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STUDY OF FERRITIN IN MALNOURISHED CHILDREN AND ITS CORRELATION WITH HORMONES AND BMI

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ABSTRACT

Micronutrient deficiency is the another form of malnutrition. Nearly all deaths linked to micronutrient deficiency are due to a lack of vitamin A, zinc or iron. Present study was designed to assess the efficacy of the study nutritional intervention in terms of ferritin levels before and after the Nutritional Intervention treatment (NIT) and to find correlation of ferritin with growth hormone, cortisol and BMI in malnourished children. This was Open label prospective parallel group active comparator interventional study, 105 Study and 100 control SAM(Severe Acute malnutrition)children of 1 to 5 years of age and either sex were randomly enrolled. Study group was given NIT, providing 2.5 to 3gm Protein and 90-100 kcal/kg body weight/day for three months. Serum ferritin, growth hormone, cortisol levels, height and weight of both groups were estimated before and after the NIT. Before NIT **P** value for Ferritin, Growth hormone, cortisol and BMI were insignificant and after NIT both were significant**.** The Correlations of ferritin with cortisol, growth hormone and BMI were noted significant with Pearson correlation coefficient **r** values 0.207, -0.711 and 0.195 respectively, while poor negative correlations of growth hormone with weight and height have also noted significant with r values -0.196 and -0.243 respectively. The investigators conclude that study nutritional intervention is the effective food supplement for the recovery of impaired ferritin status in SAM children and ferritin has significant correlations with cortisol, growth hormone and BMI.

KEYWORDS: Ferritin, Growth hormone, Cortisol, BMI, Malnutrition, Correlations.

INTRODUCTION

Protein–energy malnutrition is defined on the basis of anthropometric criteria as, -The fall below 2 standard deviations (-2S.D.) under the normal weight for age (underweight), height for age (stunting) and weight for height (wasting) is known as malnutrition." [1] Micronutrient deficiency: This is the another form of malnutrition. A long-term lack of nutritious food, or having an infection such as worms, can result in a lack of vitamins and minerals in a child's diet. Micronutrient deficiencies represent a serious risk to a child's health: they account for one-third of all malnutrition-related child deaths, and 10% of all children's deaths.[2,3] Nearly all deaths linked to micronutrient deficiency are due to a lack of vitamin A, zinc or iron. The prevalence of under nutrition and anemia is also greater among children belonging to scheduled castes and scheduled tribes and the lowest wealth quintile in Maharashtra. In addition,[4,5] The magnitude and severity of the nutritional situation in Maharashtra is defined as "risky". Actions recommended by WHO include supplementary feeding for children with moderate acute malnutrition and therapeutic feeding for children with severe acute malnutrition. [5]

MATERIAL AND METHOD

Serum Ferritin kit: **Product code: LKFE1**: **Company:** Siemens.

Method: A solid- phase, two site chemiluminescent immunometric assay. [6]

Material supplied with the kit

1. Ferritin test Units: Each barcode-labled unit contains one bead coated with polyclonal rabbit anti cortisol antibody.
2. Ferritin reagent wedge: One wedge with barcode, 7.5 mL Alkaline Phosphtase (bovine calf intestine) conjugated to polyclonal goat anti-ferritin in buffer, with preservative.
3. Ferritin adjustors: Two vials(Low and High)2.5 mL each ,of ferritin in a human protein based matrix, with preservative. [6]

viii) Cortisol kit: Product code: LKCO1: **Company:** Siemens.

Method: a solid- phase, two site chemiluminescent immunometric assay. [7]

Material supplied with the kit:

1. Cortisol test Units: Each barcode-labeled unit contains one bead coated with polyclonal rabbit anti cortisol antibody.
2. GH reagent wedge: One wedge with barcode,7.5 mL alkaline phosphtase(bovine calf intestine)conjugated to cortisol in buffer, with preservative.

3. GH adjustors: Two vials(Low and High) 3 mL each ,of cortisol in processed human serum, with preservative. [7]

ix) Growth Hormone kit: Product code: *LKGRH1*: Company: Siemens

Method: a solid- phase, two site chemiluminescent immunometric assay. [8]

Material supplied with the kit:

1. GH test Units: Each barcode-labeled unit contains one bead coated with murine monoclonal anti hGH antibody.
2. GH reagent wedge: One wedge,7.5 mL alkaline phosphtase(bovine calf intestine) conjugated to rabbit polyclonal anti-hGH antibody in buffer, with preservative.
3. GH adjustors: Two vials(Low and High)containing lyophilized hGH in nonhuman serum, with preservative. Reconstitute each vial with 3mLdeionized water. [8]

6) Hormones and ferritin Estimated on Chemiluminescence -Immulite 1000:

i) Estimation of serum Ferritin

Principle

Ferritin is a solid- phase, two site chemiluminescent immunometric assay.[6]

Procedure: As per instructions in operator's manual for preparation, set up, dilutions, adjustments, assay and quality control procedure. [6]

ii) Estimation of serum Growth Hormone and Cortisol[7]

Principle: Growth hormone and cortisol are a solid- phase, two site chemiluminescent immunometric assay.[7,8]

Procedure for hormone estimations: As per instructions in operator's manual (on immulite-1000 chemiluminescence machine) for preparation, setup dilutions, adjustments, assay and quality control procedure.[7]

METHODOLOGY

This was Open label prospective parallel group active comparator interventional study,105 Study and 100 control SAM children of 1 to 5 years of age and either sex were randomly enrolled. Study group was given NIT, providing 2.5 to 3gm Protein and 90-100 kcal/kg body weight/day for three months.

From each test and control subjects morning fasting blood samples were collected in labeled; plain vaccutainers,-such kind of blood collection was done at two different periods-first; at the time of enrollment and second; after three month's nutritional intervention treatment. All

blood samples in plain vaccutainer were centrifuged within 1 hr to obtain serum. Estimation of Ferriitn, Growth Hormone and cortisol were done on chemiluminescence machine-immulite-1000. Instructions provided by manufacturer in the all kits were followed.

Anthropometric measurements

The age and oedema of each subject was specially noted at the time of enrollment. The weight and height of each subjects were measured as per WHO guidelines. Weight was measured on calibrated regular and infant weighing scales. While Standing height of subjects above two years was measured by stadiometer and length of subjects below two years was measured by infantometer. The BMI was calculated as per standard formula and WHO guidelines by using recorded data of weight and height.

STATISTICAL ANALYSIS

Data was subjected to analysis by using SPSS S/W version -16 for variance, and differences were identified by Mean, S.D., S.E., 95 % C.I. P-value was obtained, $P< 0.05$ considered significant difference, $p < 0.000$ considered highly significant difference.

RESULTS AND OBSERVATIONS

Table 1. Descriptive statistics of baseline characteristics Anthropometric measurements at the time of Admission and After Nutritional Treatment in the study and control group.

Baseline chararcteristics	Groups	N	Mean	Std. Deviation	Std. Error Mean
Age (months) At Admission	Study group	105	36.02	13.77	1.345
	Control group	100	36.14	13.73	1.373
Age (months) After treatment period	Study group	105	39.2	13.50	1.30
	Control group	100	39.4	13.20	1.30
Weight(kg) At Admission	Study group	105	8.66	1.58	0.15
	Control group	100	8.34	1.62	0.16
Weight (kg) After treatment.	Study group	105	14.08	2.61	0.25
	Control group	100	11.28	1.81	0.18
Hight (cm) At Admission	Study group	105	84.95	8.63	0.84
	Control group	100	84.92	8.43	0.84
Hight(cm) After treatment	Study group	105	91.47	8.29	0.80
	Control group	100	86.13	7.19	0.71
BMI (KG/m^2) At Admission	Study group	105	10.57	0.39	0.28
	Control group	100	10.76	0.28	0.20
BMI (Kg/m^2) After treatment	Study group	105	15.53	0.50	0.04
	Control group	100	13.01	0.70	0.07

Equal variances assumed

Table 2. Independent sample test for Anthropometric measurements at the time of admission and After Nutritional Treatment

Unpaired t-test for Equality of Means						95% C I of the Difference	
Baseline charactcristics	**Mean Difference**	**Std. Error Difference**	**t test value**	**df**	**p value**	**Lower**	**Upper**
Age (yrs) at admission	-0.111	0.158	-0.706	203	0.481 (NS)	-0.422	0.200
Age (yrs) after treatment period	-0.215	0.198	-0.806	203	0.523 (NS)	-0.522	0.220
Weight (kg) (At Admission)	-0.172	0.223	-0.772	203	0.441 (NS)	-0.612	0.268
Weight (Kg) (after treatment)	2.799	0.316	8.857	202	0.0001	2.176	3.423
Height (cm) (At Admission)	0.037	1.192	0.031	203	0.975 (NS)	-2.314	2.387
Height (cm) (after treatment)	-1.344	1.346	-0.999	203	0.0001	-3.99	1.31
BMI (KG/m^2) At Admission	-0.195	0.340	-0.573	203	0.624 (NS)	-1.658	1.268
BMI (Kg/m^2) After treatment	2.520	0.085	29.504	203	0.0001	2.352	2.688

P < 0.05 considered Significant difference, p < 0.000 considered Highly Significant difference NS-Not Significant

Table 3. Descriptive statistics of baseline characteristics Before treatment in study and control group

Baseline charactcristics	Groups	N	Mean	Std. Deviation	Std. Error Mean
Ferritin ng/mL	Study group	105	10.40	8.28	0.81
	Control group	100	8.80	7.16	0.72
Cortisol (morng) µg/dL	Study group	105	37.04	6.29	0.61
	Control group	100	37.60	5.10	0.51
Growth Hormon ng/mL	Study group	105	15.73	3.01	0.29
	Control group	100	15.84	2.99	0.30

Equal variances assumed

Table 4. Independent sample test for Before treatment in study and control group

Unpaired t-test for Equality of Means						95% C I of the Difference	
Baseline charactcristics	**Mean Difference**	**Std. Error Difference**	**t test value**	**df**	**p value**	**Lower**	**Upper**
Ferritin ng/mL	1.627	1.083	1.502	203	0.135 (NS)	-0.509	3.763

Cortisol (morng) µg/dL	-0.558	0.802	-0.696	203	0.487 (NS)	-2.138	1.023
Growth Hormon ng/mL	-0.109	0.420	-0.261	203	0.794 (NS)	-0.937	0.718

P < 0.05 considered Significant difference, p < 0.000 considered Highly Significant difference NS- Not Significant

Table 5. Descriptive statistics of baseline characteristics After treatment in study and control group

Baseline chararcteristics	Groups	N	Mean	Std. Deviation	Std. Error Mean
Ferritin ng/mL	Study group	105	40.507	10.412	1.016
	Control group	100	11.740	9.237	0.924
Cortisol (morng) µg/dL	Study group	105	18.508	4.656	0.454
	Control group	100	33.100	4.705	0.471
Growth Hormon ng/mL	Study group	105	5.840	2.491	0.243
	Control group	100	13.130	2.482	0.248

Equal variances assumed

Table 6. Independent sample test for After treatment in study and control group

Unpaired t-test for Equality of Means						95% C I of the Difference	
Baseline chararcteristics	**Mean Difference**	**Std. Error Difference**	**t test value**	**df**	**p value**	**Lower**	**Upper**
Ferritin ng/mL	28.733	1.377	20.863	203	**0.0001**	26.018	31.449
Cortisol (morng) µg/dL	-14.617	0.654	-22.352	203	**0.0001**	-15.906	-13.328
Growth Hormon ng/mL	-7.288	0.347	-20.978	203	**0.0001**	-7.973	-6.603

P < 0.05 considered Significant difference, p < 0.000 considered Highly Significant difference NS- Not Significant

Table 7. Descriptive statistics for gender (Before treatment) in both groups

Before treatment		Study group (N=105)			Control group (N=100)		
Characteristics	**Gender**	**N (Sample size of Gender)**	**Mean**	**Std. Deviation**	**N (Sample size of Gender)**	**Mean**	**Std. Deviation**
Ferritin ng/mL	Male	42	20.12	3.39	46	16.18	2.872
	Female	63	3.92	0.82	54	2.45	0.577

Table 8. Comparison in gender (Before treatment) for their characteristics in both groups

Study group (**Before** treatment) (N=105)							
Characteristics	**Mean Difference**	**Std. Error Difference**	**t test value**	**df**	**p value**	**95% CI Lower**	**95% CI Upper**
Ferritin ng/mL	16.203	0.444	36.488	103	0.0001 (S)	15.322	17.084
Control group (**Before** treatment) (N=100)							
Ferritin ng/mL	13.731	0.4	34.353	98	0.0001 (S)	12.938	14.524

Table 9. Descriptive statistics for gender (After treatment) in both groups

After treatment		**Study group (N=105)**			**Control group (N=100)**		
Characteristics	**Gender**	**N (Sample size of Gender)**	**Mean**	**Std. Deviation**	**N (Sample size of Gender)**	**Mean**	**Std. Deviation**
Ferritin ng/mL	Male	42	49.42	8.99	40	21.01	9.13
	Female	63	34.50	6.16	60	4.47	9.38

Table 10. Comparison in gender (After treatment) for their characteristics in both groups

Study group (After treatment) (N=105)							
Characteristics	Mean Difference	**Std. Error Difference**	**t test value**	**df**	**p value**	**95% CI Lower**	**95% CI Upper**
Ferritin ng/mL	14.914	1.478	10.091	103	0.0001 (S)	11.983	17.845
Control group (After treatment) (N=100)							
Ferritin ng/mL	-0.3033	1.8949	-0.16	98	0.0001	-4.0637	3.457

Table 11. Correlations of Ferritin with Growth Hormone and cortisol after treatment in study group

Ferritin	**Growth Hormone**	**Cortisol**
Sample size (N)	105	105
Pearson Correlation r	* - 0.711	* 0. 207
p value	0.0001 (Significant)	0.034(Significant)
Interpretation	Strong negative correlation	Poor positive correlation

Table 12. Correlations of ferritin with BMI after treatment in study group

Ferritin	**BMI**
Sample size (N)	105
Pearson Correlation r	0.195 *
p value	0.0 46 (Significant)
Interpretation	Poor positive correlation

Table 13. Correlations of Growth Hormone with Height and weight after treatment in study group

Growth Hormone	Height	Weight
Sample size (N)	105	105
Pearson Correlation r	-0.243 *	-0. 196*
p value	0.013 (Significant)	0.045 (Significant)
Interpretation	Poor negative correlation	Poor negative correlation

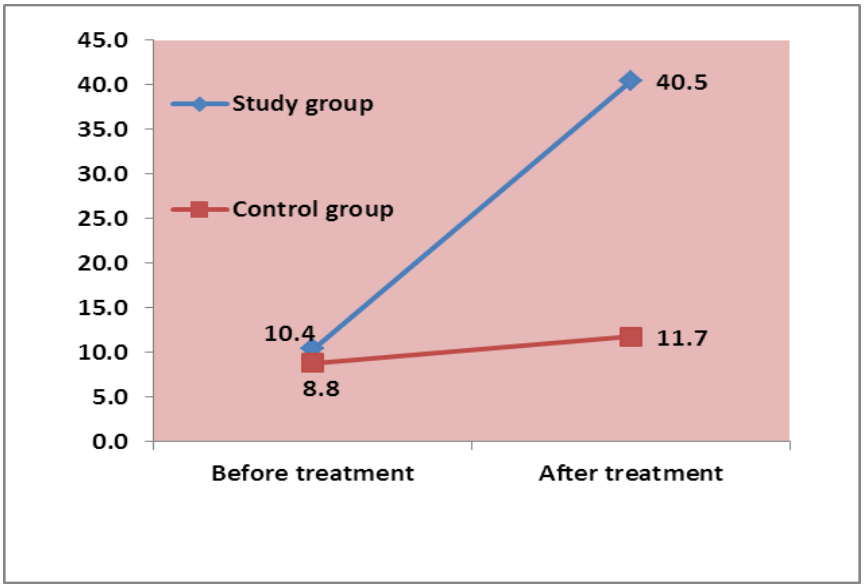

Figure 1. Ferritin ng/mL

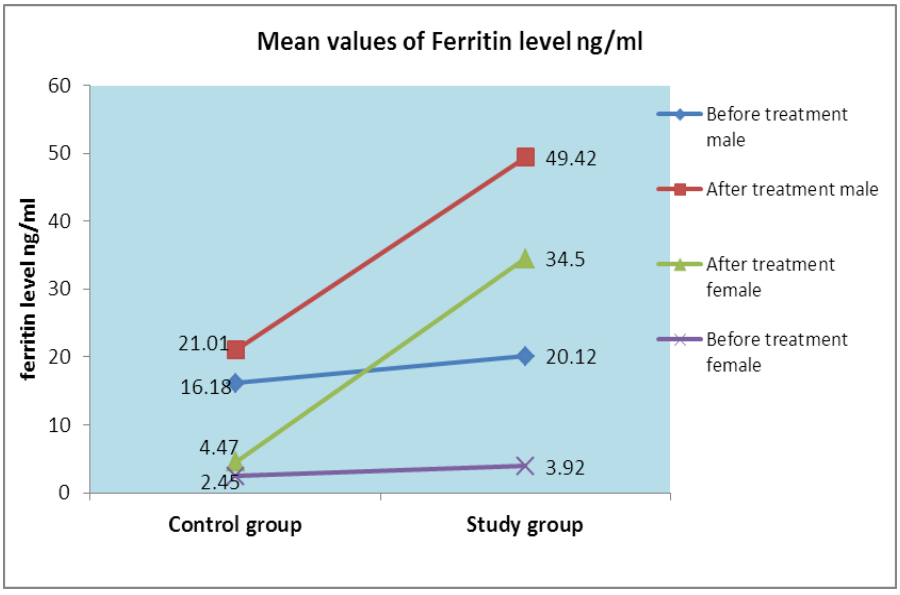

Figure 2. Ferritin (ng/mL) in male and Female

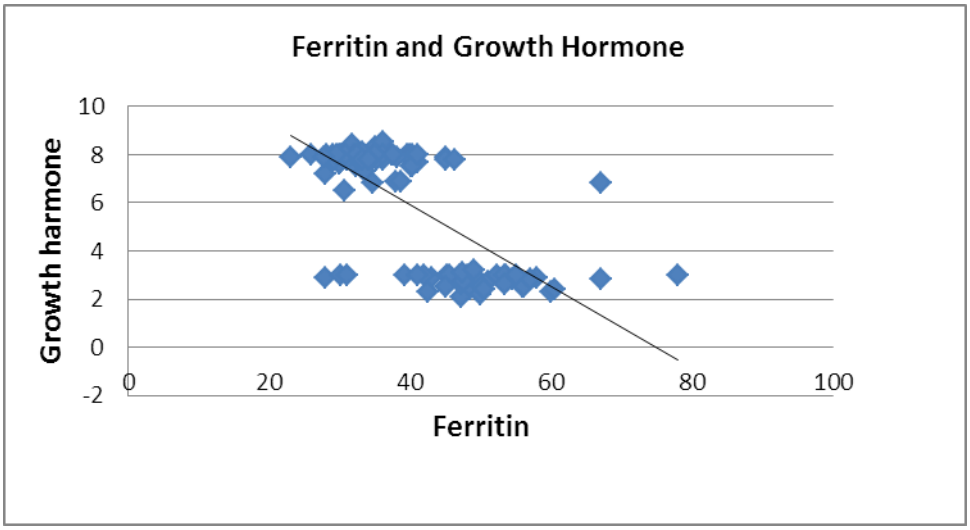

Figure 3. Correlations of ferritin with Growth hormone

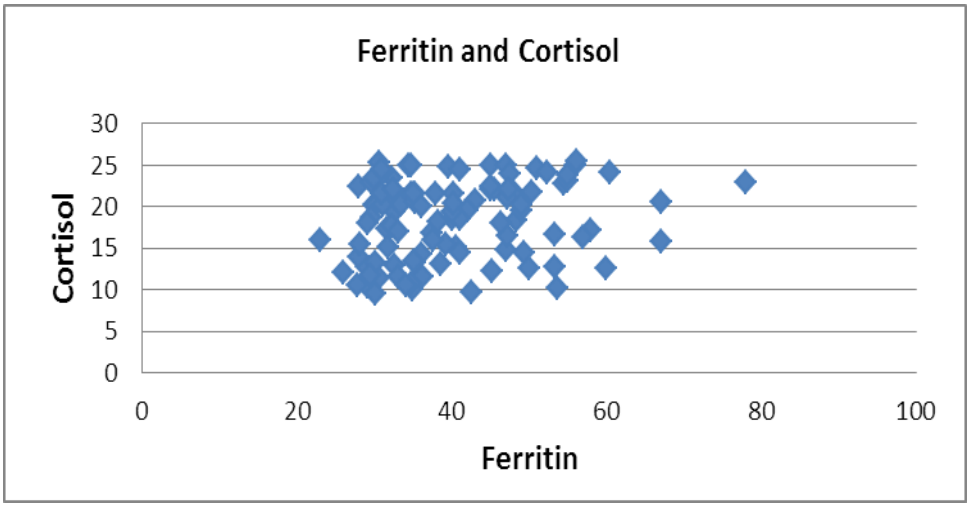

Figure 4. Correlations of ferritin with cortisol

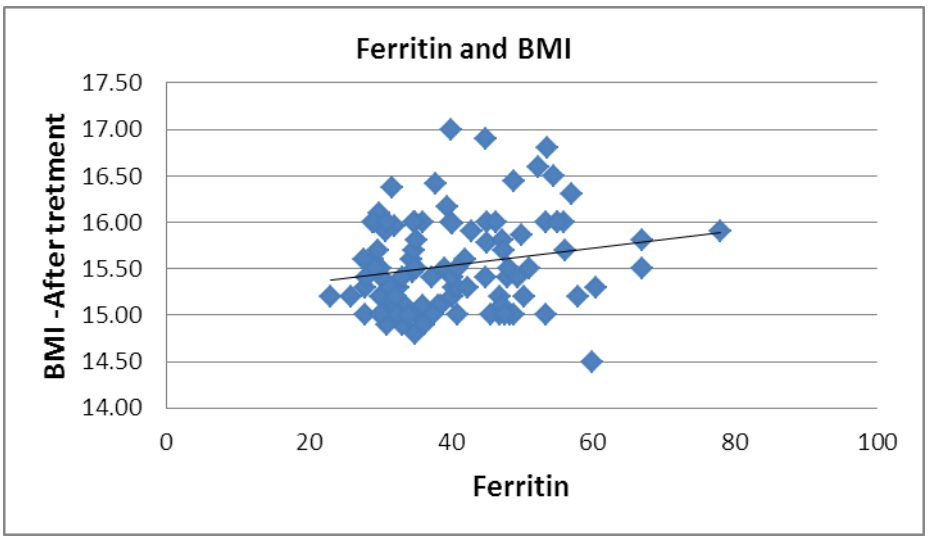

Figure 5. Correlations of ferritin with BMI

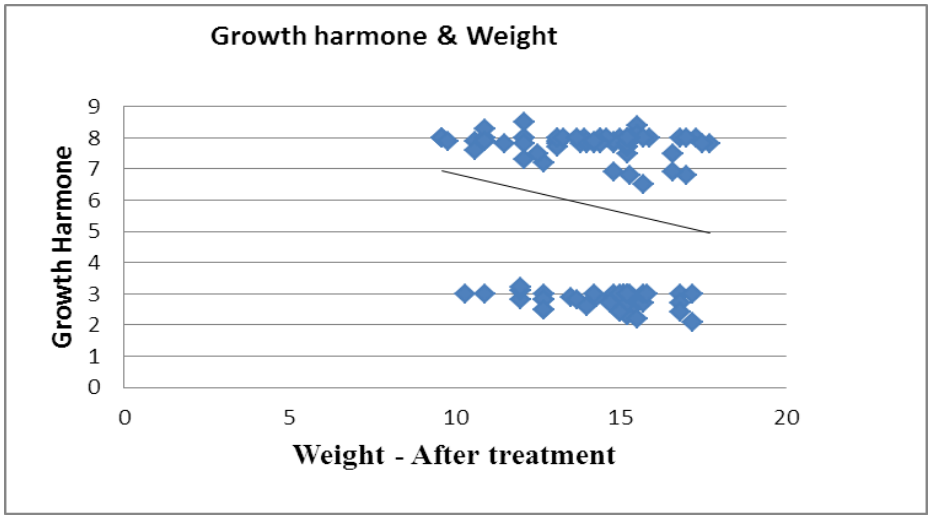

Figure 6. Correlations of Growth hormones with Weight

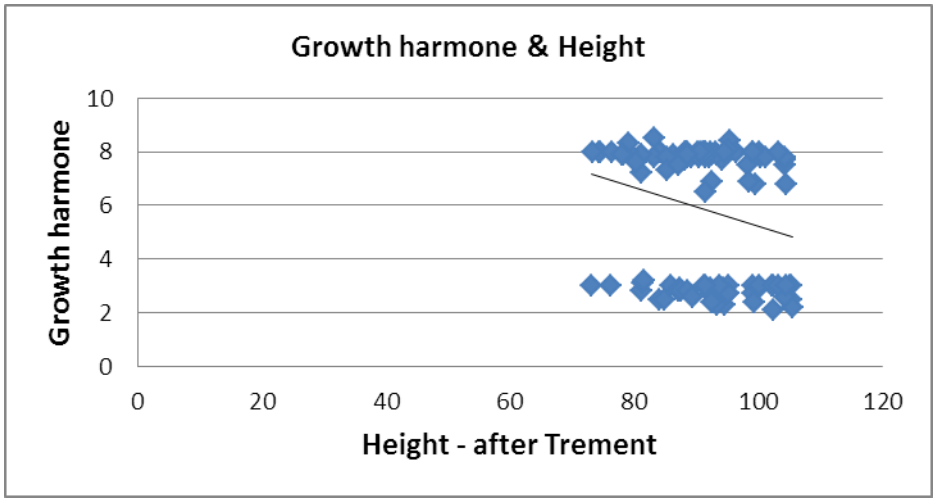

Figure 7. Correlations of Growth hormones with Height

DISCUSSION

Ferritin: it is the primary intracellular iron storage protein, is also found in small amounts in the circulation. Serum ferritin generally correlates with total body iron although, as an acute phase reactant, ferritin may be increased by inflammatory, infectious, and malignant processes. In contrast, a few conditions, including vitamin C deficiency, reduced serum ferritin, and scurvy, or vitamin C deficiency, suggestive of a potential cause of low ferritin. In general, values less than 10 µg/L are indicative of iron deficiency.[9]

In the present study decreased serum ferritin levels were noted at the time of enrollment in both study and control groups. While after the nutritional intervention therapy to the study group, the ferritin values were found to be significantly increased to the normal levels in study group, while control group has not shown such improvement.

Ferritin status: Before nutritional intervention treatment, both groups had similar ferritin status (p=0.135) Nutritional intervention resulted in significant improvement in ferritin (p=0.0001) in study group as compared to control group. (Fig:1 Table : 3-6)

Ferritin status by Gender:

Study Group: Similarly after comparison of the gender in study group before nutritional intervention treatment both gender had significant difference in ferritin status (P=0.0001).While after nutritional intervention treatment in study group both gender also had significant difference in ferritin status (p=0.0001). (Fig.2 Table :7-10)

Control Group: After comparison of the gender in control group before nutritional intervention treatment both gender had significant difference in ferritin status (P=0.0001).While after the treatment period, in control group both gender also had significant difference in ferritin status (p=0.0001). (Fig.2 Table : 7-10)

Correlations: The Correlations of ferritin with cortisol, growth hormone and BMI were noted significant with Pearson correlation coefficient **r** values 0.207, -0.711 and 0.195 respectively, while poor negative correlations of growth hormone with weight and height have also noted significant with r values -0.196 and -0.243 respectively.(Fig.3-7 Table.11-13)

Ferritin: It has been reported that preschool children (<8years) and adolescents (>15 years) during growth spurts have the greatest physiological demands for iron and are at highest risk of iron deficiency anaemia.[10] The serum ferritin levels assessment is the most sensitive methods for the detection of mild iron depletion and also for the iron stores assessment. In all the disease groups, except, malignancy, a chronic inflammatory stage, and an increased red cell turnover, the bone marrow iron content directly related to the serum levels of ferritin. There was not any clinical disorder to the enrolled subjects of this study. Serum ferritin was more sensitive indicator as compared to serum iron, TIBC, and transferrin saturation.[11]

-The following discussed various factors and conditions could also be responsible for the iron deficiency anemia in the malnourished children in present study.

-Transferrin with an electrophoretic mobility of beta globulin has a pink colour. [11] In the liver it is mainly synthesised and in various tissues also [12] In the diagnosis of iron deficiency, if the transferrins falls or if it is fail to rise, then the usefulness of the transferrin saturation is lost. Inflammation, Infections undernutrition and proteinuric conditions these are the factors which reduces transferrin level. Lowered TIBC is mainly causes due to under nutrition. [13] To

red cell precursors the transferrin mediated delivery imparts direction to the flow of iron. [14] Towards red marrow unbound iron is not oriented, instead it gets distributed into many tissues and leaves plasma rapidly. [14] In congenital atransferrinemia, biological importance of transferrin is seen [14] where red cells have morphological stigmata of iron deficiency, with no iron in the marrow, but tissues are loaded with iron. It shows that undernourished hypo-proteinemic individuals supplemented only by iron is not adequate.[14] to correct the transferrin deficiency, the protein supplementation to direct the iron towards the marrow is also equally important. [14] It is shown by McFarlane et.al. [15] that free iron may favour bacterial multiplication, transferrin has a bactericidal action and in its absence promotes growth of bacteria. It could be positively harmful if without replacing proteins only iron therapy is given to such patients. [15]

-Ferrous iron is more easily absorbed than ferric iron, and thus the usual treatment for infants and children is ferrous sulfate. Premature infants are frequently vitamin E deficient due to decreased intake, decreased stores, and poor absorption of vitamin E. Since iron therapy inhibits absorption of vitamin E [16] it could worsen the Vit-E status of these children, which leads the child to other complications, and it could enter into sever malnourishment.

-The absorption of iron on an empty stomach is about twice to that of a full stomach; therefore it is recommended that the dose be given about an hour prior to a meal. [15] It was noted that at the study site practically these important things were not followed while supplementing the child with iron therapy. Also early discontinuation of the iron/folate treatment, and non co-operation as well irregularity by the parents and child for the iron treatment was also noted at the study site. Many times there is a irregularity by government in the supplementation of multi vitamin syrup ,which creates gap in the treatment and leads to under nutrition.These facts could be attributed to the anemic results of enrolled study subjects before the start of the nutritional therapy. Hence the duration of intervention treatment of present study was 3 months in order to replenish the iron stores.

-Dallman PR, Yip Ret.al.(1993) [17] Muslimatun S. Schmidt MK,(2001) [18] in their studies have called children for follow up to see if there was no improvement,they have attributed the failure of oral iron therapy as the result of impaired absorption, incorrect diagnosis, ongoing blood loss greater than hemoglobin generation, inadequate dose, ineffective iron preparation, superimposed malignancy or inflammatory disease, or, most commonly, simple noncompliance. [15] According to them compliance can be an issue because of the taste of iron, gastrointestinal distress, or concern of parents that the drops will stain the infant's teeth. These problems could be dealt with by giving the iron with a small amount of food or liquid,

preferably something that will enhance the absorption, and by giving the drops in the back of the mouth. -The above discussed probable causes of treatment failure could also be attributed to the study site malnourished children also, due to which in spite of consumption of iron syrup, and folate tablets provided by PHC to the children who were enrolled in the present study all were suffering from iron deficiency before the nutritional rehabilitation.

CONCLUSION

The investigators conclude that study nutritional intervention is the effective food supplement for the recovery of impaired ferritin status in SAM children and ferritin has significant correlations with cortisol, growth hormone and BMI.

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