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IRON OVERLOAD AND GROWTH OF THALASSEMIC PATIENTS IN MARWAR REGION

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ABSTRACT

Growth disturbances are a major clinical feature of thalassemic patients. Regular blood transfusions and iron-chelation therapy greatly contribute to the quality and longevity of thalassemic patients. The main objective of present study was to compare the current growth of Thalassemia major patients, taking into accounts the iron overload, transfusion and iron chelation therapy, therefore we planned this study. The present study was conducted on 63 Thalassemic patients were enrolled in this study from June 2008 to October 2008. These subjects were categorised into two groups: 36 children (<10 years) and 27 adolescents (>10 years). Enrolled subjects were examined for various anthropometric parameters as height, weight and body mass index. Venous blood samples were obtained for estimating serum ferritin. Family history (carrier status of father, mother or siblings), age of diagnosis, age of first blood transfusion, frequency of blood transfusion and details of chelation therapy were recorded during the study Serum Ferritin level was very significantly elevated in the adolescents when compared to children because the number of transfusion increases as age advance. Percentile curves (NCHS growth curves) showed pronounced growth retardation in height and weight after 10 years of age in both sexes. A very significant difference ($t=3.43$, $p<0.01$)was observed between the serum Ferritin value of total no. of thalassemic children (1496.59 ±74.05 ng/ML) and the thalassemic adolescents (2397.97 ± 1199.57 ng/ML). Determination of serum ferritin and routine growth monitoring at regular intervals is necessary to detect any disturbance in growth and to establish an appropriate protocol for investigation and treatment.

INTRODUCTION: Thalassemia syndromes are a heterogeneous group of inherited hematologic disorders characterised by deficiencies in the rate of production of specific globin chains [1]. The patients of thalassemia suffer from anemia because their bodies are insufficient producer of red blood cells. As a result of anemia caused in thalassemia major, patients are pale, fatigue, have slower rate of growth and most significant is the expansion of bone marrow. This expansion of the bone marrow forces the bones to expand, and develop “Cooley’s facies”. The body attempts to compensate for the severe anemia by absorbing more iron from food passing through the gastrointestinal tract.

By absorbing more iron, the body exposes itself to new danger- iron overload and this increased iron deposits in the various tissues and organs. Many of the complications of thalassemia seen are the result of increased iron deposition from repeated blood transfusions. These complications of the chronic anemia is prevented or ameliorated by a program of routine red cell transfusions. There are about 75 mg of iron in 100 mg of packed red cells. The transfusion of 200 ml packed cells into a child every 4 weeks adds about 2 gm of iron per year.

Adolescents receive more than twice that amount of iron annually [1] Iron chelation therapy is just a supportive treatment for this disease which is associated with serious complications. The prime goal of iron chelation therapy is to control body iron. Growth disturbances are a major clinical feature of untreated patients with thalassemia [2]. With current transfusion therapy normal prepubertal linear growth is usual, but there is retardation of growth in the second decade and many patients fail to attain normal stature [3].

In countries where patients do not receive adequate treatment, chronic anemia and inadequate nutrition are the main cause of growth failure whereas, in countries where patients are well transfused but show poor compliance to chelation treatment, iron overload is the major cause of poor growth. However, in well transfused and well chelated patients, high doses of Deferoxamine may cause toxicity at the bone level, which ultimately delays growth. Impairment in growth and sexual maturation is directly related to iron overload [4, 5, 6].

Therefore we planned this study. In view of aforementioned controversial literature, it was decided to evaluate the relationship between iron overload and growth of thalassemic patients in mar war region.

MATERIAL AND METHODS: A total of 94 thalassemic patients were registered in Marwar Thalassemia society (Rajasthan). During my study period (June 2008 to October 2008), only 63 patients had received blood transfusion and they were enrolled in this study. These patients were categorized into two groups: 36 children (<10 years) and 27 adolescents (>10 years). They are further distributed according to their gender as children (22 male and 14 female) and adolescents (16 male and 11 female). Out of the 36 thalassemic children, 21 (12 males and 9 females) were of 1-5 years of age group and 15 (10 males and 5 females) were of 5-10 years age group. In 27 thalassemic adolescents, 18 (11 males and 7 females) were of 11-15 years age group and 9 (5 males and 4 females) were of 15-18 years age group. Family history (carrier status of father, mother or siblings), age of diagnosis, age of first blood transfusion, frequency of blood transfusion and details of chelation therapy were recorded during the study period when patients had continuous periodical referral for repeated blood transfusion in Department of paediatrics, Umaid Hospital for Women and Children, Dr. S. N. Medical College and associated group of Hospitals, Jodhpur.

Anthropometric assessment: Physical examination was done and the needed data including sex, age, weight and height were collected after getting written consent form and then BMI was calculated using formula BMI (kg/m^2) =weight (kg)/height (m^2) [7]. To find stature of the patients, the height for age percentile was compared to standard charts for boys and girls [8]. Each curve corresponds to the indicated percentile level. Venous blood samples were obtained for estimating serum Ferritin. It was carried out on fully auto analyzer by Ferritin UBI MAGIWEL enzyme immunoassay kit.

The UBI MAGIWEL QUANTITATIVE is a device of solid phase enzyme- linked immunosorbent assay (ELISA). This test kit provides quantitative measurement of ferritin in human serum to aid in the diagnosis of diseases affecting iron metabolism, such as hemochromatosis (Iron overload) and iron deficiency anemia)[9,10].

Transfusion: Out of the 63 thalassemics, 2 patients had received less than 10 transfusions per year, 25 patients had 10-20 transfusions per year, 24 patients had 20-30 transfusions per year, 8 patients had 30-40 transfusions per year and 4 patients had 40-50 transfusions per year. Chelation therapy: The most challenging management problem in thalassemic patients is the elimination of the toxic side effects of the excess iron acquired by transfusion therapy.

Deferoxamine, a specific iron chelator isolated from *Streptomyces pilosus* increases iron excretion through the urine and feces in those with excessive iron stores. Out of 63 thalassemic patients, 30 (22 children and 8 adolescents) patients were not on any chelation therapy due to economic and other constraints. Only 33 patients were receiving chelation therapy. Out of them 19 (6 children and 13 adolescents) were on regular chelation therapy and 14 (8 children and 6 adolescents) were on irregular chelation therapy.

RESULTS: The present study was undertaken to analyse the relationship of iron overload and growth of thalassemic patients in Marwar region. This association between iron overload and growth could be established after excluding all variables causing growth retardation (chronic anemia, inadequate nutrition and bone deformalities). Out of the 36 thalassemic children, 21 (12 males and 9 females) were of 1-5 years of age group and 15 (10 males and 5 females) were of 5-10 years age group. In 27 thalassemic adolescents, 18 (11 males and 7 females) were of 11-15 years age group and 9 (5 males and 4 females) were of 15-18 years age group (**Table 1**).

With the advancement in age group, decrease in number of thalassemics are probably due to lack of effective management of thalassemic children especially in respect to timely blood transfusion and poor use of standardized chelation regime or due to the side effects of the regime if not properly monitored Out of 63 thalassemic patients 30 (47.6%) were not on any chelation therapy due to economic and other constraints. Only 33 patients (52.3%) were receiving chelation therapy. Out of 33 patients 19 (57.5%) were on regular chelation therapy and 14 (42.4%) were on irregular chelation therapy (**Table 3**).

In the present study the mean height, body Weight and body mass index values of thalassemic children males and females were 1.02±0.13, 0.999± 0.12, 16.27±4.78, 14.85±3.65, 14.99±3.43, 14.86±2.19, respectively. The mean height , body weight and body mass index values of thalassemic adolescent were 1.39±0.12, 1.36±0.12, 30.25±10.30, 31.06±6.74, 15.17±2.55, 16.53±1.35 respectively. A non significant difference ($p>0.05$) is observed in the mean height, body weight and body mass index values of thalassemic children male and female (**Table 2**).

Similar non significant difference was observed in male thalassemic adolescent and female.

These anthropometric parameters of both thalassemic groups for both sexes have compared with NCHS standards and found that nearly 76.31% (29 out of 38) thalassemic males and 72% (18 out of 25) thalassemic females have weight less than 5^{th} percentile.

The height parameters of studied subjects when compared with NCHS standards shows that 55.26% (21 out of 38) thalassemic males and 52% (13 out of 25) thalassemic females were showing short stature i.e, height less than 5^{th} percentile by NCHS.

Body mass index at different ages for both sexes have compared with NCHS standards and found that under 10 years of age, BMI was less than 10^{th} percentile in 35.71% (5 out of 14) of thalassemic females and 36.36% (8 out of 22) of thalassemic males and above 10 years of age, BMI was less than 10^{th} percentile in 54.54% (6 out of 11) of thalassemic females and 56.25% (9 out of 16) of thalassemic males(Graph 1-5). The percentile curves showed pronounced growth retardation in height and weight after 10 years of age in males and females.

The mean serum ferritin levels in thalassemic adolescent were 1519.75±792.18, 1460.20±688.80, 2326.74±1373.43, 201.57±944.40, respectively. Statistically, a non significant variation ($p>0.05$) as noticed in thalassemic children and thalassemic adolescent (**Table 4**).

A significant difference ($t=2.10$, $p<0.05$) is observed between serum ferritin value of male thalassemic children v/s adolescents. Whereas a very significant difference is observed ($t=3.07$, $p<0.05$) between the female thalassemic children v/s adolescents.

A very significant difference ($t=3.43$, $p<0.01$) is observed between the serum Ferritin value of total no. of thalassemic children (1496.59±74.05ng/ML) and the thalassemic adolescents (2397.97±1199.57ng/ML). Statically a significant variation observed in these subjects (**Table 5**).

TABLE 1: ANTHROPOMETRIC PARAMETERS IN RELATION TO SEX IN THALASSEMIC ADOLESCENTS AND CHILDREN

Anthropometric Parameter	GROUP Studied	MALE	FEMALE	Total-mean ±SD	t-value	P value	Significant
HEIGHT (Meter)	Thalassemic Children (36)	1.02±0.13	0.999±0.12	1.01±0.13	0.75	>0.05	Non significant
	Thalassemic Adolescent (27)	1.39±0.12	1.36 ± 0.12	1.38±0.11	1.01	>0.05	Non significant
WEIGHT (KG)	Thalassemic Children (36)	16.27±4.78	14.85± 3.65	15.72±4.37	0.13	>0.05	Non significant
	Thalassemic Adolescent (27)	30.25±10.30	31.0±6.74	30.47±9.19	0.5	>0.05	Non significant
BMI (Kg/m^2)	Thalassemic Children (36)	14.99±3.43	14.86± 2.19	14.94± 2.98	0.17	>0.05	Non significant
	Thalassemic Adolescent (27)	15.17±2.55	16.53± 1.35	15.5±7 2.31	1.44	>0.05	Non significant

TABLE 2: DISTRIBUTION OF THALASSEMIC SUBJECTS ACCORDING TO THEIR AGE AND SEX

Age	MALE	FEMALE	Total
1-5 years	12	9	21
6-10years	10	5	15
11-15years	11	7	18
16-18years	5	4	9

TABLE 3: AVERAGE NO. OF BLOOD TRANSFUSION RECEIVED PER YEAR AND CHELATION THERAPY IN THALASSEMIC SUBJECTS

Average No. of blood transfusion per year	No. of subject studied	Percent %	Chelation therapy in subjects	Regular	Irregular	Not received
<10	2	3.17	Thalassemic children (36)	6	8	22
11-20	25	39.68	Thalassemic Adolescent (27)	13	6	8
21-30	24	38.09	Total subjects	19	14	30
31-40	8	12.69				
41-50	4	6.34				

TABLE 4: MEAN SERUM FERRITIN LEVEL (ng/ml) IN THALASSEMIC SUBJECTS

Groups	Male (Mean ±SD)	Female (Mean± SD)	Total	t-value	P-value	Significant
Thalassemic children (36)	1519.75± 792 18	1460.20 ±688.80	1496.59 ±744.05	0.23	>0.05	Non significant
Thalassemic adolescent (27)	2326.74± 1373.43	2501.57 ± 944.40	2397.97±1199.57	0.10	>0.05	

TABLE 5: STATISTICAL ANALYSIS OF SERUM FERRITIN LEVEL (ng/ml) IN RELATION TO SEX IN VARIOUS GROUPS OF SUBJECTS STUDIED

Groups compared	t-value	p-value	Statistical significant
Thalassemic children Male v/s Thalassemic adolescent male	2.10	<0.05	Significant
Thalassemic children female v/s Thalassemic adolescent female	3.07	<0.05	Very significant
Thalassemic children v/s Thalassemic adolescent	3.43	<0.05	Very significant

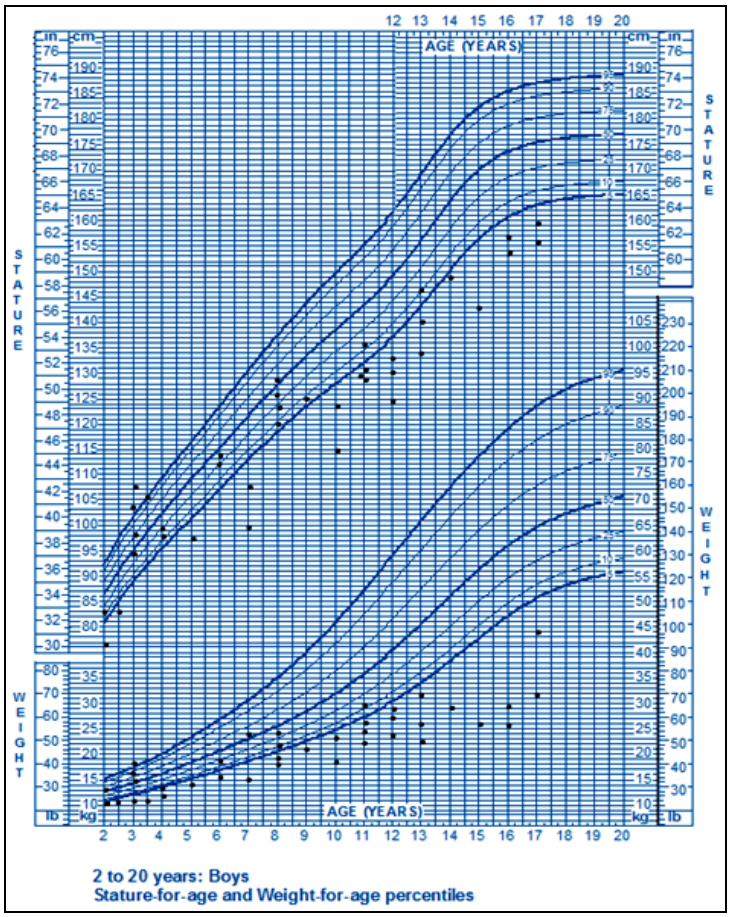

FIGURE 1

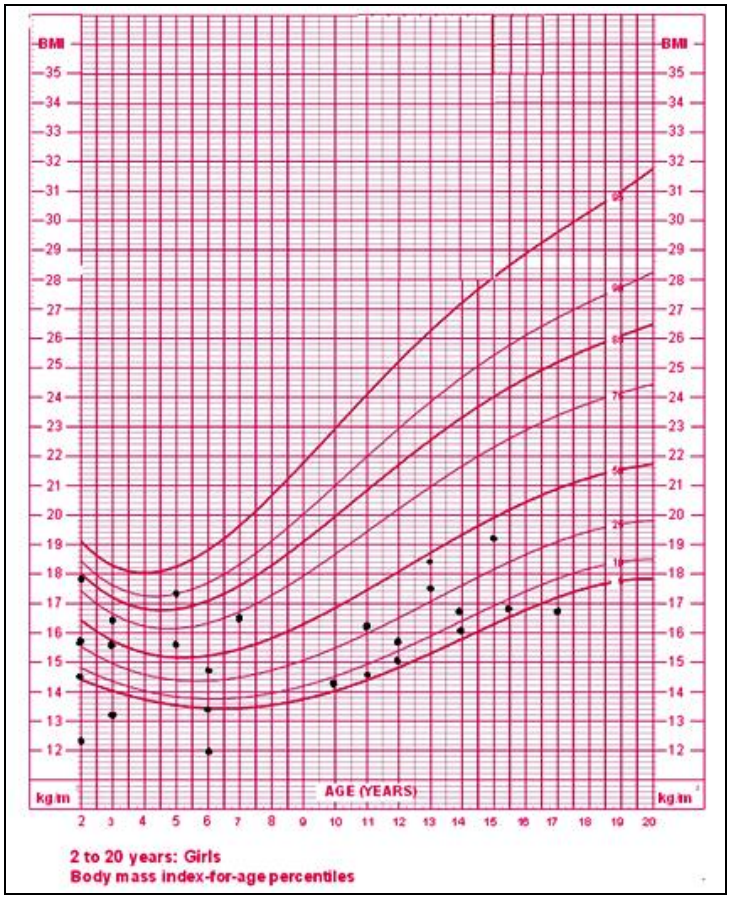

FIGURE 2

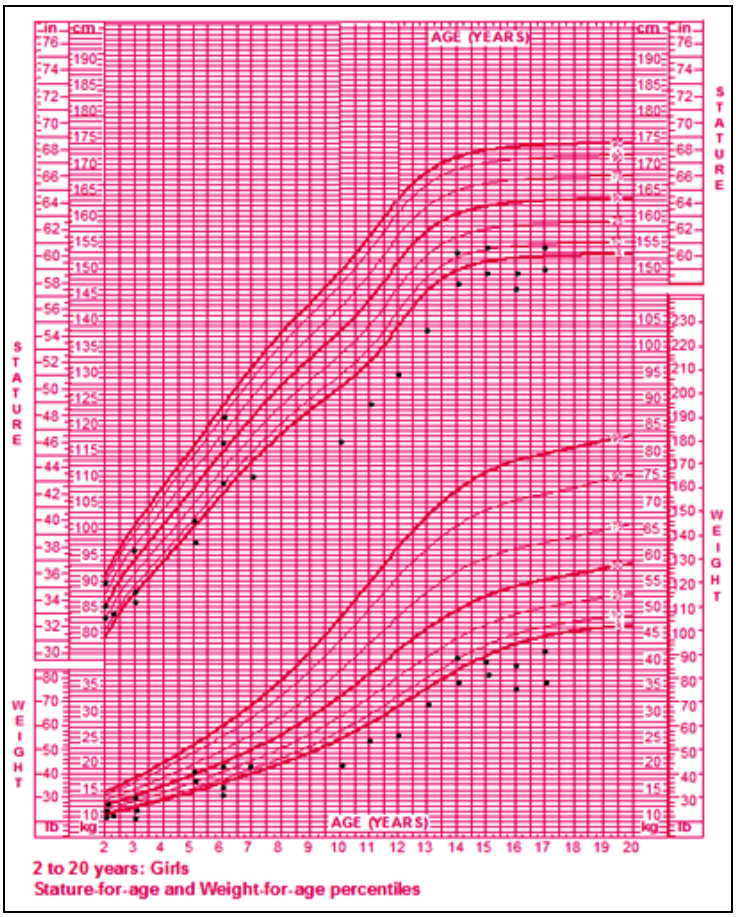

FIGURE 3

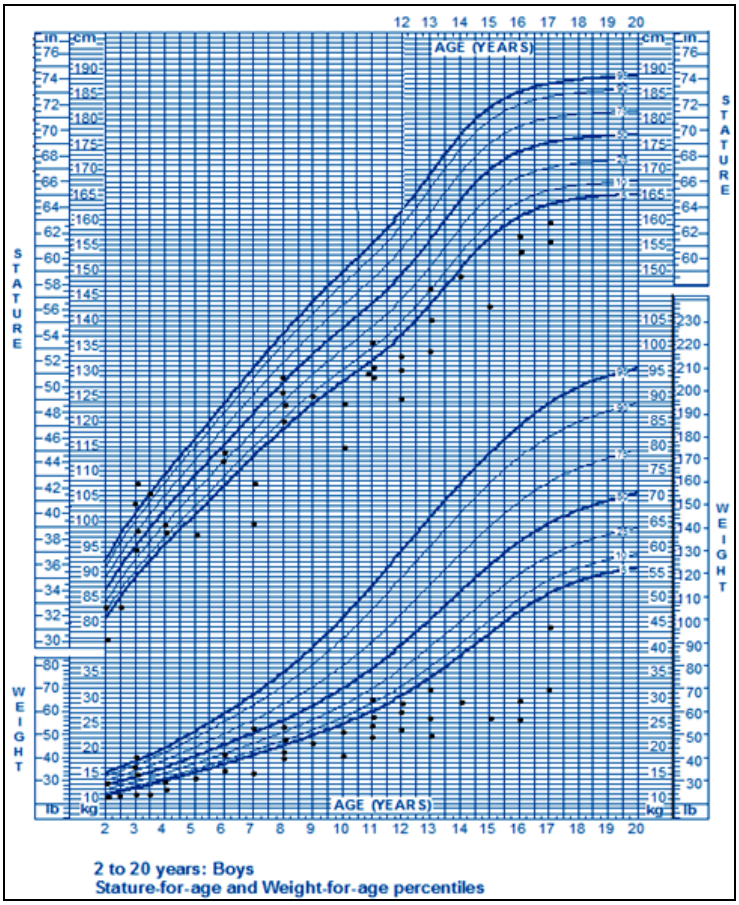

FIGURE 4

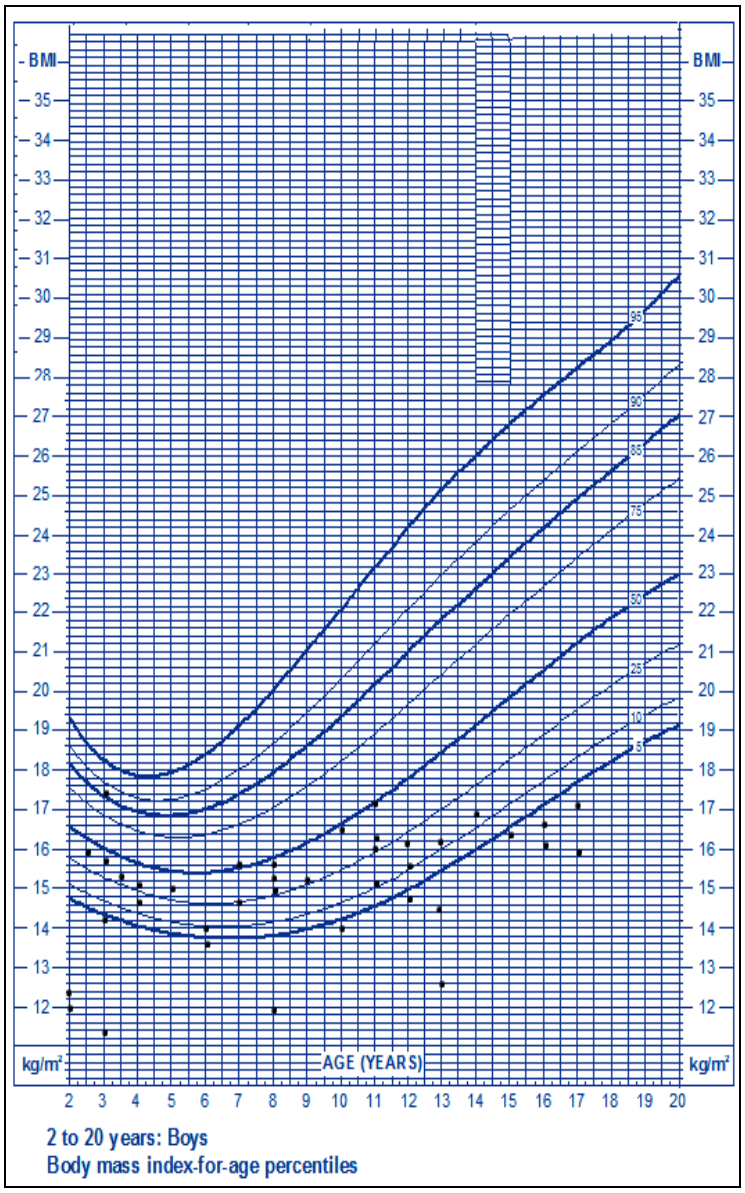

FIGURE 5

DISCUSSION: Growth disturbances are a major clinical feature of thalassemic patients. Now days, a large number of data's are available on growth of thalassemic patients. A multicentric study on thalassemic patients in North Italy reported retarded growth in height in both sexes, which was more pronounced after the age of 14 years or with advancement of disease [11].

Most of the previous studies have shown that thalassemic children were short compared to standards, BMI was less than 10th percentile for sex and age in 12.4% of thalassemic patients under 10 years of age and in 46.5% of patients above 10 year of age [12], height, weight and leg length were between 5th (and below) and 25th percentile [13].

In the present study, growth retardation became pronounced with increasing age which is in agreement with this studies[13, 14, 15, 16, 17]. Although in our study, we found that under 10 years of age, BMI was less than 10th percentile in 35.71% of thalassemic females and 36.36% of thalassemic males and above 10 years of age, BMI was less than 10th percentile in 54.54% of thalassemic females and 56.25% of thalassemic male.

The ferritin results in present study [Thalassemic children (1496.59 ±744.05ng/ML) and thalassemic adolescents (2397.97 ± 1199.57ng/ML)] were also in agreement with other studies which reported serum Ferritin between 276 and 8031ng/ML[18] and 850ng/ML[19].

There is direct relationship between Ferritin levels and degree of growth retardation [4, 13]. These finding showed that iron overload in patients with thalassemia is a common feature and continuous monitoring is thus, essential. Although modern hyper transfusion and chelation regimens have had a radical impact on growth but failure has persisted despite major treatment advances. Patients who begin treatment at a young age can be protected from the lethal complications of iron overload for at least two decades, but chelation therapy may not always prevent or ameliorated late growth failure [20, 21].

CONCLUSION: Our study supports that the Determination of serum ferritin and routine growth monitoring at regular intervals is necessary with increasing age, to detect any disturbance in growth and to establish an appropriate protocol for investigation and treatment.

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