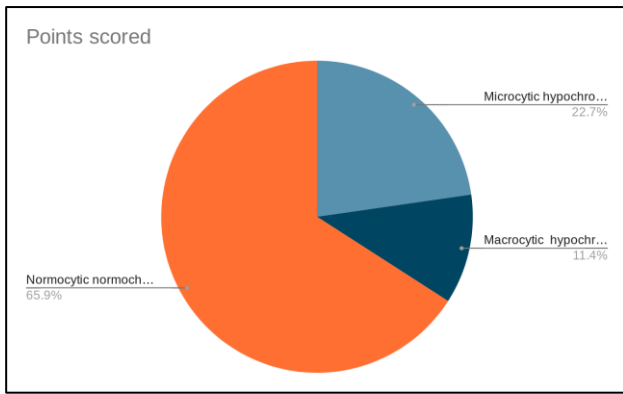


Figure 1: RBC morphology in cases.

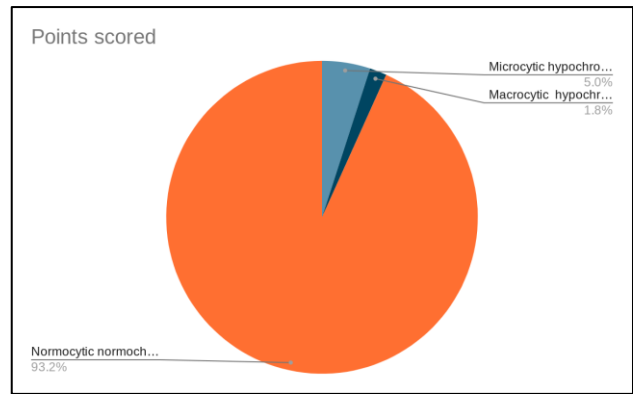


Figure 2: RBC morphology in controls.

Table 3: Serum TSH levels.

Parameter	Case (110)	Control (60)	Statistical test	P value and its interpretation
TSH	49.51±42.11	3.62±0.89	Mann Whitney test	<0.0001. TSH is significantly higher in the cases as compared to the controls

Table 4: Serum iron.

Parameter	Case (110)	Control (60)	Statistical test	P value and its interpretation
Serum iron	69.07±31.46	74.102±23.57	Unpaired T test	<0.0001. S. iron is significantly lower in the cases as compared to the controls

The serum T₃ level (ng/dl) in the cases and controls was 65.28±44.88 and 76.39±34.42 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 6.62±13.12 and 4.66±2.62 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 49.51±42.11 and 3.62±0.89, 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.

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 nonsignificant with a P value of 0.94. Vitamin B₁₂ level (pg/ml) in 10 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.

The thyroid peroxidase antibodies were found in 72.72% (80) cases and 33.33% (20) 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 426.68±558.18 IU/l.

Total number of cases with hypothyroidism was 110 in our study. Of these 70 (63.63%) patients had anemia as defined by hemoglobin <12 g/dl. Of these 70 patients, 49 patients (70%) had anti-TPO positive antibodies while 21 patients (30%) were not positive for anti-TPO antibodies. Total number of controls in the present study was 60 of these 19 (31.66%) patients had anemia as defined by Hemoglobin <12 g/dl. Of these 19 patients, 1 patients (5.25%) had anti-TPO antibodies while 18 (94.73) patients were negative for anti-TPO antibodies (Table 6).

Table 5: Anti TPO.

Parameter	Case (110)	Control (60)	Statistical test	P value and its interpretation
Anti TPO	positive: 80 (72.72%)	positive: 20 (33.33%)	Fisher's exact test	<0.0001. The incidence of positive antiTPO is significantly higher in the cases as compared to the controls
	negative: 30 (27.28%)	negative: 40 (66.67)		

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

	Cases with anemia	Controls with anemia	Total
Anti TPO positive	49	1	50
Anti TPO negative	21	18	39
Total	70	19	89

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 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 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 et al, Das et al and Dorgalaleh et al respectively.^{8,10,11} In a study by Mehmet 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 et al in hypothyroid subjects with anemia, the mean age of the patients was 36.5 years.⁸ In the study by Dorgalaleh 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 the majority of the cases (68.33%) belonged to the poor class while 31.67% belonged to the middle class. However, this might be reflected due to greater access of the 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 et al study. In a study by Mehmet 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 et al it was found that 70% of the subjects were females.⁸ The proportion of males in the study by Dorgalaleh 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 generalization occur more frequently 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 70.75±9.84 per minute and of controls was 79.43±5.94 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%. Fifty percent of cases had mild pallor and 20% had moderate to severe pallor while 13.33% had mild pallor and 6.66% had moderate to severe pallor in controls. The hemoglobin levels in the hypothyroid patients were lower (9.86±2.12%) compared to the controls (12±2.20 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 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 et al study.¹¹ In our study the MCV in the cases and controls was 83.3±11.17 and 84.11±5.26 fl respectively and was comparable in the two groups. This finding was similar to the findings in the study by Mehmet et al and Dorgalaleh et al study. In study by Mehmet 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 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 et al study was 27.4 and 29.3 pg respectively.¹¹

The study of RBC morphology in our study revealed that 65.9% of cases and 93.33% of controls were having normocytic normochromic RBCs. Microcytic hypochromic RBCs were greater in the hypothyroid patients (22.72%) 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 49.51 ± 42.11 , mIU/ml in cases and 3.62 ± 0.89 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 et al. In a study by Mehmet 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 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 Dorgaleh 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 9.09% of the hypothyroid subjects with a mean level was 150.8 pg/ml. In the study by Das et al, vitamin B₁₂ deficiency was present in 10% cases.⁸ According to study by Mehmet et al, it was found that the mean vitamin B₁₂ levels in the hypothyroid and control subjects was 400.2 and 299.1 pg/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 µg/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 et al even though the levels of serum iron of the two groups were similar to findings in our study. In study by Mehmet et al serum iron level was 69.6 and 75.5 µg/dl in the hypothyroid and control subjects respectively and it was comparable in both groups.¹⁰ The results of the direct and indirect Coombs test were similar in the hypothyroid and control

subjects in our study. In our study, TPO antibodies were positive in 72.72% of the cases and 33.33% of the controls and incidence in the hypothyroid cases was higher than in the controls. These findings were similar to the studies by Mehmet et al and Das et al. In a study by Mehmet et al, TPO antibody positivity was observed in 100% hypothyroid subjects and 22.5% controls.¹⁰ In the study by Das 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.

CONCLUSION

The prevalence of anemia in hypothyroid patients was 64.7%. It was quite higher than the prevalence of 35.3% 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, 63.63% 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.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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