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Is Body Mass Index a potential biomarker for anemia in obese adolescents?

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HIGHLIGHTS

1 Establishes role of hepcidin in obesity and its relation with anemia.
2 Endorses Body Mass Index as a biomarker for anemia in obese adolescents.

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ABSTRACT

The two paradoxical major health problems namely obesity and anemia are confirmed to affect millions around the world. Hepcidin, a protein synthesized in liver is a negative iron binding regulator. There is an affirmative relation between hepcidin and leptin levels and an inverse co-relation between hepcidin and iron status due to inflammation mediated by obesity in adolescents. So this implicates an alliance between anemia and obesity wherein weight reduction can be a powerful medium to improve iron absorption in obese adolescents. Also the Body Mass Index can serve as a preliminary non-invasive screening tool to identify potential adolescents prone to anemia.

Excessive calorie intake coupled with lack of physical activity, increases susceptibility of weight gain. In general, adolescents prefer to consume food rich in carbohydrate and fats (e.g. Low-cost junk food like pizza, burger, fried foods etc.) and indulge in sedentary pursuits such as watching television, internet navigation etc. Besides, the pubertal growth spurt affects the amount of fat accumulation and its distribution in them. Overweight (Body Mass Index $\geq 25\,kg/m^2$ to $< 30\,kg/m^2$) and obese (Body Mass Index $> 30\,kg/m^2$) adolescents face at least a two fold greater risk of becoming obese adults. Thus, posing significant risks to long term health effects such as type II diabetes, polycystic ovary syndrome, cardio vascular disorder, hypertension and coronary artery diseases [1,2]. Therefore, nutrition in formative years has a compelling impact on lifelong health.

Adolescents choose to be independent and make their own food choices influenced by peers. Meal patterns change and aspects such as what, when and how much to eat are severely compromised leading to deterioration in dietary quality. It is hard to conceive of a nutritional deficiency occurring in subjects with excessive dietary and caloric intake [2]. Nutritionist however understand that an increase in food consumption does not necessarily lead to better dietary quality and a low cost high calorie diet often leads to hidden hunger especially iron deficiency [3,20]. Moreover, consumption of such calorie rich food increases obesity that stimulates leptin, which in turn affects hepcidin levels in a manner that further downregulates iron absorption resulting to iron deficiency in obese adolescents.

Obesity is a ruling biomedical epidemic, with a predicted 170 million children (aged < 18 years) globally categorized as overweight or obese [4]. Parallely, anemia continues to be most rampant single micronutrient deficiency disease in the world. Malnutrition has two extreme poles namely obesity and anemia, caused due to overnutrition and undernutrition respectively. However, hepcidin connects the contrasting poles of obesity and anemia. Hepcidin is a 25- amino acid antimicrobial peptide majorly expressed in human liver and synthesized in small quantity in the subcutaneous and visceral adipose tissues [5,6]. It is reported to inhibit iron absorption in enterocytes, its release from macrophages, and transport across the placenta [7]. Further, an animal experiment has verified that rats with inactivated hepcidin genes developed iron overload, while the transgenic mice over expressing hepcidin revealed noticeable depletion in iron stores and eventually reported severe anemic conditions [8].

Multiple studies have identified that obese adolescents have lowered serum iron concentrations and poor iron absorption compared to

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non-obese adolescents [2,9–11]. Further, research has established that obese adolescents exhibit increased susceptibility towards hypoferremia. This pathogenic condition has been documented as prime manifestation of obesity in the experimental subjects [9,12,13]; and indicated that obese adolescents were twice as likely to be anemic than their normal counterparts (Body Mass Index ≥18.5 to < 25 kg/m^2) [14] even though they had normal dietary iron intakes and bioavailability comparable with normal weight children [15]. It can be inferred that prevalence of iron deficiency led anemia increases with subject's Body Mass Index [2]. The impact of even moderate anemia (hemoglobin 7 to < 10 g/dl) on physical, psychological and work performance of young adults is detrimental and obesity coupled with anemia may significantly retard the agility of the adolescents both physically and mentally.

The plausible mechanism describes obesity as a low grade inflammation state, stimulating the production of many cytokines and adipokines such as leptin. Leptin can upregulate hepcidin synthesis by adipocytes [16,17] and considerable accumulation of subcutaneous and adipose tissue in obesity is responsible for diminished iron status in obese adolescents [6]. Inflammatory markers such as Interleukin 6, C-reactive protein as well as hepcidin and leptin have been found to be significantly elevated in obese children and adolescents. Also, reports elucidate the mechanism that hepcidin is an acute phase response peptide and is a negative regulator of iron absorption and its cellular release because once it binds to ferroportin, the iron transporter is internalized and eventually degraded [16,18]. Likewise, hepatic hepcidin expression is negatively correlated with the rate of duodenal expression of transporters [21] and iron absorption in experimental animals [4]. Hence, hepcidin mediates the anemia through obesity induced inflammation. It is noteworthy that hepcidin levels on the body are linked with obesity alone and not any liver ailments; this information rules out the possibility of any other factor influencing relation obesity and anemia other than hepcidin [5].

Body iron content and hematopoiesis are physiologic regulators, whereas inflammation is a pathologic regulator of hepcidin in our body. Additionally, hepcidin expression had also been reported to increase at both mRNA and protein levels. Hepcidin mRNA has been reported to be higher in the adipose tissue of all obese patients. It has been previously reported that the interrelationship between prohepcidin (hepcidin prohormone), iron metabolism and obesity was further affiliated to disrupted glucose metabolism [8] leading to multiple metabolic disorientation.

The positive correlation between leptin and hepcidin levels is concomitant with obesity. Also, there is an inverse correlation between serum hepcidin and serum iron status in obese adolescents. The mutual connection between the hepcidin concentration and Body Mass Index strengthens and substantiates the correlation between diminished intestinal absorption of iron (causative reason for anemia) with the Body Mass Index. Therefore, we foresee the elevated Body Mass Index (above 25 kg/m^2) as a putative biomarker of anemia and can be identified as an immediate warning sign. Screening for iron status among adolescents with elevated Body Mass Index should be recommended. Further, weight reduction can be a useful step to reduce inflammation and subsequently improve iron absorption in obese adolescents [19]. Lifestyle management through regular exercise, reducing excessive intake of simple sugars and fats, inclusion of whole cereals, pulses, vegetables, seasonal fruits, dry fruits and dietary fibre in diet and small five/six meal pattern will lead to beneficial restoration of both healthy body weight [22] as well as improved iron levels.

Conflicts of interest

There is no conflict of interest by authors.

CRediT authorship contribution statement

Shubhra Pande: Conceptualization, Writing – original draft. **Rajeev Ranjan:** Writing – review & editing. **Valentina A. Kratasyuk:** Supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jnim.2018.11.001.

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