Research Article

A study of prevalence and pattern of anemia in primary hypothyroidism

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ABSTRACT

Background: Anemia is a common disorder affecting Indian population which may be further influenced by hypothyroidism. Hematopoietic system is one of the primary systems affected by hypothyroidism and anemia could be its first manifestation. Numerous mechanisms are involved in the pathogenesis of this anemia that can be microcytic, macrocytic, and normocytic. We designed this study to investigate the incidence of anemia its morphological pattern in hypothyroidism patients. **Objectives:** The objectives were to investigate the incidence of anemia and its morphological pattern in patients with overt and subclinical hypothyroidism. **Materials and Methods:** A prospective observational study was conducted in patients presenting with overt or subclinical primary hypothyroidism in King George Medical University from August 2016 to September 2017. Patients with age >18 years and newly diagnosed cases of subclinical hypothyroidism were included. Patients with secondary causes for anemia or patients under treatment with drugs that might affect blood parameters were excluded. **Results:** In our present study, female predominance was 82% with more common age group between 31 and 40 years. The incidence of anemia was found to be 69% in the overt hypothyroid group and 56% in the subclinical hypothyroid group. Normocytic normochromic (53%) was the most common type of anemia, followed by microcytic (30%) and macrocytic anemia (27%). Serum iron levels were significantly low in both overt and subclinical hypothyroid groups. Serum anti-thyroid peroxidase (TPO) positivity was 65.53%. Anemia was severe in cases with high thyroid-stimulating hormone (TSH). **Conclusion:** Normocytic normochromic anemia is the most common type of anemia in hypothyroid patients. The incidence of anemia was found to be 69% in the overt hypothyroid group and 56% in the subclinical hypothyroid group. Presence of anemia in subclinical hypothyroidism was almost as high as in patients with overt hypothyroidism. TPO antibodies were linked with higher likelihood of developing anemia in hypothyroidism. Higher TSH values were associated with more severe anemia.

KEY WORDS: Anemia; Subclinical Hypothyroidism; Overt Hypothyroidism

INTRODUCTION

The prevalence of hypothyroidism differs from country to country and ranges from 2 to 5% of the population all over the world. Hypothyroidism leads to deceleration of metabolic activities in the body, and almost any organ systems may be affected. The severity of signs and symptoms depends on the age of occurrence and deficiency status of hormones. Hematopoietic system is one of the primary systems affected by hypothyroidism and anemia is the most common manifestation. Anemia has been defined in 20–60% of the patients with hypothyroidism.[1,2]

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Hypothyroidism can cause a wide variety of anemic disorders. Numerous mechanisms are involved in the pathogenesis of this anemia that can be microcytic, macrocytic, and

normocytic.[3] The most frequently encountered type of anemia is normochromic normocytic anemia. The most frequent reason of this is the bone marrow repression due to thyroid hormone deficiency which also causes defective erythropoietin production. The second most common type of anemia is microcytic anemia due to iron deficiency and is largely due to malabsorption observed in hypothyroidism and menorrhagia occurring as a result of various hormonal instability. Macrocytic anemia is caused by malabsorption of Vitamin B12, folic acid, pernicious anemia, and inadequate nutrition.

Although common, anemia in hypothyroidism has been difficult to manage intriguing entity. This observation holds true owing to the fact that hypothyroidism can cause a wide variety of anemic disorders. The situation gets further tricky as the hematological presentation may not get zeroed to one particular anemic state. Both anemia and thyroid disease, due to their high prevalence and close interrelation, are significant clinical problems. Although there is abundant literature data on the association between thyroid status and anemia, due to limited number of large cohort studies, a definitive status of this entity is still eluting the clinicians posing problems in management.

The present study was carried out to investigate and explore primary hypothyroid patients, to know prevalence, types, and severity of anemia in them.

MATERIALS AND METHODS

The cases were selected randomly from subjects attending the outpatients clinics of Medicine Department of King George Medical University (KGMU), Lucknow, and from subjects referred to the Central Laboratory from other specialties for investigations during the period of 1 year, from August 2016 to July 2017. 572 patients of overt hypothyroidism or subclinical hypothyroidism were evaluated for possible inclusion in this study.

Exclusion criteria were pregnant women, patients with hemolytic anemia, gastrointestinal and genitourinary losses, comorbid conditions such as connective tissue disorders, hemoglobinopathies, bleeding disorders renal insufficiency/failure, coronary heart disease, uncontrolled hypertension, diabetes mellitus, or any endocrine disease other than hypothyroidism. Patients previously treated for hypothyroidism or on anti-thyroid medication were excluded. Patients under the treatment that might affect blood parameters such as steroids or had received anemia treatment were also not included in the study.

Out of the 572 patients of overt hypothyroidism or subclinical hypothyroidism, 383 participants were recruited for the study after fulfilling inclusion criteria. Demographic characters such as age, sex, height, and weight of all participants were noted. Serum Free T3, Free T4, and thyroid-stimulating hormone (TSH) were measured by electrochemiluminescence immunoassay method. Estimation of serum anti-thyroid peroxidase (TPO) antibodies in addition to the thyroid function test (T3, T4, and TSH) was carried out. Serum iron, iron binding capacity, ferritin, Vitamin B12, and folic acid levels were measured by immunoassay method using Cobas analyzer. Ethylenediaminetetraacetic acid samples were used for complete blood count using Sysmex Fully Automated hematology analyzer. Peripheral smears of anemic patients were examined to confirm the type of anemia due to erythrocyte morphology and to exclude other pathologies such as leukemia. Among 383 patients, there were 203 subclinical and 180 overt hypothyroidism patients as per standard definition. The patients first underwent complete blood count for characterization into anemic and non-anemic groups. On the basis of red cell indices (mean corpuscular volume [MCV]), patients having anemia were further classified as normocytic normochromic (MCV 80–96 fl), microcytic hypochromic (MCV <80 fl), and macrocytic (MCV >96 fl) and were investigated to find the etiology as well as to rule out any secondary causes of anemia, if found such patients were excluded from the study. Patients with normocytic normochromic were investigated by Coombs test and bone marrow examination. Stool for occult blood, upper GI scopy, and Iron studies were done in patients with a microcytic hypochromic type of anemia. Patients with macrocytic anemia were evaluated for Vitamin B12 and folic acid levels. Test for antiparietal cell antibodies was not done due to financial constraints.

Anemia was defined as hemoglobin (Hb) levels lower than 12 g/dL in women and 13 g/dL in men and was further classified as: Mild - Hb 10–12 g%, moderate - Hb 8–10 g%, and severe - Hb <8 g%.[4] Iron deficiency anemia is defined as serum iron levels lower than 60 μg/dL, iron binding capacity >215 μg/dL, ferritin levels lower than 10 ng/dL and with microcytosis and hypochromia in a peripheral blood smear. Folic acid deficiency anemia is defined as folic acid levels lower than 3 ng/mL together with macrocytosis in a peripheral blood smear. Vitamin B12 deficiency anemia is defined as B12 levels lower than 211 pg/mL with increased MCV levels and with macrocytosis in a peripheral blood smear.

Statistics

The collected data were analyzed by applying appropriate statistical tests- Chi-square test, (with continuity correction for all tables [2/2]) 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), and Mann–Whitney test (if data fails normality tests).

RESULTS

A total of 383 participants meeting our inclusion criteria were classified into two groups: Overt hypothyroid group and subclinical hypothyroid group on the basis of their thyroid profile. Patients were investigated for the presence of anemia and to determine the etiology of anemia. In the study population, we observed that 47% patients had overt hypothyroidism whereas 53% had subclinical hypothyroidism. The mean age of the patients was 39.28 ± 11.13 years and varied between 18 and 85 years with a maximum number of patients within the age group 31–40 years (44%).

In the subgroup analysis, we found that in the overt hypothyroid group out of 180 cases, 52 (29%) were male and 128 (71%) were female, the proportion of males and females were comparable to the subclinical hypothyroid group in which out of 203 patients, 41 patients (20%) were male, and 162 patients (80%) were female ($P = 0.06$).

Table 1: Age distribution of cases

Age group	Total cases *n* (%)
18–30	69 (18)
31–40	169 (44)
41–50	100 (26)
51–60	23 (6)
61–70	15 (4)
>70	7 (2)
Total	383 (100)

Table 2: Distribution of primary hypothyroid patients according to sex

Group	Study population	Male	Female
Overt hypothyroid	180	52	128
Subclinical hypothyroid	203	41	162
Total	383	93	290

Table 3: Comparison of prevalence of anemia in patients with overt and subclincal hypothyroidism

	Total % (*n*)	Overt % (*n*)	Subclinical % (*n*)
Anemia[a]			
Yes	62 (238)	69 (124)	56 (114)
No	38 (145)	35 (55)	41 (89)

[a]Anemia (Hb level <12.0 g/dl (F), <13 g/dl (M)); no anemia (Hb level ≥12.0 g/dl (F), ≥13 g/dl (M)). (Hb) Hemoglobin

When all the participants were evaluated for anemia, we observed that anemia was present in 238 out of 383 patients (62%) included in the study with most patients having mild-to-moderate grade anemia.

Anemia was present in 114 out of 203 patients (56%) in the subclinical hypothyroid patients and 124 out of 180 patients (69%) in the overt hypothyroid group ($P < 0.05$).

Among those with anemia, normocytic normochromic (53%) was the most common type of anemia, followed by microcytic (30%) and macrocytic anemia (27%). Among subjects with macrocytic anemia, serum levels of Vitamin B12 of almost all were low with normal serum folate. Folate deficiency was observed in only 1 patient. Bone marrow examination of the patients with normocytic normochromic anemia revealed normocellular marrow with varying degree of marrow iron store.

Normocytic normochromic anemia was most common anemia in both groups. The frequency of this type of anemia was determined to be 39% in patients with clinical hypothyroidism and 27% in patients with subclinical hypothyroidism ($P = 0.0125$).

Frequency of microcytic anemia in overt hypothyroid and subclinical hypothyroid patients was 20% and 18%, respectively ($P = 0.618$).

Frequency of macrocytic anemia in overt hypothyroid and subclinical hypothyroid patients was 10% and 11%, respectively ($P = 0.75$).

The Hb level (g/dl) in patients with overt and subclinical hypothyroidism presenting with anemia was 9.8 ± 1.1 and 10.4 ± 1.4, respectively.

MCV of patients of overt hypothyroidism and subclinical hypothyroidism presenting with anemia was 80.3 ± 9.0 and 81.2 ± 12.2, on comparing it was found that the MCV of the two groups was comparable with each other. The serum T3 level (ng/dl) in the overt and subclinical hypothyroid group was 66.28 ± 48.89 and 77.29 ± 37.47, respectively. The serum T4 level in the overt and subclinical hypothyroid group was 0.5 ± 0.18 and 1.1 ± 0.11, respectively. On

Table 4: Pattern of anemia in primary hypothyroidism

Types of anemia	Hb 12-14 g/dl	Hb 10–12 g/d	Hb 8–10 g/d	Hb <8 g/d	Total (%)
Normocytic normochromic	19	64	37	7	127 (53)
Microcytic anemia	8	31	20	13	72 (30)
Macrocytic anemia	3	28	7	1	39 (17)
Total (%)	30 (12)	123 (52)	64 (27)	21 (9)	383

(Hb) Hemoglobin

comparing, it was found that the serum T3, T4 levels of the two groups were comparable. The serum TSH level (mIU/mL) in the overt and subclinical hypothyroid group was 43.1 ± 30.2 and 9.7 ± 5.5, respectively ($P < 0.0001$) [Table 6].

Serum iron level (μg/dl) in the overt and subclinical hypothyroid group was 60.82 ± 17.84 and 71.80 ± 41.60, respectively. Thus, serum iron was significantly lower in the overt hypothyroid group as compared to the subclinical hypothyroid group [Table 6]. The total iron binding capacity (TIBC) (μg/dl) in overt and subclinical hypothyroid group 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 serum B12 levels in the overt and subclinical hypothyroid group were 327.8 ±122.7 and 342.8 ± 178.6, respectively. The serum folic acid levels in the overt and subclinical hypothyroid group were 8.2 ± 3.4 and 7.97 ± 3.9, respectively. On comparing, it was observed that the serum B12 and folic acid levels in the two groups were comparable to each other.

The TPO antibodies were found in 251 out of 383 patients (65.53%). TPO positivity was present in 94.44% of overt hypothyroid cases and 39.9% of subclinical cases.

On studying the corelationship between TSH and Hb levels, we found that there was a negative correlation between these two factors in cases. Pearson's correlation coefficient was −0.32 (95% confidence interval: −0.52–−0.07). This was statistically significant with a $P = 0.0066$.

Table 5: Demographic measures and biochemical values of subclinical hypothyroidism and overt hypothyroidism

Characteristics	Overt hypothyroidism	Subclinical hypothyroidism	*P*
n	180	203	
Gender, female	71.00%	80.00%	0.05
Age (years)	38.8±11.2	39.7±12.8	0.46
TSH (mIU/ml)	43.1±30.2	9.7±5.5	<0.0001
FT4 (ng/dl)	0.59±0.15	1.22±0.18	<0.0001
FT3 (pg/ml)	1.16±0.82	3.10±0.51	<0.0001
Hb (g/dl)	10.9±1.66	10.8±1.5	0.52
MCV (fL)	84.8±5.8	83.8±6.9	0.45
Serum iron (ug/dl)	60.82±17.84	71.8±41.6	0.38
Serum ferritin (ng/ml)	94.22±29.54	104.45±38.25	0.73
TIBC (ug/dl)	381.66±88.82	393.85±97.17	0.12
Serum B12 (pg/ml)	337.8±90.7	342.8±178.6	0.6
Serum folic acid (ng/ml)	8.2±3.4	7.97±3.9	0.25

*The data are expressed as mean±SD. *P* value was calculated at 95% confidence interval. SD: Standard deviation, TIBC: Total iron binding capacity, MCV: Mean corpuscular volume, TSH: Thyroid-stimulating hormone, (Hb) Hemoglobin

Table 6: Laboratory values of the anemic patients in all groups

Parameters	Overt hypothyroidism (*n*=203)	Subclinical hypothyroidism (*n*=180)	*P*
Hb (g/dl)	9.8±1.1	10.4±1.4	0.57
Hematocrit (%)	32.9±3.2	32.8±3.8	0.83
Serum B12 (pg/ml)	320.7±109.6	318.9±102.2	0.86
Serum folic acid	7.7±3.1	7.9±4.9	0.51
Serum iron (ug/dl)	51.3±32.1	59.4±31.9	0.4
Serum ferritin (ug/L)	75.5±37.3	89.9±66.1	0.36
MCV (fL)	80.3±9.0	81.2±12.2	0.87

*The data are expressed as mean±SD. *P* value was calculated at 95% confidence interval. SD: Standard deviation, MCV: Mean corpuscular volume

Table 7: Anti-TPO

Parameter	Overt hypothyroidism	Subclinical hypothyroidism	*P*
Anti-TPO	Positive: 170 (94.44%)	Positive: 81 (39.9%)	<0.0001
	Negative: 10 (5.56%)	Negative: 122 (60.1%)	

TPO: Thyroid peroxidase

DISCUSSION

Anemia is a severe public health problem in India, which may be precipitated by conditions such as hypothyroidism. To carry out the treatment of the patient with anemia correctly, it is necessary to determine the etiological cause.

In our study, anemia was present in 238 out of 383 patients (62%) with normocytic normochromic anemia as the most common type of anemia among hypothyroid patients. Analyzing the age and gender-wise distribution in our study, it was found that maximum patients affected were the female group under the age of 31–40 years (169 patients). Our study showed the proportion of male and female hypothyroid patients with anemia was 24% and 76%, respectively, thus we concluded that though the prevalence of hypothyroid more common in female population, the development of anemia is not related to sex.

Anemia frequency in overt and subclinical hypothyroid groups was found to be 69% and 56%, respectively, which was statistically significant ($P < 0.05$). This result gave rise to the thought that presence of both overt, as well as subclinical hypothyroidism, may be a risk factor in anemia development. Lower Hb levels were observed in the overt hypothyroid group (9.81 g %) as compared to the subclinical group (10.4 g %). On studying the relationship of TSH levels with the severity of anemia, it was found that there existed a negative relationship between the two. Thus, higher TSH values were associated with more severe anemia. We also observed negative relation of transferrin saturation with TSH levels.

Table 8: Anti-TPO in cases with anemia and without anemia

Parameter	Cases with anemia	Cases without anemia	Total
Anti-TPO positive	203	48	251
Anti-TPO negative	35	97	132
Total	238	145	383

TPO: Thyroid peroxidase

On studying the pattern of anemia, normocytic normochromic anemia was most common anemia in patients with overt and subclinical hypothyroidism. The frequency of this type of anemia was determined to be 39% in patients with clinical hypothyroidism and 27% in patients with subclinical hypothyroidism. The second most common type of anemia was microcytic hypochromic anemia, with its frequency noted to be 20% and 18% in overt and subclinical hypothyroid patients. Frequency of macrocytic anemia in overt hypothyroid and subclinical hypothyroid patients was 10% and 11%, respectively.

On analyzing the demographic measures and biochemical values of subclinical and overt hypothyroid patients participating in this study, we observed that serum iron levels in the overt hypothyroid and subclinical hypothyroid group were 60.82 and 71.80 mcg/dl and thus concluded that hypothyroidism was associated with lower serum iron levels. Vitamin B12 levels were found to be deficient in 17.33% of the hypothyroid subjects with a mean level was 335.3 pg/ml whereas folate deficiency was found in only 1 subject, thus, we concluded that macrocytic anemia in primary hypothyroidism in predominantly due to Vitamin B12 deficiency whereas folate deficiency, if present, mostly occurs secondary to an underlying disease.

We also made an observation that TPO antibodies were positive in the 83.55% of the hypothyroid cases. Moreover, since we found that higher incidence of anti-TPO antibodies in anemic cases as compared to the anemic controls, we concluded that anti-TPO antibodies may help predict the risk of anemia in hypothyroid patients.

Our observations were in accordance with the study conducted by Das *et al*. which reported the prevalence of anemia in subclinical and overt hypothyroid groups to be 26.6% and 73.2%, respectively.[5] Similar to the pattern observed by us, normocytic, normochromic anemia was the most common type of anemia and was present in 31 patients (51.6%) followed by microcytic anemia in 26 patients (43.3%). Six patients (10%) had megaloblastic anemia with Vitamin B12 deficiency including 3 cases of pernicious anemia.

Table 9: Comparison of pattern of anemia between our study and previous studies

Studies and year	Group	*n*	Normocytic normochromic (%)	Microcytic hypochromic (%)	Macrocytic hypochromic (%)
Erdogan *et al*.	Overt hypothyroid	100	34.00	5.00	10.00
	Subclinical hypothyroid	100	26.00	6.00	11.00
Das *et al.* (2015)	Overt hypothyroid	60	51.60	43.30	10.00
Kulkarni and Jadhav (2016)	Hypothyroid	60	65.90	22.72	11.36
	Euthyroid	180	99.44	5.00	1.00
Patel *et al*. (2016)	Overt hypothyroid	46	43.00	34.00	23.00
	Subclinical hypothyroid	66	18.00	54.00	28.00
Present study (2017)	Overt hypothyroid	180	56.50	28.90	14.50
	Subclinical hypothyroid	203	48.20	32.10	19.64

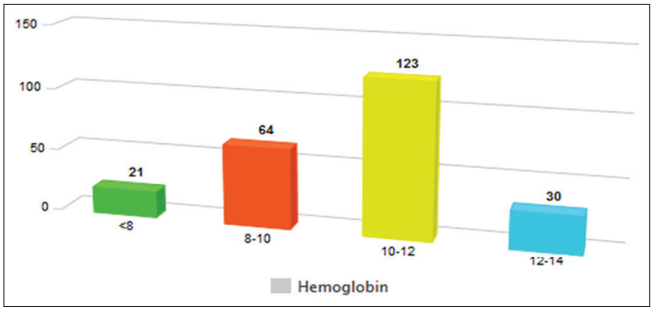

Figure 1: Hemoglobin levels

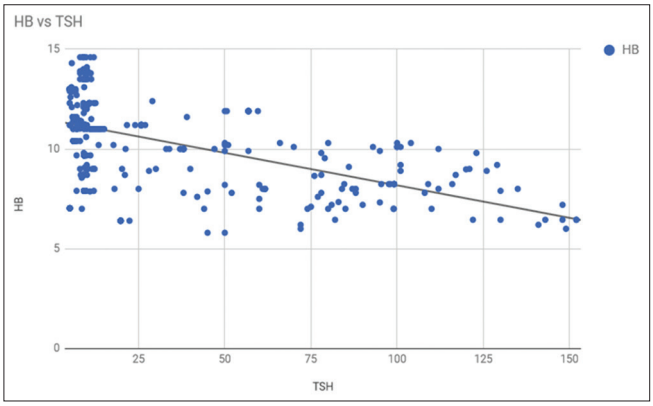

Figure 2: Scatter diagram showing a correlation between hemoglobin and thyroid-stimulating hormone levels

Kulkarni and Jadhav observed the prevalence of anemia to be 75% in hypothyroid patients with normocytic normochromic (65.9%) as the most common type of anemia, they also reported a significant corelation between TSH and Hb similar to the corelationship observed by us.[6] The previous study by Bremner *et al.* also reported significant relationships between free T3 and Hb, and inverse relationship of TSH with serum iron and transferrin saturation.[7] Bivolarska *et al.* also found slight negative statistically significant correlative association between the levels of TSH and Hb ($r = 0.217$, $P = -0.033$).[8]

In the study conducted by Larsson 52% (13 out of 25) of his patients of hypothyroidism had iron deficiency anemia.[11] Erdogan *et al.* reported the prevalence of microcytic anemia in overt hypothyroid patients, subclinical hypothyroid patients, and normal subject to be 5%, 6%, and 6%, respectively ($P = 0.116$).[12] Kulkarni and Jadhav observed microcytic hypochromic morphology in 22.72% patients.

Macrocytic anemia commonly occurs as a result of Vitamin B12 deficiency as a result of malabsorption due to pernicious anemia accompanying hypothyroidism as we observed by us.[13-15] In the study conducted by R Carmel,[16] thyroid disorder and hypothyroidism were determined, respectively, in 24.1% and 11.7% of the patients with pernicious anemia. In the study conducted by Erdogan *et al*. the prevalence of macrocytic anemia in overt hypothyroid patients, subclinical hypothyroid patients, and normal subject was 10%, 11%, and 5%, respectively, with mean Vitamin B12 levels in the overt hypothyroid and subclinical hypothyroid subjects to be 299.1 and 400.2 pg/ml, respectively. Kulkarni and Jadhav observed the prevalence of macrocytic hypochromic anemia to be 11.36% among hypothyroid patients presenting with anemia. Our study in accordance with the above studies reports the frequency of macrocytic anemia to be 10% and 11% in overt and subclinical hypothyroid cases, respectively. Vitamin B12 levels were found to be deficient in 17.33% of the hypothyroid subjects with a mean level was 335.3 pg/ml.

Folic acid deficiency occurs as a result of intestinal malabsorption.[17] Again hypothyroidism ruins folate mechanism by decreasing the hepatic level of dihydrofolate reductase such as methylenetetrahydrofolate reductase.[18] Folate deficiency was found in only 1 subject, thus, we concluded that folate deficiency in hypothyroidism almost always occurs secondary to an underlying disease.

In a study by Erdogan *et al*., TPO antibody positivity was observed in 100% hypothyroid subjects and 22.5% controls. In the study by Das *et al*., TPO antibody was positive in 58.3% cases, and it was concluded that the presence of TPO antibodies should be evaluated in the patients with a risk for development of hypothyroidism. Wang *et al*.[19] found that 16.3% of patients with positive antithyroid antibody titers presented with anemia, 14.2% were iron-deficient, and 1.1% had folate deficiency. These rates were significantly higher than in healthy controls. We, however, found a higher incidence of anti-TPO antibodies in anemic cases as compared to the anemic controls, which was not analyzed in previous studies. Thus, the presence of anti-TPO antibodies may help predict the risk of anemia in hypothyroid patients.

Thus, we found an elevated anemia frequency in hypothyroid patients consistent with the literature. We also reported that the most common type of anemia was normocytic normochromic type. Strength of the study is represented by it being a large cohort study with detailed evaluation of primary hypothyroid patients with anemia with adequate representation of all age groups. However, further studies are required to substantiate this increased association of anemia in overt and particularly in subclinical hypothyroidism. Thus, further studies could focus on the need to treat subclinical hypothyroidism in anemic patients and whether its treatment can optimize the results of treatment of iron, folate or Vitamin B12 deficiencies which can have wider implications.

CONCLUSION

Normocytic normochromic anemia is the most common type of anemia among hypothyroid patients followed by microcytic hypochromic anemia and macrocytic hypochromic anemia in studied subjects. From this study, we also concluded that anemia is a common finding in primary hypothyroidism. Presence of anemia in subclinical hypothyroidism is also

significantly high, and since there is no significant clinical manifestation of subclinical hypothyroidism at initial stages, it is advisable to routinely investigate it for early detection allowing its early management. The study advocates that both overt and subclinical hypothyroidism should be considered a risk factor for the development of anemia.

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