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Effect of Iron Deficiency Anemia on Insulin Like- Growth Factor-1 Level Among Children: A Cross-Sectional Study

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ABSTRACT

Objective: To assess the effect of iron deficiency anemia on the serum level of IGF-1 by comparison between low ferritin and low hemoglobin group and healthy control.

Study Design: Comparative case control study.

Place and Duration: Study The study was conducted at department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, from Jul to Dec 2022.

Methodology: The case control study was done in 110 children, aged between 2-14 years. Children with short stature and iron deficiency anemia (cases) were compared to a group of age and gender matched healthy children (controls). The sample size of 110 children was calculated using WHO sample size calculator. After brief history and examination, 3ml venous blood was drawn by standard technique. Complete blood picture estimation and the estimation of IGF-1 and ferritin levels was done. Parameters of complete blood picture included were Hemoglobin in (Hb), Red blood cells (RBC), Packed cell volume (PCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular volume (MCV). Data was analyzed using SPSS.

Results: Comparison of the serum levels of IGF-1, analyzed by chemiluminescent immunoassay between two groups showed lower IGF-1 levels among iron deficiency anemia group (8.60 µmol/L) as compared to control group (38.80 µmol/L) which is statistically significant (*p*-value<0.001). Results showed a positive correlation of Hemoglobin and serum ferritin with Serum IGF-1 levels with a r value of 0.78 and 0.81 (*p*-value 0.001) respectively.

Conclusion: There is a strong correlation between Iron Deficiency anemia and IGF-1 levels. Children with Iron deficiency anemia have lower levels of IGF-1 which may be the cause of short stature among these children. Hence implicating that iron deficiency need to be corrected for getting adequate effect of growth hormone on growth and development which is implemented through IGF-1.

Keywords: Hemoglobin, Iron Deficiency Anemia (IDA), Insulin like Growth Factor-1 (IGF-1), Serum Ferritin.

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INTRODUCTION

Insulin like growth factor 1 (IGF-1) is a protein produced mainly from liver, skeletal muscles and some other tissues under the influence of Growth hormone (GH).[1] Produced from anterior pituitary, GH is most important for the physiological process of linear growth that occurs throughout the fetal period, infancy, childhood, and puberty in human. IGF-1 is the major mediator of GH induced growth and development of bones and tissues.[2] This process is most important in children where cases of low GH production or decreased effect on GH receptor may cause decrease in the serum levels of IGF- and as a result the linear growth is affected. The decreased linear growth may result in short stature, which is height lass then 3rd centile as compared to age and gender matched children.[3] However, growth retardation and short stature has been observed in other childhood diseases as well. Among these Iron deficiency anemia (IDA) is specifically important because of high prevalence of the disease among children globally.[4] Multiple studies have determined the effects of IDA on growth and development of children. IDA in children is more common in developing countries like Pakistan and approximately 40 to 70% of children under five have cognitive impairment, low physical activity, and growth retardation linked to IDA.[5] The biochemical marker that is of interest which links IDA to growth effects is IGF-1. A possible mechanism for how anemia affects growth is a deficiency in GH-IGF-I secretion. Hepatocytes are placed in a hypoxic condition by IDA, which reduces protein synthesis including decreased IGF-1 production. The action of insulin-like growth factor-I (IGF-I) is decreased in low oxygen

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environments Hypoxia also prevents IGF-I-induced cell growth.[6,7] Nutritional deficiencies in children can affect serum levels of IGF-1 by modulating interaction of IGF-1 with its tyrosine kinase receptor (IGF-1R) in tissues and IGF-binding proteins (IGFBPs) in the bloodstream.[8] Evaluation of IGF-1 level in serum instead of basal growth hormone levels is the recommended first line test for the workup of short stature due to suspected GH deficiency because GH release is pulsatile and plasma half life is short whereas IGF-1 levels remain constant.[9] In Pakistan there is limited data on short stature among children resulting from iron deficiency anemia orthe effects iron deficiency on biochemical parameters of growth such as IGF-1. In our population where IDA is so prevalent it is necessary to evaluate its effects on IGF-1 so that it is not mistaken for GH abnormality.[10]

The current study was planned to assess the association between iron deficiency anemia and biochemical markers of growth like IGF-1 by comparing the IGF-1 levels of children with iron deficiency anemia to those children who are healthy. The study will help evaluate the effects of IDA on serum IGF-1 levels and provide insight to pathogenesis of short stature among children with no GH abnormality.

METHODOLOGY

A case control study, conducted at Chemical pathology and endocrinology department of Armed Forces Institute of Pathology, Rawalpindi from July 2022 to December 2022 after ethical approval from Institutional review board (IRB # BS AHS/CHP-3/IRB/22/1345, dated 19 June 2022). Sample size of 54 was calculated using WHO sample size calculator, taking a prevalence of short stature from previous studies 16.5%,[11] confidence interval of 95% and 10% margin of error. A total of 110 children, 55 cases and 55 age and gender matched healthy controls, were enrolled using non probability convenient sampling technique.

Inclusion Criteria: Patients of either gender with age ranging from 2 to 14 years, presenting to endocrine clinic AFIP with short stature(Child whose height is 2 standard deviations or more below the mean height for that age and gender which corresponds to height less than 3rd percentile for age and gender 3 as plotted on CDC growth charts for age 2 years and above 12, anemia (Hb less than 11 g/dl as per WHO guidelines on Hb concentration for diagnosis of anemia and assessment of severity6and iron deficiency having low ferritin (<30ug/ml) 13 were included in the study.

Exclusion Criteria: Patients with history of Celiac disease, liver disease & thyroid hormone disorder and having acute infection were excluded from the study.

Consent was taken from parents of participants enrolled in the study. After brief history and examination, 3ml venous blood was drawn by standard technique in K-EDTA tube for complete blood picture estimation and serum tube for the estimation of IGF-1 and ferritin levels. Parameters of complete blood picture included were Hemoglobin in (Hb), Red blood cells (RBC), Packed cell volume (PCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular volume (MCV).Complete blood picture was performed on fully automated analyzer Sysmex XP. Serum IGF-I level and ferritin analysis was performed on chemiluminescence immunoassay analyzer by Siemen health care.

The collected data was analyzed using Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistics of qualitative data were expressed with frequency and percentages. The normality of the data was accessed by Shapiro-Wilk test, the data showed non-parametric distribution. Quantitative variables were compared between patients and controls using the Mann- Whitney U Test while the relationship between the degree of anemia and IGF-I in the patients and control groups was evaluated using Spearman's correlation test. A *p*-value of less than 0.05 was considered statistical significant.

RESULTS

Samples from 110 children were analyzed in the study. The included study population was divided into two groups ''Iron deficiency Anemic or Cases'' and ''Non-Anemic or Controls''. Each group had 55 children. The mean age of children in the iron deficiency anemia group was 9.4±3.8 years whereas in the control group mean age was 8.07±4.76 years. Males were 62(56.4%) and females were 48(43.6%) in both cases and control group.

Table-I shows comparison of red cell indices of blood complete picture and serum ferritin of the two groups.

Serum insulin like growth factor (IGF-1) was analyzed and comparison of results of IGF-1levels among iron deficient children and healthy controls is shown in Table-II.

Figure-1 shows a scatterplot of Hemoglobin and Ferritin levels with serum IGF-1. increase in serum levels of IGF-1 is observed with increase in hemoglobin and ferritin level. A positive correlation was observed between Hb and IGF-1 (r value 0.78, *p*-value<0.01). A positive correlation was observed between ferritin and IGF-1 (r value 0.81, *p*-value<0.01).

Table-I: Comparison of Red Cell Indices and Ferritin Between IDA and Healthy (n=110)

Parameters	IDA group (n= 55) Median (IQR)	Healthy group (n= 55) Median (IQR)	*p*-value
Hb (g/dL)	10.200(2.0)	12.700(0.6)	<0.001
RBC (fL)	4.37(0.53)	4.54(1.14)	0.002
PCV (pg)	0.32(0.04)	0.38(0.02)	<0.001
MCH (g/dL)	.22.7(3.4)	.28.0(2.4)	<0.001
MCV	69.0(7.7)	82.60(6.9)	<0.001
Ferritin (µg/L)	7.0(4.8)	31.0(12.0)	<0.001

Table-II: Comparison of Serum IGF-1 level Among IDA and Healthy Individuals (n=110)

IGF-1	Median. (IQR) (µmol/L)	*p*-value
Cases (n= 55)	8.60 (3.75)	<0.01
Controls (n= 55)	38.80(15.60)	

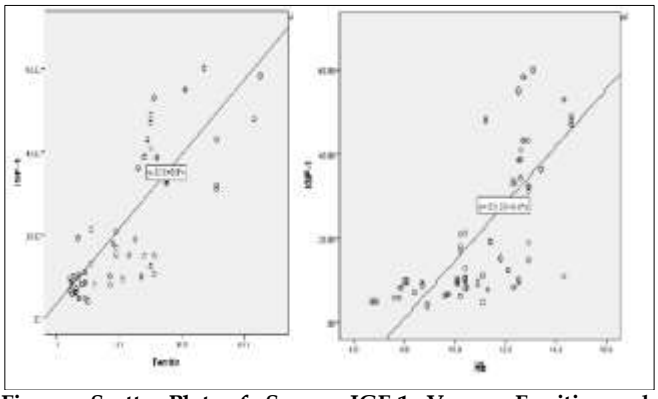

Figure: Scatter-Plot of Serum IGF-1 Versus Ferritin and Hemoglobin

DISCUSSION

The study was aimed to explore the effect of iron deficiency anemia on Serum IGF-1 levels. IGF-1 a protein produced under influence of GH is the mediator of GH dependent linear growth. Results of current study showed that in children age 2-14 yrs with Iron deficiency anemia the IGF-1 are significantly lower as compared to healthy age and gender matched children. There exists a significant positive correlation between Hb and IGF-1 (r value 0.78) and between Ferritin and IGF-1 (r value 0.81) thus, lesser the Hb levels, the less the IGF-1 levels and the effects of ferritin is similar. The current results show that IGF-1 may be the biochemical link which leads to short stature among children with iron deficiency. The relationship between IGF-1 and anemia has been explored in both in adults and pediatric population for different etiologies.[14] Zhao, Q. *et al*. studied relationship between hemoglobin and insulin-like growth factor-1 in children and adolescents with idiopathic short stature and their results showed a significant positive association between Hb and IGF-1, however the participants in the study were all healthy children with short stature and the results were not linked to specific etiology.[15]

Vihervouri studied relationship between serum concentration of IGF and Hb using Pearson's correlation analysis on 32 children and found a positive correlation.[16,17] Specifically, anemia due to iron deficiency among children is a major public health concern developing countries which may cause growth and developmental delay among growing children. A study on causes of short stature among Pakistani children reported iron deficiency anemia to be a cause of short stature in only 9% of children with short stature, with leading causes being endocrine abnormality.[17] However, authors used IGF-1 as a marker for adequacy of GH and performed GH stimulation tests in limited number of cases. Low IGF-1 according to our findings can also result from iron deficiency anemia. Our study findings show that serum IGF-1 levels are lower in iron deficiency anemic children as compared to healthy controls and the findings are consistent with international studies. Soliman, A. studied growth parameters, hematological markers and IGF-1 levels in children aged 17.2±12.4 months of iron deficiency anemia before and after treatment. The results of the study demonstrated low levels of IGF-1 and retarded growth in the children which improved significantly up on iron replacement. However, serum ferritin the specific marker for iron deficiency was not studied.[18] Isguven *et al*. studied hormones involved in growth and metabolism in 25 pre-pubertal children with IDA and 25 healthy controls. Serum IGF-1, ghrelin, and insulin levels were found to be significantly lower in the IDA group.[19] In another study Noori, D.K.R., Rabaty, A.A explored the effect of Iron Deficiency Anemia on IGF-1 Level Among 50 children aged 2 to 14, with 25 being healthy individuals as a control group and 25 being diagnosed cases of IDA with low serum ferritin levels. According to the findings, IGF-1 levels decreased in 36% of cases where as no individual among the control group had low IGF-1. The ferritin and IGF-1 levels showed a

positive correlation with a r value of 0.640. Seven Decreased IGF-1 levels in anemia have important clinical implications. Firstly, anemia needs to be ruled out as a possible cause of short stature. Correction of anemia may lead to improvement in growth of children without testing for growth hormone deficiency. Fareeq ZH *et al.* studied how iron deficiency anemia influences growth and found that children with IDA were significantly shorter in comparison to age- and sex-matched controls. After receiving therapy, serum ferritin was significantly correlated with growth velocity and BMI.Biochemical marker IGF-1 may be the mediator of improved growth velocity and BMI as studies have reported increase in IGF-1 after treatment of anemia.[16] Thus, in cases of growth retardation due to IDA among children, IGF-,1 the protein that mediated effects of GH, is reduced. Serum IGF-1 can be used to assess catch up growth in response to iron treatment in these patients.

These studies were conducted in a different environment and with a different population. There has been no national research on anemia and IGF-1 levels in Pakistan. Current studied the biochemical marker of growth IGF-1 in children with IDA. However, current study is single center based with limited sample size. Further studies with improved study design, enhanced sample size collected from multiple centers increase study impact. Also, follow up studies to analyze improvement in IGF-1 levels after treatment in iron deficiency anemia are recommended.

CONCLUSION

According to the study results there is a strong correlation between IDA and IGF-1 levels in children. Children with Iron deficiency anemia have lower levels of IGF-1 level which may be the cause of short stature among these children. The findings implicate that iron deficiency need to be corrected for getting adequate effect of growth hormone on growth and development. An effect which is implemented through the protein IGF-1.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MU & ZHH: Data acquisition, data analysis, critical review, approval of the final version to be published.

MQAK & MA : Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MY & MR: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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