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Prevalence of gynecomastia in blood transfusion beta thalassemia major adolescent boys

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The aim of our study is to evaluate the prevalence of gynecomastia among patients with thalassemia major compared to control subjects. 90 patients, aged 10-18 years, with thalassaemia were randomly selected for the presence of gynecomastia. 90 subjects age mathched selected randomly from normal population served as controls. Considering the breast stage, in thalassemia major group, 76.1% had stage 1 of gynecomastia and 20.7% and 3.3% had stage 2 and stage 3 respectively. In control group 75.8% had stage 1 and 20.9% and 3.3% had stage 2 and stage 3 of gynecomastia, respectively. Biochemical evaluation and hormonal evaluation were performed in all patients and controls. Data were analysed by Student t-test, Mann-Whitney test and Chi-square test using SPSS software. Laboratory findings revealed that biochemical blood tests of the patients were within normal except liver enzymes that were higher than normal range. Overall, in the patients group, mean estrogen level was 17.3 ± 13.9 pg/ml, mean testosterone level was 180 ± 317 ng/dL and mean dehydroepiandrosterone sulfate level was 47.9 ± 42 µg/dL. The serum levels of these hormones in patients and controls with gynecomastia were not statistically different (P value = 0.969).
Conclusion: Our study shows that gynecomastia does not seems to be more prevalent in patients with thalassemia major.

Key words: Gynecomastia, Thalassemia major, Testosterone, Estrogens.

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Introduction

Thalassemia major (TM) is an inherited autosomal recessive hemoglobinpathy that make the patient dependent to regular blood transfusion therapy for survival. Regular transfusion therapy to maintain hemoglobin level of at least 9 to 10 g per decilitre improves growth and development and reduce hepatosplenomegaly (1).
On other side multiple blood transfusions increase the body iron content that is toxic to cells and organs.Iron overload causes most of mortality and morbidity associated with thalassemia major. Iron deposition in various organs like gonads, reticuloendothelial systems, endocrine glands (2, 3) and heart causes tissue injury and at last organ dysfunction (4).
Heart failure due to iron overload is still the primary cause of death in thalassemia major patients (5, 6).
In one study performed in 220 thalassemia major patients in Tehran, 80.8% of boys and 72.6% of girls had impaired puberty or hypogonadism (7).
Since estrogens stimulate proliferation of breast tissue whereas androgens antagonize these effects, gynecomastia is observed as a result of an imbalance between these hormones (8).
Therefore we evaluate the hypothesis that gynecomastia is more common among thalassemia major adolescent boys than normal population in Shiraz, Southern Iran.

Materials and methods

This cross sectional case-control study was performed from May 2009 to January 2011 in Shiraz, Southern Iran. The study was approved by the *Ethical Committee of Medical Sciences of Shiraz University*.
90 patients were randomly selected from 10 to 18 years old thalassemia patients, who were referred to the hospital for blood transfusion. After obtaining written consent, medical history containing frequency of blood transfusion, chelation therapy and history of drugs, were taken to ensure that non of the patients were not on hormone replacement therapy.
The physical examination including evaluation of breast stage was performed.Breast staging were evaluated using Marshal-Tanner criteria (9) for breast staging as following:

- ***Stage 1:*** Preadolescent; only papillae are elevated.
- ***Stage 2:*** Breast bud and papilla are elevated and a small mount is present; areola diameter is enlarged.
- ***Stage 3:*** Further enlargement of breast mound; increased palpable glandular tissue.
- ***Stage 4:*** Areola and papilla are elevated to form a second mound above the level of the rest of the breast.
- ***Stage 5:*** Adult mature breast; recession of areola to the mound of breast tissue, rounding of the breast mound, and projection of only the papilla is evident.

Biochemical evaluations such as BUN, Creatinin, Calcium, Phosphorus and Liver function test (*ELexis, Roche, Germany*) and hormonal evaluation such as estrogen, testosterone and dehydroepiandrosterone sulfate were performed by electrochemiluminescence technique for all the participants.
90 healthy subjects with matched age were selected from normal population and were evaluated for breast stage and pubic hair stage.
Data were analysed by Student t-test, Mann-Whitney test and Chi-square test using SPSS software. P value less than 0.05 was considered significant.

Results

The mean age of patients and control group were 14.8 (standard deviation: 2.3) and 14.9 (standard deviation: 2.6) years old, respectively.
The mean age of starting blood transfusion was 1.2 years old (minimum: 2 months old, maximum: 6.5 years old). The mean age of iron chelation therapy was 2.8 years old (minimum: 1.3 years old, maximum: 7 years old).
Laboratory data showed that mean hemoglobin of patients was 9.5 gr/dl (min: 8, max: 10.5). Mean serum ferritin of case group was 1950 ± 779 ng/ml, during the study.
Laboratory results revealed that biochemical blood tests of the patients were within normal except liver enzymes that were higher than normal range.
The proportion of patients with thalassemia major and healthy subjects were compared in different

Table 1.

Comparison of serum ALT level between patients with beta thalassemia major and healthy controls in different Tanner's stages.

ALT level Breast stages	10-<40 IU/L Number	40-<60 IU/L Number	60-<100 IU/L Number	≥ 100 IU/L Number	P- value
Stage 1					
Patients n = 70	10	15	25	20	< 0.0001
Controls n = 68	40	26	2	0	
Stage 2					
Patients n = 18	2	3	9	4	< 0.0003
Controls n = 19	13	5	1	0	
Stage 3					
Patients n = 2	0	0	2	0	*
Controls n = 3	3	0	0	0	

No patient belonged to breast stages 4 or 5.

* Statistical analysis was not possible in stage 3 due to small sample size.

Figure 1.

Comparing the percentage of different breast stages in beta thalassemia major patients and normal subjects.

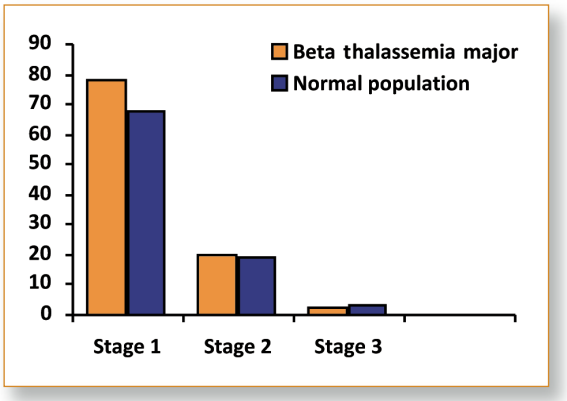

Table 2.

Comparison of the mean tesostrone, dehydroepiandrosterone sulfate, and estrogen levels between patients with beta thalassemia major and healthy controls in different Tanner's stages.

	Testosterone level (ng/dL)	P value	DHEA level (μg/dL)	P value	Estrogen level (pg/mL)	P value
Stage 1						
Reference Range	7-20		< 15-120		Undetectible-13	
Patients n = 70	8 ± 3.5	0.056	38.6 ± 15.3	0.071	11.3 ± 5.6	0,17
Controls n = 68	9 ± 2.5		42.9 ± 12.4		10.2 ± 3.5	
Stage 2						
Reference Range	8-66		< 15-333		Undetectable-16	
Patients n = 18	45.4 ± 15.3	0.282	45 ± 12.3	0.608	15.3 ± 4.5	0.274
Controls n = 19	50.4 ± 12.5		47.3 ± 14.6		13.5 ± 5.3	
Stage 3						
Reference Range	26-800		< 15-312		Undetectable-26	
Patients n = 2	486 ± 220	0.857	60.1 ± 14.5	0.675	25.3 ± 3.5	0.515
Controls n = 3	520 ± 230		65.2 ± 10.7		23.2 ± 3.4	

serum alanine transaminase (ALT) levels and in different breast stages, which showed a significantly higher ALT level in patients than controls in stage 1 and 2 (Table 1, P value < 0.0001).

Considering the breast stage, in thalassemia major group, 70 patients (77.7%) had stage 1 of gynecomastia and 18 (20.0%) and 2 (2.3%) had stage 2 and stage 3 respectively.In control group 68 subjects (75.5%) had stage 1 and 19 (21.1%) and 3 (3.3%) had stage 2 and stage 3 of gynecomastia, respectively. No significant difference was found in breast stages between thalassemia major patients and controls (P value: 0.969) (Figure 1).

Overall, in the patients group, mean estrogen level was 17.3 ± 13.9 pg/ml, mean testosterone level was 180 ± 317 ng/dL, and mean DHEAS level was 47.9 ± 42 μg/dL.

Comparisons of the mean serum levels of testosterone, dehydroepiandrosterone sulfate and estrogen were evaluated between patients with beta thalassemia major and healthy controls in different Tanner's stages (Table 2).

In different Tanner´s stages, testosterone level and DHEAS level were lower in patients than controls; however, it was not statistically significant (P > 0.05). Also estrogen level in patients was higher than controls in each stage, but it was not statistically significant (P > 0.05).

All mean values in patients group were in the normal range.

Discussion

The present study, being the so far only prospective investigation in the literature revealed that the risk of gynecomastia is not higher in thalassemia major patients compared with control group. Despite the fact that testosterone level and DHEAS level was lower in majority of thalassemia major patients the prevalence of gynecomastia does not differ significantly between thalassemia major patients and normal population. Estrogen level was also in normal range in thalassemia major patients compared to normal population.

Normally the adult testes secrete approximately 15 percent of the estradiol and less than 5 percent of the estrone in the circulation, whereas 85 percent of the estradiol and over 95 percent of the estrone are produced in extragonadal tissues through the aromatization of precursors. The

principal precursor of estradiol is testosterone, 95 percent of which is derived from the testes. Androstenedione, an androgen secreted primarily by the adrenal gland, serves as a precursor of estrone formation.

The important extraglandular sites of aromatization are adipose tissue, liver, and muscle. In addition, a substantial degree of interconversion between estrone and estradiol takes place through the action of the widely distributed enzyme 17-ketosteroid reductase, which also catalyzes the conversion of androstenedione to testosterone. Since testosterone synthesis is decreased in testes, it leads to a decrement in formation of estrogen in the body, it can inhibit the development of gynecomastia in thalassemia major patients (10-12).

On the other hand, it is well known that liver disease increase the prevalence of gynecomastia due to aromatization of testosterone to estrogen. In our study we detected significantly higher liver enzymes in patients than controls. With regard to testosterone level we detected a lower level of testosterone in patients than controls which was not statistically significant. This may be a reason of why the prevalence of gynecomastia was not significantly higher in the case group comparing to control group. However, futher and larger studies are needed to elucidate these results.

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