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IRON DEFICIENCY ANEMIA IN PATIENTS WITH HYPOTHYROIDISM, A SINGLE CENTER, CROSS SECTIONAL STUDY.

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ABSTRACT… Objectives: Iron deficiency anemia (IDA) is commonly encountered in patients with hypothyroidism. Many studies demonstrate valuable association between the two therefore further investigation was required to understand the frequency and association in order to ensure better disease outcomes. The aim of this study was to determine the frequency of IDA in patients with hypothyroidism in a tertiary care hospital of Karachi. **Study Design:** Single center, cross sectional study. **Setting:** Department of General Medicine, Liaquat National Hospital Karachi. **Period:** Feb 2018 to July 2018. **Material and Methods:** Two hundred seventy four patients with hypothyroidism were selected. Serum iron profile was sent to the institutional laboratory to assess the outcome variable i.e iron deficiency anemia. All the collected information was entered in the prescribed performa. **Results:** Out of 274 hypothyroid patients 106 (38.7%) were male and 168 (61.3%) were female with the mean age of 38.82 $\pm$ 4.009. Anemia was present in 40(14.4 %) patients and amongst them, IDA was observed in 20 (7.2%) patients. **Conclusion:** From the findings in the study, it was noted that free T4 had an influence on erythrocyte indices, namely hemoglobin levels, mean corpuscular volume and packed cell volume. This outcome therefore demonstrates some association of IDA with hypothyroidism. It is thus prudent to assess individuals with chronic IDA who have already been found negative for common causes of IDA (like chronic blood loss, menorrhagia in females, nutritional deficiencies and worm infestations) for hypothyroidism.

Key words: Anemia, Hypothyroidism, Iron Deficiency Anemia.

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INTRODUCTION

Iron deficiency anemia (IDA) is a condition where there is reduced red blood cell generation because of low iron deposits in the body. It is a well-recognized and documented health concern that represents around 50% of all cases of anemias.[1,2] There are a number of etiological factors responsible for IDA such as inadequate dietary supplementation, decreased absorption of iron in the body, increasing demands of iron in the body such as in pregnancy and finally increased loss of iron from the body as in internal bleeding, hemorrhoids, fissures and menorrhagia.

Ferritin is an intracellular protein that binds to iron, catalyzes reactions and plays a significant role in immune responses. It is a reliable tool to determine IDA in the absence of inflammation and a value of 12 to 15 µg/l is diagnostic. It is an acute phase reactant that spikes in patients with chronic inflammation or infection, as it is up regulated in the presence of inflammatory mediators. In the presence of inflammation, a value of 50 µg/l or even more may be suspect of IDA.[3]

Thyroid hormones play a fundamental role in cell metabolism, differentiation and regulation[4,5] and thyroid diseases are among the most widely recognized endocrine disorders.[6] The prevalence of hypothyroidism and subclinical hypothyroidism in Pakistan is 4.1 and 5.4% respectively, higher so in females than in males.[7] It has been hypothesized that due to a decreased metabolic demand of a hypothyroid patient, there is decreased synthesis of red blood cells. Concordant results have demonstrated this and

low levels of erythropoietin were found in patients afflicted by hypothyroidism.[8,9] There are also other hypothesis that suggest the role of thyroid hormones in influencing iron incorporation into erythrocytes and increasing iron absorption.[10] It is worth noting that there is more documentation of normocytic normochromic anemia in patients with hypothyroidism.[11]

Multiple studies have shown that patients with iron deficiency anemia and hypothyroidism have better outcomes with supplementation of iron and levothyroxine as opposed to simple iron supplementation. This is of particular importance in patients with sub-clinical hypothyroid as they may not respond to basic iron supplementation until the underlying cause is treated.[10,12] Aim of the present research was to assess the frequency of iron deficiency anemia in patients with hypothyroidism; so that we can better evaluate cases who have unexplained IDA by ruling out sub-clinical hypothyroidism.

MATERIAL & METHODS

This cross sectional study was conducted in the department of Internal Medicine, Liaquat National Hospital, Karachi from Feb 2018 to July 2018. Patients who had hypothyroidism that presented to the OPD and those that were admitted in the medical wards were enrolled in the study after they met the inclusion and exclusion criteria. Informed consent was taken from the patients after they were briefed about the study. Non-fasting, 05ml venous blood samples were collected under sterile conditions. Measurements of serum concentrations of fT3, fT4, TSH, were done using the electrochemiluminescence immunoassay (ECLIA). Serum iron concentration and total iron binding capacity were measured by Elecsys reagent kits& run on Roche/Hitachi cobas c 501 immunoassay analyzer. The diagnosis of hypothyroidism was based on elevated serumTSH > 4.0 μIU/mL, fT4 values of<4.6 ug/dl and/or fT3 levels of< 75 ng/dL. Out of 375 patients only 275 pure hypothyroid patients were included, the patients who were diagnosed as celiac and autoimmune thyroiditis were excluded. Diagnosis of Iron deficiency anemia was made with a hemoglobin concentration of < 12 g/dl, a Ferritin value of ≤30 ng per ml &/or Increased total iron-binding capacity of > 450 µg/dL, a serum iron level of < 50 µg/dL and a Transferrin saturation of < 20%. Demographics of the patients and specific information regarding iron deficiency anemia was noted and entered in the proforma.

Inclusion Criteria

Either gender with hypothyroidism

Exclusion Criteria

Female patients with menstrual problems like polymenorrhea, polymenorrhagia, history of frequent abortions, nutritional deficiencies by taking full dietary history, worm infestation was ruled out by sending stool for ova and cysts, gastrointestinal blood loss history, and a negative stool for occult blood test, comorbities like chronic kidney disease, chronic renal failure, blood disorders, autoimmune diseases by sending ANA Profile, Celiac disease by sending anti TTG antibodies and autoimmune thyroiditis by sending thyroid peroxidase antibodies (TPO).

Statistical Analysis

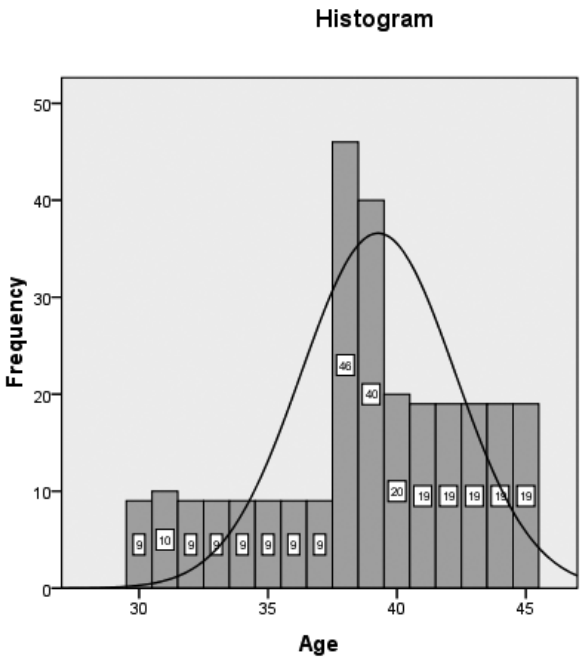
The collected data was analyzed by the SPSS software (Statistical Package for the Social Sciences, version 22, SPSS Inc, and Chicago, Ill, USA). Age of the patient, duration of hypothyroidism was presented in mean±standard deviation. Gender of the patient, and IDA were presented as frequencies and percentages. Stratification was done with regards to age, gender, duration of disease, TSH levels, free T4 level, free T3 level, and hemoglobin levels were compared. Chi square test was applied and p value less than or equal to 0.05 was considered as significant.

RESULTS

A total of 375 hypothyroid patients were included initially but later on 75 were diagnosed as celiac disease on the basis of raised anti Transglutaminase IgA antibody level and 26 patients were diagnosed as autoimmune thyroiditis on the basis of positive thyroid peroxidase antibodies (TPO) and/or thyroglobulin antibodies (TGAb) so these patients were excluded.

Finally total of 274 patients with hypothyroidism were included.

Hypothyroidism was more commonly encountered in a mean age of 38.81±4.00 years. The distribution of age is presented in Graph-1. The descriptive statistics of age is presented in Table-I.



Graph-I. Frequency distribution of age (Years)

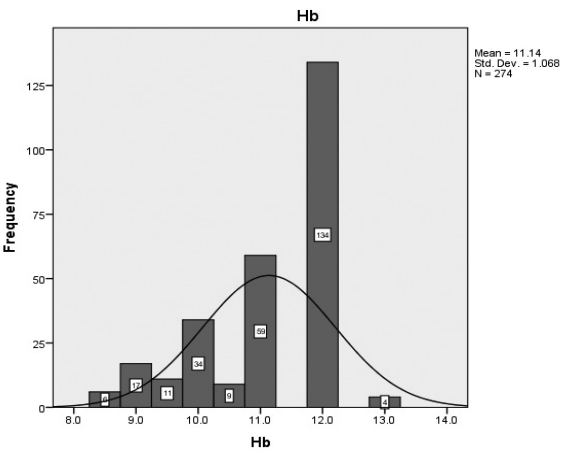
The mean duration of hypothyroidism was 13.65±0.78 months. The results showed an average hemoglobin level of 11.139±1.0677 mg/dl which fits the criteria of anemia. The distribution of hemoglobin level is presented on Graph-II.

The participants had TSH levels of 7.81±2.27 uU/ml which were significantly high,T3 levels were normal and1.14±0.25 ng/dl, and T4 levels were at the upper limit of normal at 4.90±1.11 ug/dl. This result is explained by the thyroxine treatment received by the patients.

The mean serum iron levels were decreased and were 45.33±15.017 μg/dL, mean serum (TIBC) levels were 318.29±49.461 mcg/dL which were normal. Serum ferritin was decreased with levels of 26.00±46.861 ng/ml & mean transferrin saturation was also decreased at levels of 15.185±6.5731%, as presented in Table-I. These findings were suggestive of iron deficiency anemia.

Variables	Statistics		
	Mini-mum	Maxi-mum	Mean & standard deviation
Age (Years)	30	45	38.81±4.00
Duration of hypothyroid (months)	13	15	13.65±0.78
Serum Hemoglobin level (mg/dl)	8.5	13	11.139±1.0677
Serum TSH Level (uU/ml)	4.2	12	7.81±2.27
Serum Free T3 level (ng/dl)	0.7	1.48	1.14±0.25
Serum T4 level (ug/dl)	3	6.8	4.90±1.11
Serum iron level (μg/dL)	20	65	45.33±15.017
TIBC level (mcg/dl)	250	455	318.29±49.461
Serum ferritin level (ng/ml)	200	450	26.00±46.861
Transferrin saturation level (%)	6.6	23.2	15.185±6.5731

Table-I. Frequency distribution of age, duration of hypothyroid, hemoglobin level, serum TSH level, serum free T3 level, serum T4 level, serum iron level, TIBC level, serum ferritin level & transferrin saturation level) (n=274)



Graph-II. Frequency distribution of Serum Hemoglobin level (g/dl)

In the study 106 patients (38.7%) were male and 168 (61.3%) were female, anemia was found in

77 patients (28.1%) and iron deficiency anemia was seen in 40 patients (14.6%). The distribution of iron deficiency anemia is presented in Table-II.

Gender	Frequency n=(274)	Percentage (%)
Male	106	38.7%
Female	168	61.3%
Total	274	100%
Anemia		
Yes	77	28.1%
No	197	71.9%
Total	274	100%
Iron deficiency anemia		
Yes	40	14.6%
No	234	85.4%
Total	274	100%

Table-II. Frequency distribution of gender, anemia & Iron deficiency anemia (n=274)

IDA was more common in female hypothyroid patients with age group of 38-45 years (p value however was not significant) Table-III.

Age Years	Iron deficiency anemia		Total	P-value
	Yes	No		
30-37 years	4 (1.45%)	69 (25.18%)	73 (26.64%)	0.168
38-45 years	36 (13.13%)	165 (60.21%)	201 (73.35%)	
Total	40 (14.59%)	234 (85.40%)	274 (100%)	
Duration of hypothyroidism	**Iron deficiency anemia**		**Total**	**P-value**
	Yes	**No**		
12-13 months	7 (2.55%)	89 (32.48%)	96 (35.02%)	0.029
14-15 months	33 (12.04%)	145 (198.90%)	178 (64.96%)	
Total	40 (14.59%)	234 (85.40%)	274 (100%)	

Table-III. Iron deficiency anemia according to age, duration of hypothyroidism) (n=274)

There was a positive association noticed in increasing duration of hypothyroidism and the presence of Iron deficiency anemia with a significant P value of 0.029.

DISCUSSION

The WHO documents the prevalence of iron deficiency anemia to be 24.8% all across the world, the bulk of which is more pronounced in underdeveloped countries.[12] In this research, anemia was found in 28.1% of the patients, as compared to the study conducted by Bamashmous et al which found anemia in 47.5% of the participants.[13] The study proposed a number of reasons for the various types of anemia encountered in patients with primary or subclinical hypothyroidism. Iron deficiency anemia was seen to arise due to menorrhagia in females, as hypothyroidism disturbs the menstrual cycle and brings about hormonal imbalances. This is a factor that could serve as a confounding variable in our study however; our patients did not report menorrhagia in their menstrual histories.[14] Our study tends to lean towards the direct influence of thyroid hormones on erythropoietin secretion, iron absorption and integration of iron in erythrocytes as propositioned by Cinemre et al.[15] His study led to a conclusion of better disease outcomes with levothyroxine and iron supplementation[16]; Christ et al[17] however, was unable to demonstrate a change in hemoglobin or hematocrit despite treating the patient with levothyroxine. Even so, he did notice a drastic increase in subsequent erythropoietin levels. Further studies should be done to analyze erythropoietin on a molecular level and establish the link it has with thyroid hormones through a biochemical vernacular.

In our study 38.7% patients were male and 61.3% were female. According to the study by Das C et al[18] it was found that 70% of the subjects were females.[8] The proportion of males in the study by Dorgalaleh A et al[19] was 38% and 39% in the hypothyroid and control groups, respectively While the proportion of females was 62% and 61% respectively. 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.

Our study was primarily focused on finding an association with iron deficiency anemia,

nonetheless -- it is worth noting that there is a significant occurrence of megaloblastic anemia in patients with hypothyroidism. Jabbar et al[20] found a prevalence of 39.6% of megaloblastic anemia in patients of hypothyroidism in Pakistan. This was observed to be secondary to pernicious anemia and a presence of antibodies was detected against gastric parietal cells.[21]

This could also be suggestive of decreased iron absorption due to a sluggish response of the bowels, edematous intestinal walls and bacterial proliferation.

The findings in our research demonstrated that the duration of hypothyroidism had a significant effect on iron levels in the body, which is a key factor in proving a relationship between the two disease states. It is thereby prudent that hypothyroidism particularly the subclinical variety could be implicated in long standing iron deficiency anemia when no other cause can be determined. Large scale studies need to explore the etiological factors surrounding the high level of prevalence of anemia in hypothyroidism to better evaluate temporality and causation.

LIMITATION

The main limitation was the small sizes of the sample. Only 274 patients were taken into consideration and were enrolled in this study. Another limitation of our study is that the various forms of anemia were not accounted for in our results.

CONCLUSION

From the findings in the study, it was noted that free T4 had an influence on erythrocyte profiles, namely hemoglobin levels, mean corpuscular volume and packed cell volume. This outcome therefore demonstrates an association of anemia with hypothyroidism. It is thus prudent to assess individuals with chronic iron deficiency anemia and rule out hypothyroidism.

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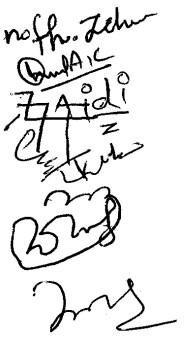
1	Syeda Nosheen Zehra	Manuscirpt writing, Literature search.	
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