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## Original Article

# Relation between Thyroid Function and Iron Deficiency Anemia in Primary School-Age Children: A Controlled Cross-Sectional Study

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## ABSTRACT

**Background:** Iron deficiency anemia [IDA] is a very common medical condition affecting primary school-age children, with several unfavorable consequences. There are some reports pointing to a possible effect of IDA on thyroid gland function.

**Aim of the work:** To assess thyroid function in primary school age children in Damietta Governorate, Egypt with iron deficiency anemia and to investigate potential related risk factors.

**Patients and Methods:** A controlled cross-sectional study included 100 primary school age children [age: 6-12 years]; 50 children with iron deficiency anemia [case group], and 50 healthy age- and sex-matched children [control group]. Complete blood count, serum iron, serum ferritin and thyroid hormone profile [thyroid stimulating hormone [TSH], free triiodothyronine [FT3] and free thyroxine [FT4] were analyzed for all children.

**Results:** In the case group, compared to the control group, there was a significantly higher TSH level [ $2.77 \pm 1.30$  vs.  $2.10 \pm 1.11$ ;  $P=0.006$ ] and lower FT3 [ $3.22 \pm 0.82$  vs.  $3.61 \pm 0.69$ ;  $P=0.011$ ]. The frequency of hypothyroid status [both overt and subclinical] was elevated in the case group [24% vs. 6%;  $P=0.02$ ]. There was a significant negative correlation between TSH with both serum iron [ $P=0.019$ ] and ferritin [ $P=0.009$ ].

**Conclusion:** Iron deficiency anemia, especially when serum ferritin and iron are very low, in primary school children is associated with liability to get subclinical hypothyroidism.

**Keywords:** Thyroid; Primary school age; Egyptian; Iron deficiency; Anemia

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\* Main subject and any subcategories have been classified according to the research topic

## INTRODUCTION

The condition of iron deficiency [ID] and subsequent iron deficiency anemia [IDA] are common medical disorders that occur almost in every country in the world [1].

Iron deficiency anemia affects about 40% of children within the school age in developing countries [2]. It is a major health problem in Egypt, as the prevalence of iron deficiency anemia among school children reported as 35.3% [3].

There is a growing body of evidence that iron deficiency can result in symptoms and signs unrelated to anemia itself and can be associated with a diversity of diseases [4]. One of the major concerns is the effect of IDA on thyroid function [5].

The function of the thyroid gland is critical for the control of metabolic activity within the human body [6]. In addition, it plays an essential role in the growth and development of children as well as, in the maturation of the central nervous system [7]. Adequate thyroid function relies on the existence of many trace elements, which are necessary for the production and metabolism of thyroid hormones

In patients with IDA, thyroid function may be affected through several mechanisms; iron deficiency can impair thyroid metabolism [9] that can be attributed to the iron-dependent haem-containing thyroid peroxidase [TPO] enzyme [10], which is accountable for the oxidation of iodide into iodine, and its organification into tyrosine residues of thyroglobulin to form Mono-Iodotyrosine [MIT] or Di-Iodotyrosine [DIT] [11]. Furthermore, TPO is a principal for the formation of T<sub>3</sub> [by the coupling of one molecule of MIT and one molecule of DIT], and T<sub>4</sub> [by the coupling of two DIT molecules] [12].

Several studies have investigated the association between thyroid function with iron status among school children, with conflicting results [12-15]. Although iodine nutrition continues to improve worldwide, thyroid dysfunction is still frequently reported in school-age children [13].

## AIM OF THE WORK

Since ID and IDA are highly prevalent among school-age children, assessment of thyroid function is critical to avoid the potential consequences on cognitive and intellectual function of these children.

The aim of the present study is to look for the possible effects of iron deficiency on thyroid function in primary school children in Damietta governorate, and to investigate potential risk factors for thyroid dysfunction.

## PATIENTS AND METHODS

A comparative cross-sectional study that included 100 primary school-age [6-12 years] children recruited from Pediatric outpatient clinic of Al-Azhar University Hospital [New Damietta]. Included children divided into two groups; 50 children with iron deficiency anemia [case group], and 50 age- and sex-matched apparently healthy children [control group]. The study was conducted during the period from April 2020 until end of December 2020.

Anemia was diagnosed in this age group when hemoglobin [HB] is < 11.5 gm/dl. Iron deficiency was diagnosed when there is microcytic [mean corpuscular volume [MCV] < 76 fl] hypochromic [mean corpuscular hemoglobin [MCH] < 25 pg] anemia, simultaneously with serum ferritin < 20 µg/l and/or serum iron < 40 µg/dl [16].

Children with other associated anemia, with acute illness or chronic diseases, having a recent history of blood transfusion or iron therapy during the past four months, children with known thyroid disorder, receiving thyroid hormones, or having family history of thyroid diseases were excluded from the study.

A systematic approach to symptoms of thyroid gland dysfunction was employed. Considered symptoms of hypothyroid dysfunction include weight gain, cold intolerance, easy fatigability, hoarseness of voice, constipation and mood impairment [17].

The following investigations were done: complete blood count, serum iron, serum ferritin, thyroid stimulating hormone [TSH], free thyroxine [FT<sub>4</sub>], free triiodothyronine [FT<sub>3</sub>].

## Laboratory analysis

Blood samples [3 ml of venous blood] were collected under complete aseptic conditions. The sample was divided to 2 portions; an aliquot was added to EDTA tube for the measurement of complete blood count, and the other part left to clot for 30 minutes, then centrifugation was allowed for 15 minutes at 3000 rpm, then stored at -20°C till time of biochemical analysis. Complete blood count [CBC] was analyzed using a coulter MAXM [Coulter Corporation]. Serum iron, ferritin and total iron-binding capacity [TIBC] were analyzed using Cobas C311 analyzer [Roche, Switzerland].

For analysis of thyroid function tests, a commercially available ELISA kit was used. Serum FT<sub>3</sub> and FT<sub>4</sub> were analyzed by using "solid phase competitive assay method". TSH was analyzed using "a solid phase sandwich assay



method". All thyroid function tests were equipped by [Calbiotech Inc., Austin Dr, CA].

The normal reference range for TSH=0.4–4.0  $\mu$ IU/mL, for FT<sub>3</sub>=1.71-4.8 pg/mL and for FT<sub>4</sub>= 0.89–1.76 ng/dl. Primary [overt] hypothyroidism defined as TSH > 4.0  $\mu$ IU/ml [0.4–4.0] and free thyroxine [FT<sub>4</sub>] levels < 0.89 ng/dl [0.89–1.76 ng/dl]. Subclinical hypothyroidism is defined when there is an elevated TSH with normal free T<sub>4</sub> [18].

**Ethical considerations:** Oral consent was obtained from the parents of all Patients of the study. The study had been approved by the local ethics committee on research involving human subjects of Damietta Faculty of Medicine, Al-Azhar University. The approval of IRB was obtained.

**Statistical analysis:** The data were evaluated using "statistical package for social sciences version 19 [SPSS Inc, Chicago, USA]", running on IBM compatible computer. Normality tests were checked using "Shapiro-Wilk's test". "Chi-square test" or "Fisher's exact test" were used for comparing categorical variables. "Independent two-sample t-test" or "Mann-Whitney-U test" were applied to compare continuous variables. Pearson's r correlation co-efficient was used for correlating parametric continuous variables. Spearman's  $\rho$  [rho] correlation co-efficient was used for correlating ordinal and non-parametric variables. For all tests, P values < 0.05 were considered significant.

## RESULTS

No significant difference between both groups as regards demographic features and anthropometric measures. The most frequent clinical findings among the case group were

easy fatigability, mood impairment and constipation. The frequency of easy fatigability was significantly higher among the case group [28% vs. 10%; P=0.039] [table 1].

Hematological profile proved the existence of IDA among the case group. Regarding thyroid hormones, there was a statistically significant higher TSH level [2.77 $\pm$ 1.30 vs. 2.10 $\pm$ 1.11; P=0.006] and lower FT<sub>3</sub> [3.22 $\pm$ 0.82 vs. 3.61 $\pm$ 0.69; P=0.011] in the case group, compared to the control group. Mean FT<sub>4</sub> was lower in the case group, but without a statistically significant difference [1.29 $\pm$ 0.45 vs. 1.42 $\pm$ 0.25; P=0.082] [table 2].

The frequency of hypothyroidism [both overt and subclinical] was significantly elevated in the case group [24% vs. 6%; P=0.02] [table 3].

There was no relation between thyroid status and any of the studied demographic [age, sex and residence] and anthropometric data [weight and height]. There was a significant increase in the frequency of easy fatigability [58% vs. 18%; P=0.022] and mood impairment [50% vs. 16%; P=0.024] among children with hypothyroidism, compared to euthyroid children. Furthermore, serum iron and ferritin were significantly lower among children with hypothyroidism, compared to children with euthyroidism [for ferritin: 15.45 $\pm$ 4.16 ng/ml vs. 11.58 $\pm$ 5.19 ng/ml; P= 0.011; for iron: 31.09 $\pm$ 12.78  $\mu$ g/dl vs. 21.45 $\pm$ 8.41  $\mu$ g/dl; P= 0.018] [table 4].

There was significant negative correlation between TSH with both serum iron [r: - 0.33, P= 0.019] and ferritin [r: - 0.37, P= 0.009]. In addition, free T<sub>3</sub> had a significant positive correlation with serum ferritin [r: 0.29, P= 0.042] [table 5] and figure [1].

**Table [1]:** Comparison of demographic and clinical data between the study groups

Variables	Case group [n=50]	Control group [n=50]	P value
Age [years] [Mean $\pm$ SD]	8.21 $\pm$ 1.75	8.24 $\pm$ 1.98	0.94
Sex	Male	27 [54%]	30 [60%]
	Female	23 [46%]	20 [40%]
Residence	Rural	31 [62%]	34 [68%]
	Urban	19 [38%]	16 [32%]
Heart rate [beat/min] [Mean $\pm$ SD]	91.8 $\pm$ 16.5	86.2 $\pm$ 13.1	0.063
Weight percentiles [Mean $\pm$ SD]	52.5 $\pm$ 23.6	48.4 $\pm$ 21.3	0.38
Height percentiles [Mean $\pm$ SD]	45.1 $\pm$ 19.7	39.6 $\pm$ 17.2	0.14
Easy fatigability	14 [28%]	5 [10%]	0.039*
Mood impairment	12 [24%]	4 [8%]	0.054
Constipation	8 [16%]	3 [6%]	0.2
Disturbed sleep	4 [8%]	3 [6%]	1
Weight gain	4 [8%]	2 [4%]	0.68
Cold intolerance	3 [6%]	2 [6%]	1

\* = significant

**Table [2]:** Comparison of laboratory findings between the study groups

Variables	Case group [n=50] Mean ± SD	Control group [n=50] Mean ± SD	P value
White blood cells [ $\times 10^3/\text{cm}^3$ ]	8.24±2.12	7.79±1.95	0.27
Platelets [ $\times 10^3/\text{mmol}$ ]	264±85	239±101	0.18
Hemoglobin [g/dL]	9.25 ± 1.58	12.14 ± 1.13	< 0.001*
Hematocrit [%]	28.76±4.04	35.51±3.56	< 0.001*
MCV [fl]	64.12±5.32	79.24±3.14	< 0.001*
MCH [pg/cell]	23.02±2.91	27.83±2.22	< 0.001*
RDW [%]	16.26±2.45	13.78±1.22	< 0.001*
Serum iron [ $\mu\text{g}/\text{dl}$ ]	28.16±9.30	50.81±18.52	< 0.001*
Ferritin [ng/mL]	14.18±4.47	43.12±15.04	< 0.001*
TIBC [ $\mu\text{g}/\text{dL}$ ]	433.1±48.2	310.6±52.9	< 0.001*
TSH [ $\mu\text{IU}/\text{ml}$ ]	2.77±1.30	2.10±1.11	0.006*
Free T <sub>3</sub> [pg/ml]	3.22±0.82	3.61±0.69	0.011*
Free T <sub>4</sub> [ng/dl]	1.29±0.45	1.42±0.25	0.082

\* = significant; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, Red cell distribution width; TIBC, total iron-binding capacity; TSH, thyroid stimulating hormone.

**Table [3]:** Thyroid function status among the study groups

Thyroid status	Case group [n=50]	Control group [n=50]	P value
Euthyroidism	38 [76%]	47 [94%]	0.02*
Hypothyroidism	12 [24%]	3 [6%]	
Hypothyroidism [n=12]			
Overt hypothyroidism	2 [4%]	0 [0%]	0.49
Subclinical hypothyroidism	10 [20%]	3 [6%]	0.071

\* = significant

**Table [4]:** Comparison of demographic, clinical and laboratory data in relation to thyroid status among the case group

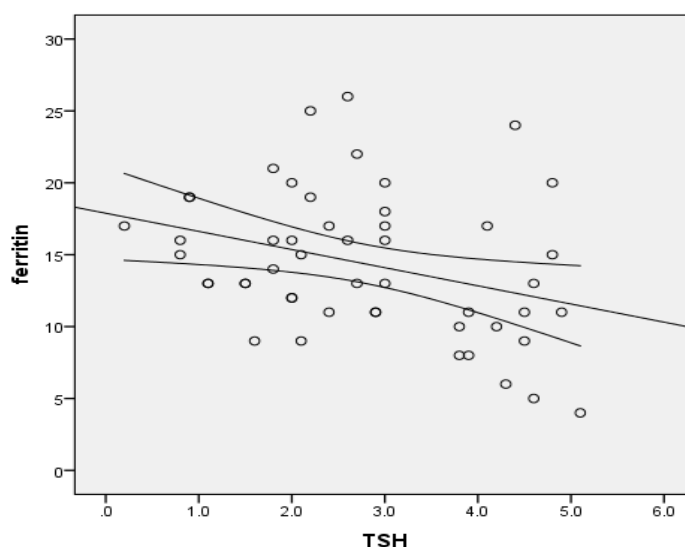
Variables	Euthyroidism [n=38]	Hypothyroidism [n=12]	P value
Age [years] [Mean ± SD]	8.34±1.65	7.94±2.17	0.50
Sex	Male	5 [42%]	0.51
	Female	7 [58%]	
Residence	Rural	9 [75%]	0.33
	Urban	3 [25%]	
Heart rate [beat/min] [Mean ± SD]	95.3 ± 16.7	86.4 ± 22.9	0.14
Weight percentiles [Mean ± SD]	50.4±28.3	59.8±20.1	0.29
Height percentiles [Mean ± SD]	46.9±23.7	43.5±17.4	0.65
Easy fatigability	7 [18%]	7 [58%]	0.022*
Mood impairment	6 [16%]	6 [50%]	0.024*
Constipation	5 [13%]	3 [25%]	0.38
Hemoglobin [g/dL] [Mean ± SD]	9.37 ± 1.52	8.84 ± 1.79	0.32
MCV [fl] [Mean ± SD]	67.05±6.17	64.42±7.01	0.22
MCH [pg/cell] [Mean ± SD]	23.04±2.93	22.95±2.86	0.92
RDW [%] [Mean ± SD]	16.21±2.87	17.02±3.17	0.41
Serum iron [ $\mu\text{g}/\text{dl}$ ] [Mean ± SD]	31.09±12.78	21.45±8.41	0.018*
Ferritin [ng/mL] [Mean ± SD]	15.45±4.16	11.58±5.19	0.011*
TIBC [ $\mu\text{g}/\text{dL}$ ] [Mean ± SD]	425.6±51.3	458.4±62.5	0.07

\* = significant; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, Red cell distribution width; TIBC, total iron-binding capacity.

**Table [5]:** Correlation between thyroid hormones with various demographic and laboratory variables

Variables	TSH		FT <sub>4</sub>		FT <sub>3</sub>	
	r/ρ	P	r/ρ	P	r/ρ	P
Age [years]	- 0.12	0.39	0.089	0.54	0.082	0.57
Heart rate [beat/min]	- 0.22	0.12	0.11	0.47	0.14	0.33
Hemoglobin [g/dl]	- 0.19	18	0.22	0.1	0.23	0.09
MCV [fl]	- 0.15	0.3	0.27	0.06	0.25	0.08
MCH [pg/cell]	- 0.20	0.16	0.13	0.39	0.17	0.23
RDW [%]	0.26	0.067	- 0.057	0.69	- 0.15	0.3
Serum iron [µg/dl]	- 0.33	<b>0.019*</b>	0.23	0.09	0.27	0.06
Ferritin [ng/ml]	- 0.37	<b>0.009*</b>	0.25	0.074	0.29	<b>0.042*</b>
TIBC [µg/dL]	0.26	0.07	- 0.21	0.13	- 0.25	0.077

\*: significant; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, Red cell distribution width; TIBC, total iron-binding capacity; TSH, thyroid stimulating hormone.



**Figure (1):** Correlation between serum ferritin and TSH among the case group

### DISCUSSION

Both iron deficiency anemia and thyroid dysfunction have adverse consequences on cognitive function and may impair the learning abilities and acquisition of new skills, especially during childhood. The co-occurrence of both diseases in children will negatively impact their capabilities. An Egyptian study demonstrated that poor total intelligence quotient [IQ] in children with iron deficiency anemia was significantly correlated with thyroid dysfunction [5].

Health supervision and global screening programs are still major concerns in the developing world. Many children are out of reach proper medical care. There is an increasing need for addressing frequent medical issues, especially those with adverse impacts on the individual and national health, through conducting scientific research and establishing the current medical dilemmas within the community. Iron deficiency anemia and thyroid dysfunction are among the major concerns within the pediatric population and the relationship between them should be explored [19].

The age of studied children ranged from 6-12 years, and the mean age was 8.2 years. This mean shows a trend toward the lower limits of the range, which points to the association between IDA and early childhood [20].

Regarding sex distribution, males were more frequent [54%] than females, which agree with many reports. In the study by Khatiwada *et al.* [13], 55.5 % of studied iron-deficient anemic primary school children were males and 44.5 % were females. Also, El-Masry *et al.* [12] reported that, among 60 children, 34 were males [57%] and 26 [43%] were females. The majority of studied children were rural residents [62%], which come to an agreement with Al Ghwass *et al.* [21] who reported that rural areas were significant risk factors [P = 0.026] for IDA in Egypt.

The main finding of the study was illuminating the association between IDA and thyroid dysfunction. In the case group, there was statistically a significant higher TSH levels and lower FT<sub>3</sub>. Furthermore, the frequency of hypothyroid status [both overt and subclinical] was elevated in the case group with statistical significant difference.

An initial report has shown that iron therapy in children with goiter and IDA has been proved to enhance the effect of iodized oil intake, resulting in a gland reduction [22]. Likewise, Azizi *et al.* [23] found a relation between the frequency of goiter and low serum ferritin level among Iranian school children and stated that the occurrence of goiter was related to ID. In Egypt, Metwalley *et al.* [5] compared thyroid functions between 60 primary school children with IDA and 20 healthy children. In their study,  $TT_3$  and  $TT_4$  were significantly lower while TSH was higher in children with IDA compared to control. A cross-sectional study conducted among 227 children aged 6-12 years in Nepal, reported that 1.3% of children had overt hypothyroidism and 16.3% had subclinical hyperthyroidism. The relative risks of hypothyroidism in IDA and ID were 5.5 and 1.9, respectively. In a larger cohort of Nepali school children, low urinary iodine excretion was common in children with ID and IDA [24]. On the other hand, Tienboon and Unachak [14] reported no difference in thyroid hormone levels in children with IDA anemia before versus after iron therapy. Recently, Thapa *et al.* [15] found that the difference between the median TSH levels in children with IDA and iron sufficient group was not significant.

Iron deficiency can modify the production of thyroid hormones by several mechanisms; ID causes inefficient erythropoiesis, therefore decreasing oxygen transport to body tissues needed for various enzyme reactions [25]. ID also increases in-vitro hepatic reverse  $T_3$  deiodination, suggesting the presence of inactivating metabolic routes for thyroid hormones [26]. Also, ID may lower TPO activity, interfering with the production of thyroid hormones [10]. Given the lack of TSH response due to a decrease in peripheral hormones, a recent study had suggested the implications of further hypothalamic pituitary mechanism [27]. For an explanation of our results, a combination of mechanisms may be relevant, as there is no other mechanism that fully explains the results found in our study.

In the present study, the occurrence of hypothyroidism was related to the severity of iron deficiency. Likewise, Khatiwada *et al.* [13] reported that hemoglobin level was negatively correlated with TSH [ $P < 0.001$ ], but weakly correlated with  $FT_3$  [ $P = 0.249$ ] and  $FT_4$  [ $P = 0.787$ ]. Similar results are obtained by El-Masry *et al.* [12]. In contrast, Akhter *et al.* [28] demonstrated that serum ferritin had non-significant correlation with serum TSH. Also, both serum  $FT_4$  and  $FT_3$  revealed a non-significant positive correlation with serum ferritin.

In this work, children with hypothyroidism demonstrated higher frequency of easy fatigability and mode impairment. Thus, we suggest special caution for the observation for the presence of these symptoms among children with iron deficiency anemia. The need for a simple screening

evaluation is of great importance in developing countries, where many people lack ease of access to continuous medical care.

The main limitation of the present study was the cross-sectional nature of the analyses, so we cannot infer causal mechanisms; however, the results may have clinical implications on the cognitive function of the included children. Also, we could not explore the effect of iron supplementation on the outcome of thyroid function. Furthermore, we did not analyze the total  $T_3$  and Total  $T_4$ , thus the relationship between IDA and thyroid hormone binding could not be clarified.

## CONCLUSION

The present study emphasized the association between IDA and thyroid dysfunction, especially the occurrence of subclinical hypothyroidism, and pointed to the potential influence of anemia severity on the incidence of thyroid dysfunction. These results warrant special attention to those children in order to avoid potential adverse consequences on cognitive and learning abilities.

## Financial and Non-financial Relationships and Activities of Interest

None

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