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# The effect of iron deficiency anemia on plasma thyroid hormone levels in childhood

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*Summary*

**Aim:** There are limited number of studies concerning thyroid functions in iron deficiency anemia which is frequently seen in childhood. The present study was planned to investigate the effects of iron deficiency anemia on thyroid hormone metabolism.

**Material and Method:** The study was approved by the Ethics Committee and conducted in 90 patients with iron deficiency anemia (study group) and 38 healthy children (control group) aged between 1 and 14 years prospectively. Complete blood count, iron, iron binding capacity, ferritin, TSH, TT4, TT3, fT4, fT3 were determined in all the children included in the study. Social Package for

**Results:** Gender and age distribution of the groups were not different, while mean birth and height values of the study group were lower than the control group ($p<0.001$). TT3 and TT4 values were also statistically lower in the study group ($p=0.002$, $p<0.001$, respectively). There was no difference between the groups in terms of fT4 and fT3 levels. There was a positive correlation between TT3 and ferritin and between TT3 and transferrin saturation levels.

**Conclusions:** Although our study suggests that iron deficiency anemia effects the total thyroid hormone levels, biologically active free thyroid hormone fractions are sustained within normal limits. Further studies are required to investigate the mechanism, reversibility and clinical impact of this effect. *(Turk Arch Ped 2011; 46: 122-5)*

**Key words:** Iron deficiency, anemia, thyroid hormone.

## Introduction

Currently, iron deficiency is the most common nutritional deficiency worldwide. According to the estimation of the World Health Organization (WHO), 24.8% of the population in the world have iron deficiency (1). In our country, 32.6% of preschool children have iron deficiency anemia according to 2001 data of WHO (2). In a study performed in 1997 in İstanbul, the frequency of iron deficiency anemia in children and adolescents between 6 months and 19 years of age was found to be 44.3% (3). Since iron is essential for all cells, many systems are affected in iron deficiency in addition to anemia. Psychomotor retardation in addition to growth and development retardation is observed in children with iron deficiency anemia. In some studies performed in animals and in humans, thyroid hormone metabolism has been reported to be disturbed in iron deficiency (4,5). The studies on this subject are mainly animal studies or studies performed in adults. There are limited number of studies related to thyroid function in children with iron deficiency anemia. In this study, it was planned to investigate the effects of iron deficiency anemia which is seen frequently in children on thyroid hormone metabolism.

## Material and Method

The study was conducted in patients who presented to the pediatrics outpatient clinic between 12.01.2008 and 06.01.2009 after obtaining Ethics Committee approval.

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**Subject groups**

In this study, 90 patients between 1 and 14 years of age with a diagnosis of iron deficiency anemia made by physical examination and laboratory findings (study group) and 38 children with no history of disease or drug use (control group) were evaluated prospectively.

Physical examination was performed in all subjects. Age, gender and weight and heigth percentiles were recorded. "Patient follow up form" was completed for each patient.

**Laboratory tests**

Venous blood sample was taken from all patients and complete blood count, serum iron (Fe), total iron binding capacity (TIBC), ferritin, thyroid stimulating hormone (TSH), TT4, TT3, fT4 and fT3 levels were measured.

For evaluation of hematologic variables, approximately 2 mL venous blood was placed in a hemogram tube with K3 EDTA. Complete blood count was automatically done using Beckman Coulter LH 780 device.

Serum Fe and TIBC levels were measured automatically in blood samples placed in dry tubes following fasting of 8-12 hours by calorimetric method using COBAZ Integra 800 device. Serum transferin saturation value was assessed by calculating serum Fe and TIBC levels.

Serum TSH, TT4, TT3, fT4, fT3 and ferritin levels in the patient's serum were measured by immun chemiluminescence method using Immulite 2000 device.

Lower limits of hemoglobin (Hb) and mean erythrocyte volume (MEV) regarded for a diagnosis of anemia are shown in Table 1 (6).

**Table 1: Lower limits of hemoglobin (Hb) and mean erythrocyte volume (MEV) by ages (6)**

| Age | Hb (g/dl) | MEV (fl) |
|---|---|---|
| 6 months–2 years | 10.5 | 70 |
| 2–6 years | 11.0 | 73 |
| 6–12 years | 11.5 | 77 |
| 12–14 years | - | - |
| Female | 12.0 | 78 |
| Male | 13.0 | 78 |

**Table 2: Thyroid hormone levels in the study and control groups**

| | Study group Mean±SD (n=38) | Control group Mean±SD (n=90) | t | p |
|---|---|---|---|---|
| TSH (mU/L) | 3.20±1.80 | 2.62±1.47 | 1.736 | 0.085 |
| TT4 (µg/dL) | 9.05±1.57 | 10.57±2.96 | 3.140 | 0.002 |
| TT3 (nmol/L) | 156.39±29.68 | 188.24±34.40 | 5.287 | <0.001 |
| fT4 (ng/dl) | 1.40±0.18 | 1.43±0.25 | -5.81 | 0.06 |
| fT3 (pg/dl) | 5.18±1.58 | 4.69±1.17 | -1.946 | 0.055 |

Red cell distribution width (RDW), serum Fe, TIBC, transferrin saturation and ferritin levels were assessed in patients who had a hemoglobin and MEV value below the lower limit. For a diagnosis of iron deficiency anemia the following criteria were used: RDW>14, serum Fe<30 µ/dL, TIBC>350 µ/dL, transferrin saturation <16%, ferritin<12 ng/mL (for the patients younger than 5 years old), <16 ng/mL (5-12 years old).

The relation between thyroid hormones and hematologic variables, serum iron, TIBC and ferritin was examined.

**Analysis of data and assessment**

Data obtained were analysed using SPSS (Social Package for Social Sciences) 15.0 program. Pearson's chi-square test was used for comparison of qualitative data and independent t test was used for comparison of paired groups. The results were evaluated in a 95% confidence interval and at a significence level of $p<0.05$.

## Results

Mean age of 128 children included in the study was found to be 3.89±2.23 years. While there was no difference between the study group and the control group in terms of age and gender ($p>0.05$), mean weight and height values of the control group were found to be significantly higher compared to the study group ($p=0.021$). Weight and height values of the subjects included in the study were between the 3rd and 95th percentiles. Patients with obesity or malnutrition were not included in the study.

When complete blood counts were assessed, mean Hb value was found to be 9.63±1.04 g/dL in the study group and 12.45±0.47 g/dL in the control group. As expected, Hb and MEV values were found to be statistically significantly lower in the study group compared to the control group and RDW was found to be significantly higher ($p<0.001$). Mean serum Fe, TIBC and ferritin values were found to be 19.45±7.45 µg/dL, 410.01±57.49 µg/dL and 7.62±3.27 ng/mL, respectively in the study group and 81.46±32.64 µg/dL, 278.26±44.15 µg/dL and 36.04±21.25 ng/mL, respectively in the control group. A statistically significant difference was found between these values ($p<0.001$).

Mean serum TSH, TT4, TT3, fT4 and fT3 levels in all subjects are shown in Table 2. All subjects who were included in the study were euthyroid.

A statistically significant difference was found in TT4 and TT3 values between the study and control groups. Mean TT4 and TT3 values were found to be significantly lower in the study group ($P=0.002$ and $p<0.001$, respectively). There was no significant difference in fT3 and fT4 values between the two groups ($p=0.055$ and $p=0.060$, respectively). When the relation between thyroid hormone levels and hematologic variables, serum Fe, TIBC, transferin saturation and ferritin was examined, a moderate positive relation was found between TT3 and ferritin and TT3 and transferrin saturation.

## Discussion

Iron is an essential element for many living organisms and has a vital importance. Since it is necessary for structure and function of many enzymes and is used widely in the human body, all systems are affected in its deficiency and many systemic symptoms and clinical findings occur. If iron deficiency anemia is not treated in the childhood, it results in physical, intellectual and cognitive retardation. Iron deficiency was reported to decrease intellectual and motor development test scores in children even if anemia was not present (7,8).

The relation between thyroid function and intellectual function is also well known. In rats with iron deficiency, T3 and T4 values were found to be normal in some studies (9,19) and low in other studies (11). The effects of iron deficiency anemia on thyroid metabolism have been attempted to be explained by anemia and low oxygen delivery, changes in thyroid metabolism by central nervous system control and nuclear T3 binding (12-14).

There are limited number of studies investigating the relation of iron deficiency anemia and thyroid hormones in humans. Martinez et al. (15) reported that humans with iron deficiency did not show normal thermoregulation process during bathing in cold water. Beard et al.(9) found that plasma T4 and T3 levels in both basal conditions and after cold stress were lower in women with iron deficiency anemia compared to the controls. They explained the fact that thermoregulation in cold stress conditions could not be provided in patients with iron deficiency anemia by poor thyroid hormone response (9). Another reason for low thyroid hormones in iron deficiency anemia may be related to the important role of iron in the synthesis of thyroid hormones. The first steps in the synthesis of thyroid hormones are catalysed by thyroid peroxidase containing heme. Heme protein bound to ferriprotoporphyrin IX is necessary for thyroid peroxidase function. In contrast to this assumption, Tienboon and Unachak (16), found no difference in TT4, TT3, fT4, fT3, TBG TSH levels in children with iron deficiency anemia before and after iron treatment.

In Iran, many studies were conducted, because the expected decrease in the frequency of goitre could not be observed, although iodide deficiencey was corrected. Azizi et al.(17) found a relation between the frequency of goitre and serum ferritin level in 2002 and reported that the frequency of goitre in school children in Iran was related to iron deficiency.

In our country, the first study on the effects of iron deficiency anemia on thyroid hormones was performed in 1992 by Gündüz et al.(18) and T4 and T3 levels in the group with iron deficicency anemia were found to be higher compared to the control group. In 2004, Gökdeniz et al.(19) reported that subclinical and secondary hypothyroidsm might occur in iron deficiency anemia with high rates.

In our study, TT4 and TT3 levels in the study group were found to be significantly lower compared to the control group, although TSH, TT4, TT3, fT4 and fT3 levels in patients with a diagnosis of iron deficiency anemia were within normal limits by age. However, there was no significant difference between the study group and control group in terms of fT4 and fT3 levels. The fact that total hormone levels were decreased, while levels of free hormones which are biologically active were within normal limits may be an adjustment developing against iron deficiency anemia. When the relation between hematologic variables and thyroid hormones was examined, a positive correlation was found between TT3 and ferritin and TT3 and transferrin saturation. This result was intrepreted as follows: In the presence of iron in the body, thyroid hormone synthesis would not be affected and so TT3 level did not decrease. It is known that plasma thyroid hormone levels decrease, peripheral conversion of T4 to T3 decreases, activity of hepatic thyroxine 5'-deiodinase decreases and thyrothropine response to thyroid stimulating hormone (TSH) decreases in iron deficiency (11,13,20). Thus, in severe iron deficiency anemia, thyroid hormone synthesis is affected and the activity of thyroperoxidase which contains iron decreases (21). Since the difference of height and weight between the study group and the control group may affect the results, limitations may occur in the interpretation of the results and this should be kept in mind.

Since iron deficiency affects growth, psychomotor development and intellectual function, taking diagnostic, therapeutic and preventive precautions for children in Turkey where this deficiency is still being observed frequently is a rather important subject. However, more comprehensive studies are needed to elucidate the mechanisms by which iron deficiency anemia affects thyroid hormone metabolism, if this effect is reversible or not and the systemic contribution of these mechanisms to iron deficiency.

**Conflict of interest: None declared.**

## References

1. Worldwide prevalence of anaemia 1993-2005. WHO Global Database on Anaemia. Geneva, World Health Organization, 2008. (available at http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf).
2. Iron deficiency anemia: assessment, prevention and control. A guide for programme managers. Geneva, World Health Organization, 2001 (WHO/NHD/01.3). (available at http:/www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/WHO_NHD_01.3/en/index.html).
3. Çetin E. İstanbul'da yaşayan çocuk ve adolesanlarda anemi prevalansının araştırılması. Cerrahpaşa Tıp Fakültesi Pediatri Uzmanlık Tezi, 1997.
4. Yazar A, Pata C, Altıntaş E, Kıykım AA, Gen R, Polat G. Demir eksikliği anemisi ve demir tedavisinin plazma tiroid hormon düzeylerine etkisi. İstanbul Tıp Fakültesi Mecmuası, 2002; 65: 125-8.
5. Beard J, Tobin B, Gren W. Evidence for the thyroid hormone deficiency in iron deficient anemic rats. J Nutr 1989; 119: 772-8.

6. Aydınok Y. Eritrosit ve hemoglobin hastalıkları. İçinde: Türk Pediatrik Hematoloji Derneği. Eritrosit hastalıkları tanı ve tedavi el kitabı. 2007: 4-8.
7. Berrak SG, Türkan E, Canbolat C, Kahveci S. Çocuklardaki demir eksikliği tedavisinin düşük gelişim test skorlarına etkisi. İstanbul Tıp Fakültesi Mecmuası 2002; 65: 188-96.
8. Ağaağlu L, Torun O, Sefil Y, Demir D, Ünüvar E. Demir eksikliği anemisi ve zeka üzerine etkisi. Çocuk Dergisi 2004; 4: 241-7.
9. Beard J, Borel MJ, Derr J. Impaired thermoregulation and thyroid function in iron deficiency anemia. Am J Clin Nutr 1990; 52: 813-9.
10. Dillman E, Gale C, Gren W, Johnson DG, Mackler B, Finch C. Hypothermia in iron deficiency due to altered triiodothyronine metabolism. Am J Physiol 1980; 239: 377-81.
11. Tang F, Wong TM, Loh TT. Effects of cold exposure or TRH on the serum TSH levels in the iron deficient rat. Horm Metab Res 1988; 20: 616-9.
12. Galton VA. Some effects of altitude on thyroid function. Endocrinology 1972; 91: 1393-403.
13. Beard JL, Brigham DE, Kelley SK, Gren MH. Plasma thyroid hormone kinetics are altered in iron-deficient rats. J Nutr 1998; 128: 1401-8.
14. Smith SM, Finley J, Johnson LK, Lukaski HC. Indices of in vivo and in vitro thyroid hormone metabolism in iron-deficient rats. Nutr Res 1994; 14: 729-39.
15. Martinez-Torres C, Cubeddu L, Dillmann, et al. Effect of exposure to low temperature on normal and iron deficient subjects. Am J Physiol 1984; 246: 380-3.
16. Tienboon P, Unachak K. Iron deficiency anemia in childhood and thyroid function. Asia Pac J Clin Nutr 2003; 12: 198-202.
17. Azizi F, Mirmiran P, Sheikholeslam R, Hedayati M, Rastmanesh R. The relation between serum ferritin and goitre, urinary iodine and thyroid hormone. Int J Vitam Nutr Res 2002; 72: 296-9.
18. Gündüz Z, Kumandaş S, Kurtoğlu S, Üzüm K. Demir eksikliği anemisinin tiroid hormonları üzerine olan etkileri. Türk Tıp Araştırma 1992; 10: 205-9.
19. Gökdeniz E, Dilek İ, Demir C. Demir tedavisinin tiroid fonksiyonları üzerine etkisi. Turk J Haematol 2004;21 (Suppl 3):80.
20. Hess SY, Zimmermann MB, Arnold M, Langhans W, Hurrell RF. Iron deficiency anemia reduces thyroid peroxidase activity in rats. J Nutr 2002; 132: 1951-5.
21. Hurrell RF. Bioavailability of iodine. Eur J Clin Nutr 1997; 51: 9-12.