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Research Article

Relationship between Soluble Transferrin Receptor 1, Thyroid Function, and Hematological Parameters in Children with Iron Deficiency Anemia

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ABSTRACT

Iron deficiency anemia (IDA) has been determined as the most common type of anemia in children. The objective of the study was to evaluate the changes and relationships among soluble transferrin receptor 1 (sTfR1), thyroid function, and hematological parameters in children with IDA. Ninety children (55 patients with IDA and 35 healthy controls) enrolled in this study. Hemoglobin (Hb) and serum ferritin were used to diagnose IDA in different age groups. An unpaired t-test or Mann–Whitney U test was used for comparisons of two different groups, using Pearson's correlation coefficient or Spearman rho correlation coefficients according to the distribution of data. The average age of the individuals included was 3.132 ± 1.67. IDA patients had significantly decreased levels of red blood cells (RBCs) ($P < 0.0146$), mean corpuscular volume (MCV) ($P < 0.0001$), and mean cell Hb (MCH) ($P < 0.0001$), but significantly higher levels of sTfR1 ($P < 0.0001$) and non-significantly higher levels of thyroid-stimulating hormone (TSH) ($P = 0.1658$) compared to the healthy controls. The identical value determined for free thyroxine (fT4) in IDA and healthy control children was non-significant ($P = 0.9350$). The majority of the IDA patients had characteristics of microcytic and hypochromic anemia. Significantly positive correlations were observed between MCV and MCH (r = 0.8251, $P < 0.0001$), and MCH and fT4 (r = 0.2661, $P < 0.0495$). In addition, non-significant positive correlations were found between RBC, MCV, MCH, and fT4, as well as between sTfR1 and TSH. Non-significantly negative correlations were found between RBC, MCV, MCH, fT4, and sTfR1 and TSH. The investigation showed differences in parameter levels between the IDA and healthy control groups and a relationship between them.

Keywords: Anemia, thyroxine, soluble transferrin receptor 1, thyroid gland, preschool children

INTRODUCTION

Iron deficiency anemia (IDA) has been recognized as the most common and widespread type of anemia in children.[1] Anemia is the most common hematological disorder seen in children, and it occurs when hemoglobin (Hb) or hematocrit (Hct) or the amount and size of red blood cells (RBC) fall below a certain threshold that depends on age, gender, and physiological condition.[2,3] Iron deficiency (ID) is diagnosed when a reduction occurs in the levels of serum ferritin (Sf), which reflects the level of iron stored in the body.[4] Anemia particularly affects children and is a significant public health problem worldwide. Anemia affected 24.3% of the world's population in 2021, which is approximately 1.92 billion people. Globally, 39.8% (269 million) of preschool children suffer from anemia.[5,6] Pre-school children are the age group most exposed to IDA. IDA is responsible for more than 50% of anemia cases.[7]

Major causes and risk factors of IDA in children include reduced iron stores (maternal ID and prematurity); increased requirements for iron (for growth in early childhood); inadequate iron uptake (inadequate dietary iron content and diets low in heam [iron]); poor absorption of dietary iron (by tea and coffee in children, insufficient acidity of the stomach, celiac disease, and inflammatory bowel disease); and loss of blood (hookworm infestation and cow's milk colitis).[8,9] On the other hand, extended breastfeeding is known to be linked to ID. There are two peaks in the incidence of IDA during childhood. These peaks occur in infancy and adolescence, when there is a disparity between the amount of food consumed and the high demand for iron, based on the remarkable development rate.[9] The Hb, Hct, RBC count, mean corpuscular volume

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(MCV), mean cell hemoglobin (MCH), mean corpuscular Hb concentration, reticulocyte Hb content (CHr), total iron binding capacity, serum iron, Sf, soluble transferrin receptor (sTfR), transferrin (Tf) saturation, and Tf are among the numerous hematological and biochemical parameters used in the diagnosis of IDA.[1,9,10]

sTfR, which represents the soluble form of the Tf receptor, a relatively newer assay, is used for the determination of ID. All iron in the blood is bound to Tf as Fe^{3+}Tf. It is taken up by erythroblasts (or hepatocytes and macrophages) through TfR1. The ferrireductase STEAP3 enzyme reduces Tf -coupled Fe^{3+} to Fe^{2+} in the endosome. Following endocytosis, divalent metal transporter 1 transports iron to the cytosol and the labile iron pool; TfR1 is recycled to the cell surface.[11] TfR1 is a homodimer Type 2 transmembrane glycoprotein with a molecular weight of 97 kDa. TfR1 is synthesized in the endoplasmic reticulum and, after translation, modified with phosphates and fatty acyl groups. The molecule consists of two identical monomers connected by two disulfide bonds. It contains three domains: A short cytoplasmic N-terminal domain (residues 1–67), a single transmembrane region (residues 68–88), and a large soluble extracellular domain (residues 89–760) with a trypsin-sensitive site.[12,13]

Iron-deficient erythropoiesis and IDA are associated with increased serum sTfR concentrations, which indicate early functional ID.[10,14] TfR1 is a part of the cell membrane. Iron is taken in after it attaches to TfR1. The quantity of iron inside a cell determines the amount of TfR1 that is present on its membrane. Reduced intracellular iron causes an increase in cell membrane TfR1 expression.[15] The Tf receptor is a primary glycoprotein that plays an important role in cell uptake of iron. Tf -iron uptake is essential for avoiding iron overload because the quantity of iron that can enter the cell is closely associated with the number of TfR1 molecules present on its surface.[13,16] Due to lacking standardization in the laboratory assessments, the estimation of sTfR is at present usually not widely available. Since it is less affected by the inflammatory condition than other indicators, it may be particularly useful in diagnosing ID.[17]

Human health depends on trace elements, which are also critical for metabolism, particularly thyroid metabolism and function. A deficiency in traces of minerals such as iron, iodine, copper, zinc, and manganese can potentially have a negative effect on the functioning of the thyroid. Thyroid hormones have an effect on a wide variety of physiological processes as well as metabolic activities.[18,19] The thyroid gland creates triiodothyronine (T3) and thyroxine (T4) in response to thyroid-stimulating hormone (TSH) secreted by the pituitary gland. Thyroid gland dysfunction occurs when it secretes excessive amounts of T3/T4, whereas TSH decreases as a result of feedback inhibition (negative feedback); this condition is known as hyperthyroidism. In hypothyroidism, thyroid hormone production is low; the anterior pituitary secretes more TSH because it does not acquire negative feedback.[20] When essential trace elements are deficient, thyroid function is impaired.[18,19] Studies in children have shown the relationship between thyroid function and iron status.[21,22] Iron levels (Sf and Hb) showed a negative association with TSH but a positive correlation with free forms of T4 (fT4) and T3 (fT3).[23,24]

The available studies on the relationship between hematological and biochemical markers of IDA and thyroid function parameters in children are very limited, especially in children at the age ranges of 6 months to <6 years of age. Therefore, the primary objective of the present study is to investigate the changes in hematological markers, sTfR1, and thyroid function parameters in children under the age of 6 years with IDA, compare these changes to those in healthy controls, and identify variations in the levels of these markers based on the severity of anemia caused by ID. The secondary objective of this study is to find correlations between these above-mentioned parameters.

MATERIALS AND METHODS

Study Design

This investigation was carried out from November 2024 to December 2025. The study included 90 children living in the Garmian province, Kurdistan region of Iraq, ranging in age from 6 months to 6 years. The children who had not been included in the study were those who were either younger than 6 months or older than 6 years; those who had a history of receiving blood transfusions and iron or thyroid hormone therapy within <1 month; and those who had an existing diagnosis of other related anemias, long-term illnesses, or known hemoglobinopathies (such as thalassemia).

Ethical Approval

The Ethics Committee of the Faculty of Science and Health at Koya University in the Kurdistan region of Iraq gave the study ethical approval (Form code: 13Bio, dated December 23, 2024). The parents of children gave their informed consent to take part in this study. The parents of the children were formally questioned using a questionnaire that took their sociodemographic information. This information included the children' ages, genders, places of residence, heights, and weights, as well as whether or not there was a history of blood illnesses in their families.

Laboratory Assessments

The blood samples were collected in two different private medical laboratories in Kalar City, which include Zanko Medical Laboratory and Marina Medical Laboratory. From each participant, about 4 mL of venous blood samples were collected. About 1 mL of the blood is placed in a lavender-cap tube that contains the anticoagulant ethylenediaminetetraacetic acid for the purpose of doing a complete blood count (CBC) test, and the blood is well mixed by inverting 10 times (or by a rotator mixer). Immediately after blood collection, a CBC test is performed by a Medionic M51 hematology analyzer (Boule Diagnostics, Sweden) in Zanko Medical Laboratory or by a Swelab Alfa Plus Standard hematology analyzer (Boule Diagnostics, Sweden) in Marina Medical Laboratory.

For obtaining serum for the purpose of applying biochemical tests, 3 mL of the blood was placed into a tube with a yellow cap, which contains a gel or clot activator, and by centrifuging the blood at 4000 rpm for 5 min using either the LC-04L centrifuge (Zenithlab, China) or the EBA 200 centrifuge (Hettich, Germany), the serum was separated from

the blood. The collected serum was divided into small portions (aliquoted), placed in a small Eppendorf tube, and stored at −86°C for future analysis. For the aims of evaluation of concentrations of SF, TSH, and fT4, serum was analyzed using a Cobas E411 immunoassay analyzer (Roche Diagnostics, Japan). For the purpose of detecting sTfR1, human diagnostic enzyme-linked immunosorbent assay kits were bought from Shanghai Ideal Medical Technology Co., Ltd. (China); the analysis was performed using a Bio-Tek 800TS microplate reader (USA).

Statistical Analysis

The statistical data analysis of the current study was doing by GraphPad Prism software version 8.0.2. Descriptive statistics were displayed as mean, standard deviation (SD), 95% confidence interval (95% CI), median, interquartile ranges, and minimum-maximum. The D'Agostino-Pearson omnibus normality test was used to evaluate the normality of data. An unpaired t-test (for comparisons of means when the distribution of data is normal) or a Mann–Whitney test (for comparisons of medians when the distribution of data is non-normal) was used for the comparison of the continuous variables of two unrelated groups. To evaluate the relationship between the hematological, sTfR1, and thyroid function parameters at a 95% CI, Pearson correlation coefficients (for the normal distribution of data) or Spearman's rho correlations (for the non-normal data distribution) were used for different parameters. However, for all the test parameters, statistically significant differences between the IDA and the healthy group were determined ($P < 0.05$).[21,25]

RESULTS

The participants' ages ranged from 6 months to <6 years, with a mean age of 3.132 years (SD = 1.67). A total of 55 patients were diagnosed with IDA (29 [52.73%] were males, and 26 [47.27%] were females). A total of 35 participating children were diagnosed as 35 healthy controls (17 [48.57%] were males, and 18 [51.43%] were females). During comparison of test parameters between healthy controls and IDA patients, the RBC count, MCV, MCH, and fT4 exhibited a distribution pattern aligned with normality ($P > 0.05$). Conversely, sTfR1 and TSH were not normally distributed ($P < 0.05$). In spite of these, most of the variables did not follow a normal distribution; the specific statistical test approaches were used for parametric and non-parametric data distribution throughout the investigation.

Hb and Sf levels were used to diagnose IDA according to World Health Organization thresholds for different age groups.[26,27] When the Hb level is <11 g/dL and the Sf level is <12 μg/L in children <5 years, and when the Hb level is <11.5 g/dL and the Sf level is <15 μg/L in children aged 5–<6 years, IDA is diagnosed. The degree of anemia of iron-deficient children <5 years of age, with an Hb level between 10 and 10.9 g/dL, is diagnosed as mild; 7.0–9.9 g/dL is diagnosed as moderate. For children between the ages of 5 and 6 years, an Hb level between 11 and 11.4 g/dL is diagnosed as mild, and 8–10.9 g/dL is diagnosed as moderate.[26]

The comparison of hematological parameters between healthy controls and IDA patients was exhibited in Table 1 and Figure 1. The findings of the present study illustrated that the levels of RBC count were between 4.15 and 5.23 × 10^6/μL (mean = 4.641, SD = 0.285, CI = 4.543–4.739) in healthy children and, in IDA patients, were between 3.18 and 5.23 × 10^6/μL (mean = 4.416, SD = 0.483, CI = 4.286–4.547). In comparison of MCV and MCH levels between IDA and healthy groups, it was found that the levels of MCV and MCH varied from 72.0 to 87.5 fL (mean = 81.04, SD = 3.949, CI = 79.68–82.39) and 24.4–29.2 pg (mean = 27.18, SD = 1.228, CI = 26.76–27.60) in healthy control children, respectively. Whereas the observed values of MCV and MCH in IDA children were varied from 47.9 to 88.7 fL (mean = 67.71, SD = 8.892, CI = 65.31–70.12) and 14.5–28.6 pg (mean = 22.64, SD = 3.195, CI = 21.78–23.51), respectively.

According to the findings of the study, the mean and median values of RBC count, MCV, and MCH were lower in individuals with IDA compared to healthy controls, and there was a statistically significant difference in RBC count ($P < 0.0146$) as well as in MCV and MCH ($P < 0.0001$) between healthy controls and IDA patients, indicating a decrease in the average size of RBCs and the presence of hypochromia.

Microcytic and hypochromic anemia is diagnosed by MCV <78.0 fL and MCH <27.0 pg.[28] Figure 2 showed that the most of the iron-deficient anemic children, which account for 51 (93%), had microcytosis and hypochromia, which is characterized by a decrease in MCV and MCH. Whereas 4 (7%) had normocytic and normochromic anemia.

Table 2 and Figure 3 display the levels of sTfR1, TSH, and fT4 in relation to healthy controls and IDA patients. Descriptive statistics showed that the sTfR1 levels were between 1.47 and 2.83 mg/L (mean = 2.08, SD = 0.367, CI = 1.955–2.207) in healthy control children. From such data, it could be noticed that the sTfR1 levels were 1.65 and 4.30 mg/L (mean = 3.37, SD = 0.865, CI = 3.137–3.605) in IDA children. According to the study findings, the sTfR1 showed significantly higher mean and median values in the IDA group than in the healthy control. In the obtained results, sTfR1 was found to be statistically significantly different between IDA and healthy control individuals ($P < 0.0001$).

The majority of IDA children had normal thyroid function, and there were not found to be significant differences in TSH ($P = 0.1658$) and fT4 ($P = 0.9350$) between IDA and healthy control individuals. The current results of the study exhibited that the levels of TSH and fT4 were in the range of 0.670–3.93 mIU/L (mean = 1.957, SD = 1.022, CI = 1.606–2.308) and 13.38–22.32 pmol/L (mean = 16.68, SD = 2.105, CI = 15.96–17.41) in healthy control children, respectively. Whereas the TSH and fT4 levels were 2.235 mIU/L (mean = 2.235, SD = 0.893, CI = 1.994–2.476) and 9.98–23.0 pmol/L (mean = 16.73, SD = 2.796, CI = 15.97–17.48) in children with IDA, respectively.

Table 3 and Figure 4 display the distribution of levels of sTfR1 and thyroid function parameters in relation to the severity of anemia in children with IDA. The findings of the study revealed that there was no significant difference in the distribution of sTfR1, TSH, and fT4 in mild and moderate anemia ($P > 0.05$). However, mean and median values of

Table 1: Comparison of hematologic parameters of healthy controls and IDA groups

Parameters	Healthy (n=35)				IDA (n=55)				*P*-value
	Min–Max	Mean	±SD	95% CI	Min–Max	Mean	±SD	95% CI	
RBC (10^6/μL)[a]	4.15–5.23	4.641	±0.285	4.543–4.739	3.18–5.23	4.416	±0.483	4.286–4.547	<0.0146
MCV (fL)[a]	72.0–87.5	81.04	±3.949	79.68–82.39	47.9–88.7	67.71	±8.892	65.31–70.12	<0.0001
MCH (pg)[a]	24.4–29.2	27.18	±1.228	26.76–27.60	14.5–28.6	22.64	±3.195	21.78–23.51	<0.0001

[a]RBC, MCV, and MCH values were normally distributed (D'Agostino-Pearson Omnibus test >0.05 a t-test was used for comparison. SD: Standard deviation, CI: Confidence interval of mean, RBC: Red blood cells, MCV: Mean corpuscular volume, MCH: Mean cell hemoglobin, IDA: Iron deficiency anemia

Table 2: Comparison of sTfR1, thyroid-stimulating hormone, and free thyroxine levels of healthy controls and IDA groups

Parameters	Healthy (n=35)				IDA (n=55)				*P*-value
	Min-Max	Mean	±SD	95% CI	Min-Max	Mean	±SD	95% CI	
sTfR1 (mg/L)[a]	1.47–2.83	2.08	±0.367	1.955–2.207	1.65–4.30	3.37	±0.865	3.137–3.605	<0.0001
TSH (mIU/L)[a]	0.670–3.93	1.957	±1.022	1.606–2.308	0.637–3.53	2.235	±0.89	1.994–2.476	0.1658
fT4 (pmol/L)[b]	13.38–22.32	16.68	±2.105	15.96–17.41	9.98–23.0	16.73	±2.796	15.97–17.48	0.9350

[a]sTfR1, and TSH values were non-normally distributed (D'Agostino-Pearson Omnibus test <0.05). Therefore, [a]Mann–Whitney U test was used for comparison. [b]fT4 values were normally distributed (D'Agostino-Pearson Omnibus test >0.05). Therefore, [a]t-test was used for comparison. SD: Standard deviation, CI: Confidence interval of mean, IDA: Iron deficiency anemia, TSH: Thyroid-stimulating hormone, sTfR1: Soluble transferrin receptor 1

Table 3: sTfR1, thyroid-stimulating hormone, and free thyroxine levels across different grades of anemia of the IDA group

Parameters	Severity of anemia		*P*-value
	Mild	Moderate	
	Median (IQR)		
sTfR1 (mg/L)[a]	3.48 (2.50, 4.04)	3.93 (3.28, 4.11)	0.1020
TSH (mIU/L)[a]	2.51 (1.153, 2.894)	2.569 (1.757, 3.169)	0.6748
fT4 (pmol/L)[b]	16.72 (15.25, 18.98)	16.71 (13.99, 18.29)	0.4014

[a]sTfR1, and TSH values were non-normally distributed (D'Agostino-Pearson Omnibus test <0.05). Therefore, a Mann–Whitney U test was used for comparison. [b]fT4 values were normally distributed (D'Agostino-Pearson Omnibus test >0.05). Therefore, a t-test was used for comparison. SD: Standard deviation, CI: Confidence interval of mean, IDA: Iron deficiency anemia, TSH: Thyroid-stimulating hormone, sTfR1: Soluble transferrin receptor 1, IQR: Interquartile range

sTfR1 and TSH were relatively increased in IDA patients who had moderate anemia compared to IDA patients with mild anemia. The mean values of fT4 were decreased in IDA patients who had moderate anemia compared to IDA patients with mild anemia, but the median values of fT4 were identical between mild and moderate degrees of anemia. That indicates the sTfR1, TSH, and fT4 can change even in mild cases of IDA.

In Table 4, correlation coefficients for hematological, sTfR1, TSH, and fT4 are displayed. The use of correlation coefficients was dependent on whether the data distribution was normally distributed or not. On the other hand, the RBC count, MCV, MCH, and fT4 followed a normal distribution pattern ($P > 0.05$). Even so, the sTfR1 and TSH did not follow a normal distribution pattern ($P < 0.05$); the study used both parametric and non-parametric statistical test methods. For the purpose of investigating relationships, Pearson's correlation coefficients for normal distributions and Spearman's rho coefficient of correlation for non-normal distributions are typically utilized.

The statistical analysis confirmed that RBC has a weak positive and statistically non-significant correlation with MCV (r = 0.01067, $P = 0.9384$), MCH (r = 0.01382, $P = 0.9202$), and fT4 (r = 1945, $P = 0.1547$). On the other hand, a weak negative and non-significant relationship was found for sTfR1 (r = −0.0962, $P = 0.4848$) and TSH (r = −0.05908, $P = 0.6683$) with RBC, confirming that when the levels of RBC increase, they tend to increase MCV, MCH, and fT4 and decrease sTfR1 and TSH levels. The presence of this interaction is reflected in the quantity of RBCs and their capacity to carry oxygen, as well as their size and shape. In addition, the negative association between RBC and sTfR1 and TSH provides additional evidence that various red cell shapes arise as the likelihood of IDA develops.

The findings of the study indicated that the MCV has a strong positive and significant correlation with MCH (r = 0.8251, $P < 0.0001$) and a weak positive and non-significant correlation with fT4 (r = 0.2297, $P < 0.0916$); this finding reveals the interrelationship of those parameters. In a way, the high levels of MCV are associated with high levels of MCH and fT4. As noticed, weak negative and non-significant correlations were determined between MCV and sTfR1 (r = −0.1628, $P = 0.2351$) and TSH (r = −0.1565, $P = 0.2538$); it was observed that as the value of MCV increased, those of levels of sTfR1 and TSH decreased, which is a possible interdependency between their regulations.

The MCH has a statistically significant correlation, which is a moderate positive, with fT4 (r = 0.2661, $P < 0.0495$). Non-significant weak negative correlations were identified between MCH and sTfR1 (r = −0.03304, $P = 0.8107$) and TSH (r = −0.1242, $P = 0.3661$). This finding confirms that elevated MCH levels tend to elevate the level of fT4, but conversely, sTfR1 and TSH levels decrease.

However, a weak positive and non-significant relationship was determined between TSH and sTfR1 (r = 0.1340, $P = 0.3296$), and a moderate negative, which is statistically significant, was found in the correlation between TSH and fT4 (r = −0.3172, $P < 0.0183$). Among the findings of the present

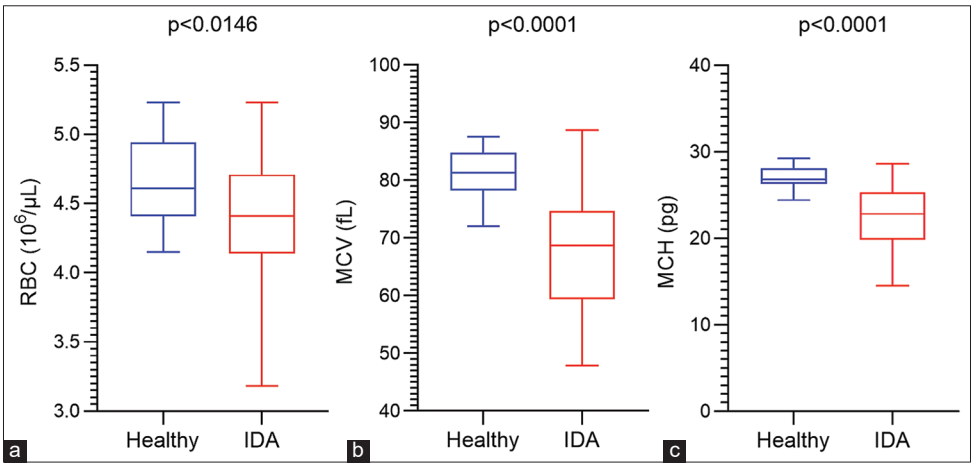

Figure 1: Box and whisker plots exhibit the levels of red blood cells (a), mean corpuscular volume (b), and mean cell hemoglobin (c) in the study groups; the horizontal line in the box is the median, the box indicates the interquartile range (25th–75th percentile), and the whiskers are short lines extending top and bottom from the boxes to show the minimum and maximum values

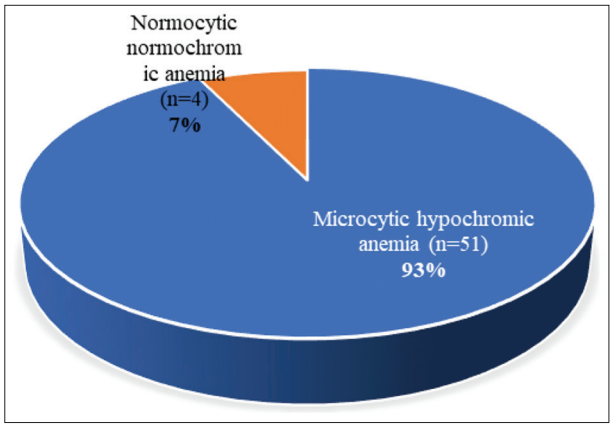

Figure 2: Number and percentage of children with microcytic hypochromic and normocytic and normochromic anemia depending on red blood cell size and forms

study, it was found that the fT4 had a negative and non-significant association with sTfR1, which illustrated that there was a positive association between TSH and sTfR1, reflecting that TSH and sTfR1 increased together, but fT4 decreased, showing an inverse relationship. These findings of this study confirm that hematological parameters such as RBC count, MCV, and MCH can effectively reflect underlying iron status when interpreted alongside sTfR1 levels. sTfR1 enhances diagnostic accuracy in IDA when supported by CBC indices. The physiological mechanisms, such as erythropoiesis and endocrine regulation, by evaluating the correlations between the RBC count, MCV, MCH, sTfR1, TSH, and fT4, can be better understood.

DISCUSSION

Around the world, IDA in children remains seen as a serious health concern. This is due to the fact that there are long-term impacts on cognitive abilities, immunity, and overall health.[29] ID is the most prevalent nutrient deficiency in infants, in preschool children, and in adolescents.[30]

In the present study, in comparison of hematologic markers of IDA and healthy control groups, it could be noticed that the levels of RBC count, MCV, and MCH of children with IDA were significantly decreased in comparison with the healthy control group, and a statistically significant difference was determined between IDA and the healthy control group ($P < 0.05$). These observations are similar to the previous studies by Mohammed-Mujib *et al.*[31], Nouri *et al.*[32], Gamal *et al.*[22], and de Paiva Lourenção *et al.*[28] Hematological parameters derived from a CBC test (such as Hb, RBC count, MCV, MCH, and red cell distribution width [RDW]) play an essential role in assessing anemia.[33] MCV, which stands for the average volume of RBC, is a metric that is provided in automated analysis. MCV can be used to classify anemia into three categories: Macrocytic, normocytic, and microcytic.[34] As one of the findings of the present study, microcytic hypochromic anemia was determined in most of the IDA children. These findings were consistent with the previous study.[28] IDA is a hypochromic and microcytic anemia characterized by decreased Hb values based on the normal range for sex and age, and decreased values of MCV and MCH.[9,35,36]

According to the findings of the current study, the levels of sTfR1 increased in IDA patients more than in healthy controls. Similarly, these results were previously reported from different studies.[9,10,15,17,37,38] In addition, the results of the present study confirm statistical significant differences between IDA patients and healthy control individuals; similar results were reported by Abd Elmageed *et al.*[39] In contrast to this, the results reported by de Paiva Lourenção *et al.*[28] were not found to have a statistically significant difference in the levels of sTfR between IDA and healthy children. sTfR is a reliable marker of erythropoietic activity when stored iron is sufficient, and it becomes a good diagnostic of iron status when iron stores are depleted. In the cases where erythropoietic activity is low, the sTfR is decreased, and elevated in situations where erythropoietic activity is high.[40,41] Whereas sTfR concentration is a non-acute-phase reactant indication of functional ID, there is a lack of assay standardization, uniform reference ranges, and typical cutoffs, which makes its interpretation challenging.[42] In turn, the sTfR is an indicator used to evaluate iron status in children and has been described as an essential indicator

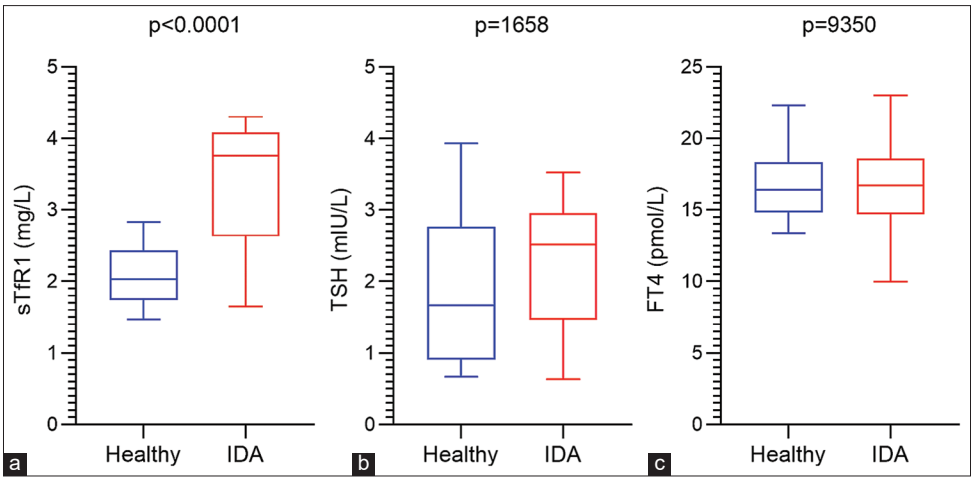

Figure 3: Box and whisker plots exhibit the levels of soluble transferrin receptor 1 (a), thyroid-stimulating hormone (b), and free thyroxine (c) in the study groups; the horizontal line in the box is the median, the box indicates the interquartile range (25th–75th percentile), and the whiskers are short lines extending top and bottom from the boxes to show the minimum and maximum values

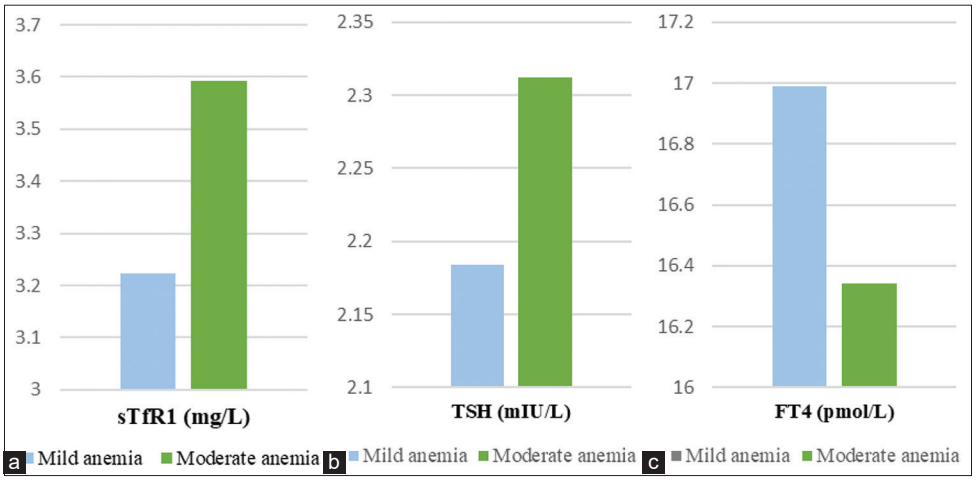

Figure 4: Comparison mean of soluble transferrin receptor 1 (a), thyroid-stimulating hormone (b), and free thyroxine (c) across different grades of anemia of the iron deficiency anemia group

in differentiating between IDA and inflammatory anemia. sTfR1 concentrations rise when cellular iron concentration drop, and they may even rise slightly during an inflammatory response.[43] The continual increase of sTfR levels with the worsening of ID makes it a useful tool for evaluating the development of ID.[15,44]

Rusch *et al*.[10] recommended the normal range for sTfR concentrations in adult males is 2.2–5.0 mg/L, whereas the normal range for adult females is 1.9–4.4 mg/L for the diagnosis of IDA. As reported by Bhatia *et al*.[45] the normal range for children is lower than for healthy adults, ranging between 0.8 and 3.3 mg/L. Vázquez-López *et al*.[46] suggested 0.78–1.9 mg/L (mean value is 1.22) as the reference range for sTfR in children <6 years old. de Paiva Lourenção *et al*.[28] have used the mean value for sTfR of 1.5 mg/L as the cutoff for ID. Mei *et al*.[47] proposed use of higher geometric mean sTfR concentrations (4.20 mg/L; CI: 4.15–4.26) for preschool children. As described by Gattermann *et al*.[38], sTfR in the condition of IDA increased to 4.2 mg/L. Mantadakis *et al*.[36] suggested the ID was diagnosed as sTfR >35 nmol/L. According to Virtanen *et al*.[48], prepubertal boys have greater sTfR concentrations than males, whereas infants have higher amounts than prepubertal boys. High sTfR concentrations were linked to low Sf concentrations and vice versa; the authors also found that this association remained accurate even when the iron and ferritin levels were within the normal physiological range.

IDA and thyroid dysfunction both have negative effects on cognitive ability, which may delay learning and the acquisition of new skills, particularly in children.[22] Having both disorders at the same time in youngsters will have a negative impact on their health and talents. Researchers in Egypt found a strong correlation between thyroid dysfunction and low intelligence quotient in children with IDA.[49] It is believed that the relationship between iron status and thyroid hormones is bidirectional. Thyroid hormones enhance the ability of the body to absorb iron and incorporate it into RBC.[50] It is believed that thyroid hormones stimulate the synthesis of RBCs by raising oxygen consumption and promoting the development of erythroid progenitor cells.[51] ID can decrease

Table 4: Pearson's correlation coefficients or spearman rho correlation coefficients of hematological, biochemical, and thyroid function parameters

Parameters	RBC (10^6/μL)	MCV (fL)	MCH (pg)	sTfR1 (mg/L)	TSH (mIU/L)
RBC (10^6/μL)					
r	-	0.01067[a]	0.01382[a]	−0.0962	−0.05908
P	-	0.9384	0.9202	0.4848	0.6683
MCV (fL)					
r	-	-	0.8251[a]	−0.1628	−0.1565
P	-	-	<0.0001	0.2351	0.2538
MCH (pg)					
r	-	-	-	−0.03304	−0.1242
P	-	-	-	0.8107	0.3661
TSH (mIU/L)					
r	-	-	-	0.1340	-
P	-	-	-	0.3296	-
fT4 (pmol/L)					
r	0.1945[a]	0.2297[a]	0.2661[a]	−0.01665	−0.3172
P	0.1547	0.0916	<0.0495	0.9057	<0.0183

[a]Pearson's correlation coefficients. RBC: Red blood cell, MCV: Mean corpuscular volume, MCH: Mean cell hemoglobin, sTfR1: Soluble transferrin receptor 1, TSH: Thyroid-stimulating hormone

thyroid peroxidase and 5′-deiodinase activity, inhibit T3 from adhering to its nuclear receptor, and result in a slower rate of T3 utilization from the blood pool.

Iron is incorporated into the structure of the thyroperoxidase (TPO), a heme-dependent enzyme. TPO catalyzes the first two steps of thyroid hormone production. ID can decrease thyroid peroxidase and 5′-deiodinase activity, inhibit T3 from adhering to its nuclear receptor, and result in a slower rate of T3 utilization from the blood pool, which in turn reduces the thyroid hormone production and raises levels of TSH.[52-55]

In evaluating thyroid gland function parameters, the results of the present study show that TSH levels are higher in IDA than in the healthy group but still within the reference range, as well as the results also show that fT4 is the same in both groups. There were not statistically significant differences for TSH and dT4 between IDA and healthy control individuals ($P > 0.05$). Similar to these results previously reported by Ipek *et al*.[25], when they evaluated thyroid function parameters in children with IDA aged between 1 and 14 years. They found that the mean serum TSH and fT4 values were found to be 2.62 ± 1.47 mIU/L and 1.43 ± 0.25 ng/dL in healthy controls, respectively, and 3.20 ± 1.80 mIU/L and 1.40 ± 0.18 ng/dL in IDA patients, respectively. There was not a statistically significant difference in TSH and fT4 values between the healthy control and IDA groups ($P = 0.085$ and $P = 0.060$, respectively). Mean TSH values were found to be significantly higher in the IDA group, and mean fT4 values were found to be similar in both groups. Although physiologically active free thyroid hormone fractions are still within acceptable ranges, they proposed that IDA affected total thyroid hormone levels.

In a cross-controlled study, Gamal *et al*.[22] reported there was a significantly higher mean TSH level in the IDA children compared to the control group (2.77 ± 1.30 μIU/mL vs. 2.10 ± 1.11 μIU/mL, and $P = 0.006$) and a slightly lower mean fT4 level in the IDA children compared to the control group (1.29 ± 0.45 ng/dL vs. 1.42 ± 0.25 ng/dL, and $P = 0.082$). They proposed that subclinical hypothyroidism is more likely to occur in children with IDA, particularly in cases when Sf and iron levels are extremely low.

As reported by the study of Thapa *et al*.[50], the mean ± SD of serum fT4 and median (IQR) of TSH levels were 1.21 ± 0.26 ng/dL and 3.03 (2.26, 4.34) mIU/L, respectively; there was no significant difference in mean fT4 and median TSH levels between the iron-sufficient group and children with IDA ($P = 0.877$ and $P = 0.914$). Metwalley *et al*.[49] evaluated the thyroid functions of 60 children with IDA against those of 20 healthy children. In their study, the researchers found that compared to the control group, IDA children had significantly lower total T3 (tT3) and total thyroxine (tT4) levels and higher TSH levels. In contrast, Tienboon and Unachak[56] found no change in thyroid hormone concentrations (tT3, tT4, fT3, fT4, and TSH) between pre- and post-iron treatment in children with IDA anemia. Both Khatiwada *et al*.[57] and Chaudhari *et al*.[58] found that thyroid dysfunction was more common among school-aged children.

Hashemipour *et al*.[59], Aziza *et al*.[60], and Yavuz *et al*.[61] investigated thyroid hormones with various iron status parameters in different age groups from different parts of the world and found no significant difference. Bakry[21] discovered that anemic and iron-deficient children had significantly higher TSH, similar fT4 levels, and lower fT3. In addition to children in the group who had been iron-deficient and anemic, they displayed reduced thyroid functioning; hence, they proposed that thyroid dysfunction, particularly hypothyroidism, is connected to anemia and ID. Akhter *et al*.[62] found that in a different survey conducted in Bangladesh among individuals in the general public, individuals with

ID had significantly lower serum fT4 levels ($P < 0.05$) and significantly higher serum TSH levels ($P < 0.05$) compared to control subjects, whereas the levels of serum fT3 were nearly identical. As a result of a reduced demand for oxygen, erythropoietin production can be reduced, and bone marrow suppression can occur in cases of thyroid hormone insufficiency, both of which are believed to influence the process of hematopoiesis. Furthermore, it has been found that thyroid hormones regulate the expression of the *Tf* gene.[63] Researchers have shown that IDA slows down peripheral T4 to T3 conversions, lowers plasma tT4 and tT3 levels, and impacts thyroid metabolism.[64] ID is usually thought to have a negative impact on thyroid physiology and thyroid hormone metabolism. Iron is essential for thyroid hormone metabolism and production; however, it did not appear to have a great impact on thyroid hormone metabolism in the groups that were investigated.

In the evaluation of the relationship between hematological, sTfR1, and thyroid function parameters, the achieved results revealed that there was a positive association between RBC, MCV, MCH, and fT4, as well as between sTfR1 and TSH. Although sTfR1 and TSH were found to be negatively correlated with RBC, MCV, MCH, and fT4, Yoon *et al*.[15] performed a study to evaluate the relationship between sTfR and hematological and biochemical parameters; in the IDA patient groups, sTfR showed a negative correlation with Hb, MCV, serum iron, ferritin, and Tf saturation, whereas it exhibited a positive correlation with total iron binding capacity and RDW. In Bangladesh, Mohammed-Mujib *et al*.[31] determined a significant strong positive correlation between MCV and MCH, a non-significant weak positive correlation between RBC count and MCV, and a non-significant negative correlation between RBC count and MCH. Gamal *et al*.[22] found a non-significantly positive correlation between MCV and MCH with fT4 and a non-significantly negative relationship with TSH. The positive relationship between sTfR1 and TSH suggests compensated pituitary stimulation, whereas the negative relationship with RBC, MCV, MCH, and fT4 indicates that ID affected hematological parameters and thyroid hormone production. There have been studies that have shown that IDA has a negative impact on thyroid metabolism. In addition, it has been found to lower plasma tT4 and tT3 levels and to limit the peripheral process of converting T4 to T3.[57,64] The relationship of iron metabolism and the thyroid gland and its associated regulatory roles is indicated in numerous studies,[57,65,66] on the other hand, are based on the results achieved in some other study; the correlation between thyroid function and anemia or ID has not been found.[50,59,61-63,67,68]

CONCLUSION

The findings of the study indicated that in comparison with healthy controls, children with IDA had an increase in sTfR1 and TSH levels, a decrease in levels of hematological parameters (RBC, MCV, and MCH), and identical fT4 levels. Microcytic and hypochromic anemia was determined in most of the anemic and iron-deficient children. In addition, in cases with mild anemia, changes in these parameters were indicated. A negative correlation was determined between RBC, MCV, MCH, fT4, and sTfR1 and TSH. There was a positive correlation between sTfR1 and TSH, as well as between RBC, MCV, MCH, and fT4, when considered separately.

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