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The Association Between Iron Over Load and Tanner Stage Retardation in the Females with B-Thalassemia Major

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ABSTRACT

Despite optimal therapy of patients with B- major thalassemia included repeated transfusion of blood program and iron chelation agents helped by increasing survival of these patients but remained a major problem in adolescents of these patients such as growth failure and hypogonadism. This study was aimed to determine the relationship between iron overload and tanner stage retardation among female patients with B- major thalassemia in Thalassemia Hospital in Diwaniyah Governorate. The current study occurred on all female patients diagnosed β-thalassemia major depends on the blood tests, with their age range from 13years to 16 years who registered in Thalassemia unit in Al- Diwaniyah Governorate, Republic of Iraq. In the physical examination, the patients were assessed for weight, height, Tanner stages, and body mass index(BMI), which recorded. S. Ferritin value was used to assess the iron load, and pelvic ultrasound was checked to assess the size of the uterus and both ovaries. The results of the currents study revealed that the total numbers of B- thalassemia major female patients are 31 patients, aged 13-16 years. Age of patients at which diagnosed of B- major thalassemia range from 0.17 to 5 year. The frequency of Blood transfusion (time/Year) ranges from 6 to 33 times/Year. The level of serum ferritin of the patients was ranged from 913-12000 ng/ml with. Tanner stage I was predominant, accounting for 87%, whereas stage II and III accounted for 10% and 3%, respectively. There was a significant negative relation between times transfusion of blood and Tanner. There was a significant correlation between Uterus size, ovarian size, and Tanner stage. Because of inflammation falsely increase serum ferritin or due to the relation between body iron in the body and level of serum ferritin is not always within the linear range, especially in the condition of inflammation or tissue damage. So that level of serum ferritin is not an adequate measure of iron stores in patients with major thalassemia.

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INTRODUCTION

Thalassemia is a congenital blood disease that informs of a defect in the production of a globin chain, result in absence production of ß- globin chain completely (major - thalassemia), or a partial reduction (intermediate thalassemia) (Michael *et al.*, 2016; Sarnaik, 2005). B-major thalassemia is mostly diagnosed in the early months of age when the fetal hemoglobin (HbF) level is decreased. The usual symptom of anemia like pallor is present.

Patients with β -major thalassemia require regular

transfusion of red cells each 2-5 weeks for long life to keep hemoglobin levels (Hb level before transfusion more than the level 9-10.5 gm/dl &Hb level after transfusion of blood should not increase more thanthe level 14-15 gm/dl), obtain normal growth and development and suppress the erythroid hyperplasia and skeletal abnormalities. Before starting transfusion of blood therapy, aphenotype of the red cell is required; blood should be leukoreduced and phenotypically matched for the Rh antigens to avoidinfusion of unnecessary plasma proteins and white blood cells, and so that prevents nonhemolytic febrile transfusion reactions (Cappellini *et al.*, 2008b). Iron overload results from two sources firstly from transfused blood (each 250ml of packed red cells gives 200-240 mg of iron) and secondary from absorption of iron by gastrointestinal tract. The body iron stores present saturated after receiving approximately 20-30 times transfusion of blood (500 mg iron/Kg) (Jose *et al.*, 2004). Increased iron accumulation after this level will lead to hepatic, cardiac, and endocrine ironloaded results in apparent signs of organ damage (Cappellini *et al.*, 2008b). β -major thalassemiapatients are receiving repeated times of blood therapy also require iron-chelating agents, including desferrioxamine (Desferal, DFO) administered as an intravenous infusion or slow subcutaneous through a pump 30-60 mg/kg/day through 8-12 hr, 5-6 days/week. About 8 mg of iron is bound by 100 mg of desferrioxamine. Adverse effects of desferrioxamine are often allergy at the location of the injection and febrile reaction; the more serious side effect is *Yersinia enterocolitica*infection and severe mucormycosis. Late-term toxicities include auditor toxicity and ocular toxicity. Another chelating agent for is Deferasirox (Exjade) administered per oral of 20 – 40 mg/kg one time daily pre-breakfast. Adverse effects of Deferasirox are often gastrointestinal upset, increased creatinine, and increased hepatic enzymes. *Another* chelating agent is Deferiprone also administered per oral of 75mg/kg three doses daily, before meals. Side effects of deferiprone are agranulocytosis, arthropathy, which necessitates discontinuation of the therapy. Gastrointestinal intolerance, zinc deficiency, and fluctuation of liver enzymes are other side effects. The aim of the chelating agent is to keep iron level in the body (level of serum ferritin between 500-1000 microgram /liter, or iron level between 4 -7.5 mg/gm dry weight) (Thein, 2005; Cappellini *et al.*, 2008a). The Tanner staging system for females and the appearance of changes in the sequence is presented below (Figures 1 and 2) (ACOG, 2010).

Breast development

Pubic hair

Puberty delayed and breast growth failure is the more common endocrine abnormalities in female patients with β - major thalassemia due to iron overload leads to damage to the hypothalamic-pituitary axis. Delayed puberty is defined as there is no sign of puberty at females age 13 years and at males age 14 years. Hypogonadism is known as the disappear development of testicular tissues in males and breast growth in females at 16 years) (Toumba *et al.*, 2007). Regular follow up to the patients with β - thalassemia major for delayed puberty and hypogonadism is important to start therapy and to avoid complications. Frequent follow-up of Tanner staging 6 monthly for preadolescent patients and yearly assessment of endocrine hormones (luteinizing hormone, follicular stimulating hormone, insulin-like growth factor (IGF), and IGF-binding protein-3 for patients with age from 8to10 years are required.Gonadal steroids (Ethinyl estradiol) must be started for girls with age more than 13 years not appearing pubertal signs as orally administrated (2.5-5ug per day)for six months, then monitoring of hormonal investigations. If the puberty signs does not present through six months after complete the management, starting with oral estrogen (Ethinyl estradiol) with increased the dosages from 5 to 10ug per day for next 1year. If vaginal bleeding does not happen, low level of estrogen-progesterone hormone therapy is the required treatment (Rachmilewitz *et al.*, 2006). This study was described to detect the association between iron overload and tanner stage retardation among female patients with B- major thalassemia in Thalassemia Hospital in Diwaniyah Governorate. The association of the female tanner stages with certain variable factors including the age of the patients, age of diagnosis of B-thalassemia, number of blood transfusion, serum ferritin, pelvic ultrasound examination to assess the size of the uterus and both ovaries.

PATIENTS AND METHODS

The study has occurred on all female patients diagnosed β- major thalassemia depend on the blood tests. Total numbers of B- thalassemia major female patients are 31 patients, with their age range from 13 years to 16 years who registered in Thalassemia unit in Al- Diwaniyah Governorate, Republic of Iraq. The Data collection was carried out during the period from the 1^{st} of April of 2016 to the 30th of December of 2016. They were studied to determine the association between iron overload and tanner stage retardation among female patients with B-

Stage 1:	B1:Prepubertal
Stage 2	B2: Early puberty (thelarche)
Stage 3:	B3: Mid puberty (enlargement of breast and areola; no separation contour)
Stage 4:	B4: Advanced puberty (separation contour between areola and nipple of the breast)
Stage 5:	B5: Adult type(complete breast development, nipple projects, areola part of breast contour)

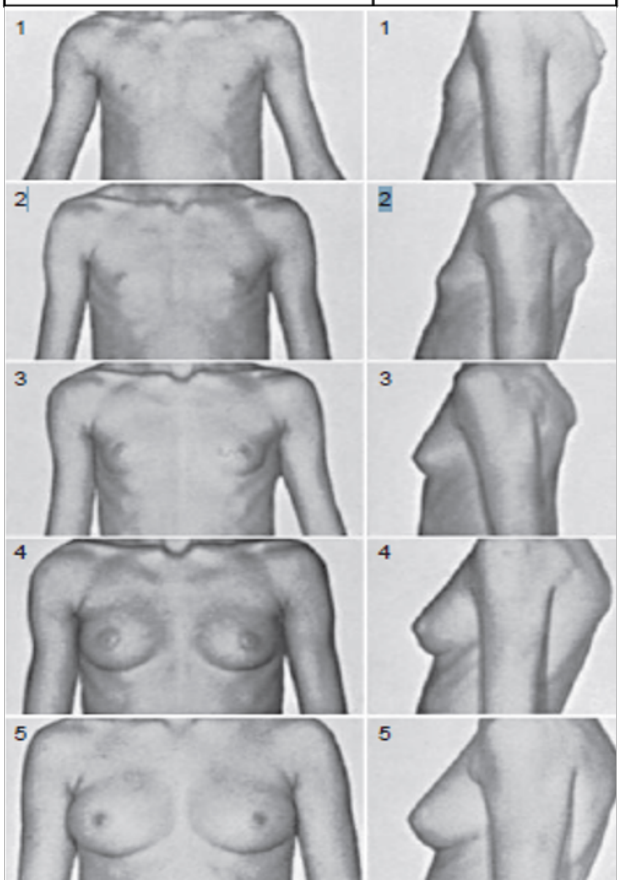

Figure 1: Breast development - Tanner stages (1-5) of the breast.

Stage 1:	PH1:Prepubertal (same to the abdominal wall)
Stage 2	PH2: Early puberty (Sparse growth, lightly pigmented hair, straight, at along inner border of labia).
Stage 3:	PH3: Mid puberty (darker, starting to curl, and distance over pubic junction)
Stage 4:	PH4: Advanced puberty(Hair Coarse, curly, abundant, same to adult growth, but covering fewer area than in the adult; no extend to an inner surface of thighs)
Stage 5:	PH5: Adult type, hair fulling the feminine triangle, spread to the inner surface of the thighs.

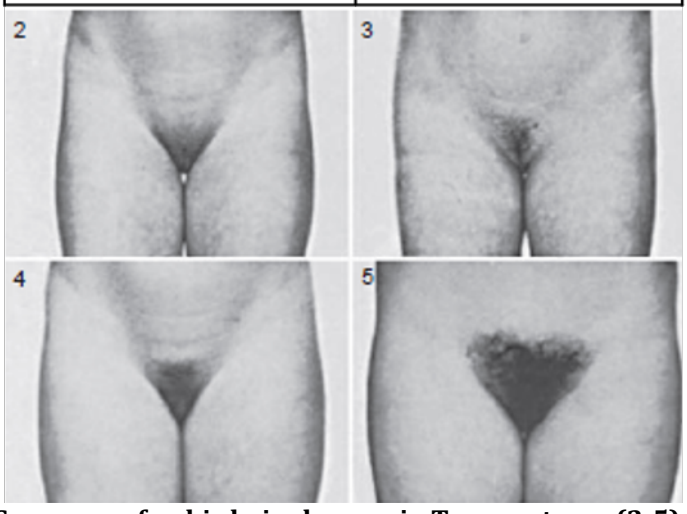

Figure 2: Pubic hair - Sequence of pubic hair changes in Tanner stages (2-5).

major thalassemia. All these patients were managed with frequent blood transfusion based on the level of hemoglobin and iron-chelating agent doses according to the level of serum ferritin.

The collection of data

The answers were obtained by asking the patients or their relatives (mother, father) and from the follow-up paper about age, age at which discovered of disease, times of transfusion of blood per year, types of the chelating agent

Assessment of stages of Tanner stage (breast size and pubic hair) by the researcher based on the Tanner staging system for a female that published by‹Marshall and Tanner›.

measurements are height by using a stadiometer and measure of weight by using a weight scale.

Laboratory Investigation: Serum ferritin level was used to assess the iron load, pelvic ultrasound was checked to assess the size of the uterus and both ovaries.

RESULTS AND DISCUSSION

General characteristics of the study sample

Total numbers of B- thalassemia major female patients are 31 patients, aged 13-16 years (mean age: 14.13 ±1.20). Age of patients at which diagnosis of B- major thalassemia range from 0.17 to 5 year with Mean ± SD (1.40 ±1.30). The frequency of Blood transfusion (time/Year) ranges from 6 to 33 times/Year with Mean ± SD (16.68 ±4.98). The female patients with B- thalassemia major were taken Dosage of chelating agents range from 30 to 40 mg/kg/day with Mean ± SD (37.42 ±3.62).

Weight, height and body mass index (BMI) of patients were 22-55 kg, 122-155 cm, 13.02 -25.25 kg/m2 respectively. With Mean ± SD34.64 ±8.15, 136.10 ±8.38, 18.57 ±3.26 respectively. The level of serum ferritin of the patients was ranged from 913-12000 ng/ml with Mean ± SD (4963.60 ±3580.39). Uterus and Ovarian sizes of the patients measured in (mm) by pelvic ultrasound were 18.00 -57.00mm, 12.00 -36.00mm, respectively, with Mean ± SD 27.35 ±9.98, 16.39 ±6.78, respectively. The general characteristic of the sample is shown in Table 1.

Tanner stage I was predominant, accounting for 87%, whereas stage II and III accounted for 10% and 3% respectively, as shown in Figure 3

There was no significant relationship between the age of the patient and Tanner stage and also no significant relation between age at the time of diagnosis (P>0.05). There was a significant negative correlation between the frequency of blood transfusion

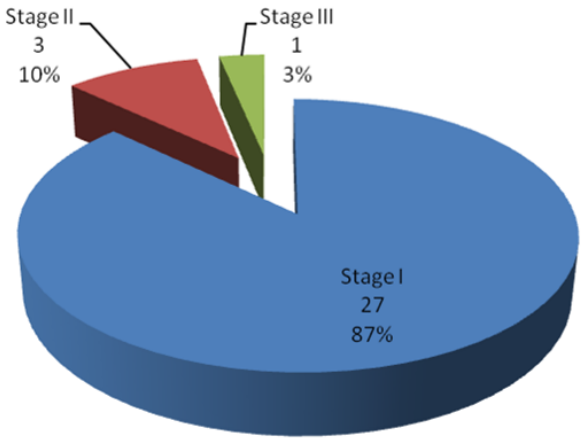

Figure 3: Tanner staging

and Tanner (r=-0.385, P= 0.045) so that the higher the frequency of transfusion, the lower the tanner stage is. No correlation was found between the dose of chelating agent and Tanner stage (P=0.599). Measurements of patients were significantly correlated with the Tanner stage (P=0.028 and P=0.007, respectively). No significant relation was found between serum ferritin and Tanner stage (P=0.444). There was a significant correlation between Uterus size, ovarian size, and Tanner stage (P=0.007and P=0.007, respectively). These results were shown in Table 2.

The study was performed to assess the relation between Tanner stages and iron overload in B-major thalassemia female patients and correlated with a different variable. The results of our study showed that height (short stature) and weight (weight failure) of patients were significantly correlated with the Tanner stage (P=0.028 and P=0.007, respectively). Our results are similar to other studies done in other areas of the world like Heshmat Moayeri MD study in Tehran, Iran, and M. G. Vogiatzi study in North America (De *et al.*, 2014). There are multifactorial pathogenesis explained growth failure in thalassemia and commonly iron accumulation due to frequent transfusion of blood and iron toxicity on endocrine gland (Puberty retardation, hypogonadism, GH deficiency, hypothyroidism, and diabetes), Side effect of chelating agents especially desferrioxamine, Another factors such as chronic anemia, hypersplenism, deficiency of folate, mineral such as Calcium and zinc (Vogiatzi *et al.*, 2009). There was a significant negative relation between times of transfusion of the blood and Tanner (r=-0.385, P= 0.045) so that the more frequency of transfusion, the early numbers the tanner stage. Also, there was a significant correlation between Uterus size, ovarian size, and Tanner stage (P=0.007and P=0.007, respectively). These results were shown

Table 1: General characteristic of the study sample

Characteristic	Mean ± SD	Range
Age (year)	14.13 ±1.20	13.00 -16.00
Age at time of diagnosis (year)	1.40 ±1.30	0.17 -5.00
Frequency of Blood transfusion (time/Year)	16.68 ±4.98	6.00 -33.00
Dose of chelating agents (mg/kg/day)	37.42 ±3.62	30.00 -40.00
Weight (kg)	34.64 ±8.15	22.00 -55.00
Height (cm)	136.10 ±8.38	122.00 -155.00
BMI (kg/m2)	18.57 ±3.26	13.02 -25.25
Serum ferritin (ng /ml)	4963.60 ±3580.39	913.00 -12000.00
Uterus size (mm)	27.35 ±9.98	18.00 -57.00
Ovary size (mm)	16.39 ±6.78	12.00 -36.00

Table 2: Correlation between Tanner staging and other variables

Parameter	r	P-value
Age	-0.035	0.854
Age of Diagnosis	-0.213	0.251
Transfusion frequency	-0.385	0.045
The dose of chelating agent	-0.098	0.599
Weight	0.395	0.028
Height	0.473	0.007
BMI	0.245	0.184
Serum ferritin	0.143	0.444
Uterus size	0.478	0.007
Uterus size	0.478	0.007

r: correlation

in Table 2. These results are consistent with the Sutay NR study in Australia (Sutay *et al.*, 2017) and De Sanctis V study in Indian (Sanctis *et al.*, 2013). Chronic blood transfusions are the essential cause of iron overload in B- major thalassemia leads to iron accumulation in gonadotrophic cells result in the failure of gonadotrophin production. The small size of uterus and ovaries resulted from hypogonadotropic hypogonadism or from iron deposition in both ovaries, which lead to pubertal failure. This fact One unit of blood transfused includes about 250 mg of iron. 25 units of blood transfused to the patient per year lead to accumulating 5 grams of iron per year without chelating therapy. The iron deposition and oxidative damage by free radicals damaged the pituitary and ovarian follicles, resulting in dysfunction of the hypothalamic-pituitary-gonadal axis result in pubertal failure.

No significant relation was found between the level of serum ferritin and Tanner stage (P=0.444). Shown in Table 2. Because of inflammation falsely increase serum ferritin or because of the relation between body iron and level of serum ferritin is not always within the linear range, especially in the condition of inflammation or tissue damage. So that serum ferritin level is not an adequate measure of total iron stores in patients with thalassemia major, therefore; we needed another indicator to measure iron stores in patients with thalassemia major such as the liver iron concentration, this result correlates with Adamkiewicz study (Adamkiewicz *et al.*, 2009).

CONCLUSIONS

In summary, in the current study, we tried to clarify the association between tanner stages retardation and overload of iron in female patients diagnosed as β- major thalassemia. The results showed that no significant correlation between tanner stages retardation and iron accumulated in female patients with β- major thalassemia measured by serum ferritin. Because of inflammation falsely increase serum ferritin or because of the relation between body iron and level of serum ferritin is not always within the linear range, especially in the condition of inflammation or tissue damage. So that serum ferritin level is not an adequate measure of iron stores in

patients with β- major thalassemia; therefore, we needed another indicator to measure iron deposit in patients with β- major thalassemia such as the liver iron concentration.

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