

Funding: None; Competing interest: None

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REFERENCES

1. Palazzi DL. Fever without source and fever of unknown origin. In Cherry JD, Harrison GJ, Kaplan AL, Steinbach WJ, Hotez PJ, editors. Textbook of Pediatric Infectious Diseases, 7th ed. Philadelphia: Elsevier Saunders;

2014.p.837-8.

2. Kejarawal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S. Pyrexia of unknown origin: a prospective study of 100 cases. J Postgrad Med. 2001;47:104.-7.
3. Bandyopadhyay D, Bandyopadhyay R, Paul R, Roy D. Etiological study of fever of unknown origin in patients admitted to medicine ward of a teaching hospital of eastern India. J Glob Infect Dis. 2011;3:329-33.
4. Joshi N, Rajeshwari K, Dubey AP, Singh T, Kaur R. Clinical spectrum of fever of unknown origin among Indian children. Ann Trop Paediatr. 2008;28:261-6.

Hypoferraemic State in Overweight and Obese Children

Children with high body mass index (BMI) are at risk of iron deficiency. In present study, 71 children with overweight or obesity were screened for iron deficiency. Mean BMI, ferritin and plasma soluble transferrin receptor (sTrfR) levels were 26.1 kg/m², 41.9 µg/L and 0.375 mg/L, respectively. Twenty (28%) children had anemia, and 44 (62%) had an underlying hypoferraemic state.

Keywords: Anemia, Body Mass Index, Iron deficiency.

Obesity is a low grade chronic inflammatory state with subclinical elevated levels of cytokines like IL-1b and TNF-α, which can affect iron sequestration and lead to a state of functional iron deficiency [1]. In addition children who are overweight or obese are at high risk of development of true iron deficiency primarily due to deficient iron intake and food fads and also due to deficient stores because of increased iron requirement owing to their larger blood volume [2]. The present study was undertaken to screen overweight and obese children in our institute for true hypoferraemic state based on serum ferritin and soluble transferrin receptor levels.

This cross-sectional study was conducted on 71 children aged 2-14 years between July 2015 to June 2016. Body mass index (BMI) was determined by calculating body weight/height² (kg/m²), and BMI Z scores (BMIZ) were estimated using WHO reference charts. Enrolled cases were divided into overweight (BMIZ +1 to +2), obese (BMIZ +2 to +3) and morbid obesity (BMIZ +3 Z). Anemia in 2-14 year age group and the ferritin cut-off to

define hypoferraemic state were based on WHO criteria [3]. Plasma soluble transferrin receptor assay (sTrfR) was performed using sandwich ELISA method (Sincere Biotech). We had established a normal range for pediatric sTrfR assay in our healthy cohort as 0.17-2.1 mg/L [4]. Iron deficiency (ID) was defined as combination of either normal hemoglobin (Hb) for age and ferritin <30 µg/dL or normal for age and sTrfR levels >2.1 mg/L, while iron deficiency anemia (IDA) was defined as low Hb for age and ferritin <30 µg/dL or low Hb for age and sTrfR levels >2.1 mg/L. This study was approved by the ethics committee of the institute.

The demographic and hematological parameter are detailed in **Table I**. Serum ferritin was low in 44 (62%), normal in 25 (35%), and high in only 2 (3%) children. Among these, 69 (97.2%) had normal transferrin receptor level and only one child each had high or low levels. Anemia was noted in 20 (28%) cases; however, a hypoferraemic state could be identified in 44 (62%) cases. Out of 20 cases with anemia, 7 (35%) had anemia of chronic disease while 13 (65%) had iron deficiency anemia. In 44 cases with hypoferraemic state, 31 (70%) had evidence of iron deficiency alone and 13 (30%) had iron deficiency anemia. Anemia and hypoferraemic state was noted to be present in all three groups without any statistical difference (**Table I**). The mean sTrfR level among three groups had a rising trend but the difference was not statistically significant.

As studies from our subcontinent have been limited on normal reference ranges for sTrfR levels in pediatric age groups as well as its utility in diagnosing iron deficiency in inflammatory states, a higher ferritin cut-off (<30ug/L), as suggested by WHO [3], was used in this study to define hypoferraemic state. Gartner, *et al.* [5], have recently highlighted the importance of using a correction factor for

TABLE I DEMOGRAPHIC AND HEMATOLOGICAL PROFILE IN CHILDREN WITH HIGH BODY MASS INDEX

Parameters	Overweight (n=6)	Obese (n=35)	Morbid Obesity (n=30)	P value	Total
Age (y)	10.5 (1.5)	10.2 (2.5)	7.9 (2.6)	0.00	9.3 (2.7)
Male/Female	3/3	26/9	19/11	0.409	48/23
BMI (kg/m ²)	21.1 (2.3)	24.8 (2.5)	28.74 (5.2)	0.00	26.1 (4.5)
Hb (g/dL)	11.5 (1.6)	12.2 (0.8)	11.80 (1.3)	0.143	12.0 (1.1)
MCV (fL)	77.7 (12.1)	80.0 (5.2)	76.17 (7.7)	0.89	78.2 (7.1)
Ferritin (µg/L)	16.5 (18.6)	54.0 (124.0)	32.9 (48.4)	0.106	41.9 (93.1)
sTrfR (mg/L)	0.23 (0.26)	0.36 (0.35)	0.42 (0.76)	0.791	0.38 (0.50)

BMI: Body mass index, sTrfR: Soluble transferrin receptor; Value in mean (SD).

serum ferritin before interpreting the test as a marker for iron deficiency in obese individuals.

In this study, we noted a high prevalence (60.5%) of hypoferraemic state in children with high BMI. Studies from West show much lower prevalence of iron deficiency state in obese children ranging from 2% to 15.6% [6,7]. This is contrast to studies from Asian sub-continent, where combined prevalence of ID and IDA is noted to be around 36-42% [8,9].

Lecube, *et al.* [10] have highlighted the importance of sTrfR levels as a better marker for iron deficiency in obesity due to underlying confounding effect of low grade inflammation on serum ferritin levels. However, in our study we did not find sTrfR levels helpful in identifying true hypoferraemic state; sTrfR levels were within normal limits in 97% cases despite serum ferritin being low. This could be due to sTrfR levels being affected by variable rate of erythropoietic activity which could reflect influence of age and hormonal levels in children being higher as compared to adolescents and adults. Our study also found a prevalence of anemia to the tune of 28% in children with high BMI. The anemia was predominantly IDA (65%), while in 35% cases it was anemia of chronic disease. These findings suggest that component of nutritional or dietary micronutrient deficiency is possibly playing a greater role than inflammation-related iron sequestration in obese children in our population. Another reason could be the effect of low grade inflammation leading to relatively high hepcidin levels, which block iron absorption from gut, negatively affecting the already higher adipose tissue demands for iron.

Acknowledgements: Ms Deepashika, Technician, Pediatric Hematology Laboratory for estimation of sTrfR.

Funding: Department of Science and Technology, Chandigarh.

Competing Interest: None stated.

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REFERENCES

- Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. *Am J Clin Nutr.* 2006;83:461S-5S.
- Rogers JT. Ferritin translation by interleukin-1 and interleukin-6: The role of sequences upstream of the start codons of the heavy and light subunit genes. *Blood.* 1996;87:2525-37.
- World Health Organization, Iron Deficiency Anaemia: Assessment, Prevention and Control. A Guide for Programme Managers. Geneva:WHO/NHD/01.3;2001.
- Bhatia P, Siyaram D, Deepshikha, Marathe R, Dayal D. Lower plasma soluble transferrin receptor range in healthy Indian pediatric cohort as compared to Western and Asian data. *Indian J Hematol Blood Transfus.* 2017;33:405-7.
- Gartner A, Berger J, Bour A, Ati JE, Traissac P, Landais E, *et al.* Assessment of iron deficiency in the context of the obesity epidemic: importance of correcting serum ferritin concentrations for inflammation. *Am J Clin Nutr.* 2013;98:821-6.
- Bouglé D, Brouard J. Iron in child obesity. Relationships with inflammation and metabolic risk factors. *Nutrients.* 2013;5:2222-30.
- Hercberg S, Preziosi P, Galan P. Iron deficiency in Europe. *Public Health Nutr.* 2001;4:537-45.
- Akramipour R, Rezaei M, Rahimi Z. Prevalence of iron deficiency anemia among adolescent schoolgirls from Kermanshah, Western Iran. *Hematology.* 2008;13:352-5.
- Ghadimi R, Esmaili H, Kheirkhah D, Tamaddoni A. Is childhood obesity associated with iron deficiency anemia? *Caspian J Pediatr.* 2015;1:59-66.
- Lecube A, Carrera A, Losada E, Hernandez C, Simo R, Mesa J. Iron deficiency in obese postmenopausal women. *Obesity.* 2006;14:1724-30.