Assessment of Gonadal and Thyroid Function for Adult Transfusion- Dependent- β- Thalassemic Patients in Palestine

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Abstract

β-thalassemia is an inherited hemoglobin disorder. It is considered as a health problem in Palestine thus, premarital screening for thalassemia became compulsory. The aim of this study was to determine the prevalence and risk factors for hypogonadism and hypothyroidism among Palestinian transfusion-dependent β-thalassemic patients. Across-sectional study was conducted in 2010-2011 which involved β-thalassemic patients in four Palestinian districts. Sixty one adult (>14 yr) patients, 30 cases and 31 healthy controls, were tested for gonadal and thyroid function tests, the first included free testosterone, estradiol, leutinizing hormone (LH) and follicular-stimulating hormone (FSH) while the latter included thyroid-stimulating hormone (TSH), free T3 and free T4.

The prevalence of hypogonadism in the case group was 47% compared to 9.6% in the control group which is statistically significant ($p<0.005$). None of the subjects in the case group suffered from overt hypothyroidism except for two subclinical cases (6.7%) while the control group was completely free from hypothyroidism. The thalassemic patients are significantly shorter and lighter than the controls ($P<0.05$). The mean hemoglobin level in the case group (8.1 (1.1) g/dl) is significantly lower than a normal cut-off value of 12 g/dl. The mean ferritin level (4260 ng/ml) is significantly higher than the upper limit (282ng/ml). About 47% of the case group is not on chelation therapy and 53% are splenectomized. However, Splenectomy and chelation therapy had no statistical association with hypogonadism ($P>0.05$).The high rate of hypogonadism and related disturbances reveal the insufficient healthcare the patients are receiving. This puts forward the priority for a close and continuous follow-up for thalassemic patients in Palestine.

Keywords: β-thalassemia, Hypogonadism, hypothyroidism, Palestine.

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Introduction

β-thalassemia is an inherited genetic disorder characterized by inadequate/or complete absence of globin chain synthesis, leading to severe anemia and chronic disease in adulthood.[1] Treatment with regular blood transfusion and chelating therapy has considerably prolonged survival in thalassemic patients.[2] However, prolonged transfusion therapy leads to iron overload in tissues, which is themain cause of morbidity and mortality in

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patients on regular transfusion.[3]

There is a high incidence of endocrine disorders in children, adolescents and young adults with thalassemia major. Aydinok*et al*., had showed that 59.5% of thalassemic patients had at least one endocrine abnormality.[4] The endocrine complications include hypogonadism and short stature (the most frequent), followed by hypothyroidism, hypoparathyroidism, diabetes mellitus, and osteoporosis.[5,6] The prevalence of hypogonadism, delayed puberty and short stature in thalassemic patients ranges from 18%-77% in different thalassaemic populations, with no or slight differences between boys and girls.[4, 6-11] Subclinical and/or compensated hypothyrodisim were reported to be between 16-43% in different thalassemic populations of ≥ 10 years old.[4, 9]

The main risk factor for endocrine abnormalities in thalassemic patients is iron overload. However, several studies found different relationships between serum ferritin levels and endocrine disorders.[12- 15] Although the severity of endocrine disorder is significantly related to iron overload, other risk factors may also play a role.[11]

In Palestine, a surveyamong university students in the West Bank suggested a carrier frequency of 3–4%[16]. Official figures from the Thalassemia Patients' Friends Society (TPFS) in Palestine put the numbers of patients with β-thalassemi major or intermediaat around500 patients in the West Bank and 300 in the Gaza Strip (personal communication). An increase in the lifespan of patients with *β*-thalassemia was observed during the last two decades, due to improved medical care and the health awareness of the patients and their families. However, no data were available on the prevalence of endocrine disorders among the Palestinian β-thalassemic patients.

This cross sectional study aimed to determine the prevalence and identify risk factors for hypogonadism and hypothyroidism among adult transfusion-dependent β-thalassemic Palestinian patients.

Materials and Methods

Patientsand controls

Transfusion-dependent patients with β-thalassemia were randomly selected from 4 Palestinian districts, Al-Khalil, Ariha (Jericho), Ramallah and Jenin. Selected patients were above 14 years old and had not been transfused for the last 2 weeks. Thirty patients met these criteria and were enrolled in the study. Parallel to the patient group, 31 healthy individuals were randomly selected from the Palestinian population as a control group. Both groups were matched for sex, age group and geographical distribution.

All participants were interviewed, a questionnaire was filled, anthropometric measurements were taken and blood samples collected as described below. The questionnaire included demographic data, age, sex, address and clinical history, including age at first transfusion, frequency of transfusion, chelation therapy, last three readings of hemoglobin and ferritin levels, menstruation status and hormone therapy. In addition thepatients' medical files were reviewed and compared with interview data.

The study was approved by TPFSethics committee, and informed consent was obtained from each participant.

Anthropometric measurements

Anthropometric measurements, height and weight, were taken for cases and controls. Weight was measured in light clothing and without shoes to the nearest 100 grm using digital scale (Medel crystal-Italy); height was measured (with subjects shoeless) to the nearest 0.1 cm using a drop-down measuring tape. The weight and height for each subject were taken by two health professionals to ensure reliability. Height measuring and weighing tools were calibrated prior to each single measurement by using a standard 5 kg weight; 5 (0.1) and a 100-cm long ruler; 100 (0.1).

Gonadal and thyroid profiles

Three blood samples were collected from fasting participants at 30 minute-intervals starting from 8:00 am. Sera were directly separated, equally-pooled and stored at -80 °C till analyzed as one batch. The gonadal profile included tests for follicle-stimulating hormone (FSH), luteinizing hormone(LH) and estradiol (E2) for females, and free testosterone for males. Free testosterone was preferred over total testosterone as the latter may be erroneous in cases like hypothyroidism and acromegaly. Hypogonadotropic (secondary) hypogonadism was defined a slow or inappropriately normal LH and FSH levels, with low estradiol concentration in females and low testosterone concentration in males. Thyroid function was assessed by Free T3, Free T4 and thyroid-stimulating hormone (TSH). Primary overt hypothyroidism was defined as low FT4levels and elevated TSH, but when FT4 and FT3 are normal with increased TSH; its defined as primary subclinical hypothyroidism.

Microparticle enzyme immunoassay (MEIA; Abbott AxSYM, Abbott Laboratories. Abbott Park, Illinois, U.S.A) was used to measure serum LH, FSH, FT3, FT4, TSH, and estradiol. Free testosterone was measured by radioimmunoassay (RIA) from Beckman Coulter using gamma counter (Wallac wizard 1470).

Statistical analysis

Data is presented as means with standard deviation(SD). Differences between means of groups were compared using the non-parametric Mann–Whitney test. Correlations between parameters were determined by the non-parametric Spearman's rank correlation coefficient. Wilcox on signed rank was used for comparison of values against a hypothetical median. Fischer's exact test was used to test for association. Two-tailed p-values of less than 0.05 were considered significant. All statistics were calculated using GraphPad Prism version 5.0 for Windows, GraphPad Software, San Diego California USA (trial version) and EpiInfo version 3.4.3 (software developed at the Centers for Disease Control and Prevention (CDC) Atlanta, GA, USA) for frequencies, distributions and other descriptive statistics.

Results

Demography and anthropometry of study population

A total of 61 individuals, 30 transfusion-dependent thalassemia patients and 31 healthy human controls were enrolled in the study. The demographic data are summarized in Table 1. The demography in both groups, cases and controls, is comparable.

Table 1. Demographic and anthropometric parameters for study subject, (mean (SD))

	Cases	Controls	P-value	Significance (P<0.05)
Age (yr)	20.5 (7.5)	19.8 (6.7)	--	--
Sex				
Male	17	17	--	--
Female	13	14	--	--
Height (cm)	157.7 (10.2)	167.5 (9.5)	0.0042	S
Weight (kg)	49.7(10.3)	62.2 (13.8)	0.0005	S

S: significant

As shown in the table 1, the mean height of the thalassemia patients (case group), 157.7 cm is significantly shorter than that of the control group, 167.5 (P<0.005). Also, the mean weight of the case group participants, 49.7 kg, is significantly lower that of the control group, 62.2 kg (P<0.005). Statistical significance in height and weight between males of the two groups and females of the same groups was also seen (P<0.005).

Table 2. Laboratory findings for gonadal and thyroid profiles in case and control groups (mean (SD))

	Unit	Case (n=30)	Control (n=31)	P-value (2-tailed)	Significance (P<0.05)
Gonadal profile					
FSH (both)	mIU/ml	4.2 (3.5)	4.8 (2.1)	0.123	NS
LH (both)	mIU/ml	4.1 (4.0)	3.5 (5.8)	0.049	S
E2 (females)	pg/ml	49.8 (57.9)	116.5 (85.7)	0.015	S
free	pg/ml	5.6 (5.9)	16.1 (5.3)	0.0001	S
Testosterone (males)					
Thyroid profile					
TSH	mIU/ml	3.1 (1.6)	1.8 (0.6)	0.0002	S
FT3	pg/ml	2.3 (0.4)	2.6 (0.3)	0.005	S
FT4	ng/ml	0.9 (0.1)	1.05 (0.1)	0.0024	S

NS: Not Significant, S: significant

Laboratory findings: Hypogonadism and hypothyroidism

The laboratory findings for both gonadal and thyroid profiles are shown in table 2 based on comparison between thalassemia cases and healthy controls. In the gonadal profile, FSH was not significantly different between cases and controls (P>0.05). Cases had significantly lower concentrations of estradiol and free testosterone than controls (P=0.01 and P= 0.0001, respectively), but nearly significantly higher for LH (P=0.04). As for the thyroid profile, both FT3 and FT4 are significantly lower in case group while TSH is significantly higher compared to control group. The incidence rate of Hypogonadism among cases was 47% (14/30) compared to 9.6% (3/31) among the healthy controls. Majority of the hypogonadism cases in both case and control groups were males (82%, 14/17). About 65% (11/17) of the hypogonadism cases in the case group were males. All hypogonadism cases

were of secondary type which is the hypothalamic-pituitary hypogonadism. Within the thalassemic group, no significant difference was found between mean ferritin levels in hypogonadism and non-hypogonadism cases (P>0.05). Also, the difference was not significant between ferritin levels and those of gonadal and thyroid profiles (P>0.05). No statistical significance was found between thalassemia patients suffering from hypogonadism and those non-hypogonadism patients in terms of height and weight (P>0.05).

On the other hand, neither cases nor controls showed any primary overt hypothyroidism based on test profile. Only two primary subclinical hypothyroidism cases among thalassemia patients were found which showed increased TSH levels and normal levels of FT3 and FT4.

Table 3. Clinical history parameters for case group subjects (mean (SD))

	Cases (n=30)	Cut-off	P-value	Significance (P<0.05)
Blood transfusion				
Age at starting transfusion (yr)**	0.4 (0.3)*	--	--	--
Frequency, %				
2 per month	23	--	--	--
1 per month	50	--	--	--
Hb (g/dl)	8.1 (1.1)	12	0.0001	S
Chelation therapy				
Patients on therapy, %	53			
Age at starting therapy***	8.1 (6.2)	--	--	--
Ferritin (ng/ml)	4260 (2236)	282	0.0001	S
Others				
Lack of menses/menarche,%	30			
Hormone therapy, %	10	--	--	--
Diabetes mellitus	0	0	--	--
Splenectomy, %	50	--	--	--

* Calculations did not include the five patients who started at 6 years or more.
** Date of birth - date of starting transfusion
***Age at diagnosis- Age at starting therapy

Clinical history of case group

As shown in table 3, half of the patients in the case group are transfused once a month and 23% are transfused twice a month. Twenty-five patients started blood transfusion in the first year of life (0.4 (0.3)) and five started transfusion when they were 6 years old or more. The mean hemoglobin level is significantly lower than the hypothetical normal cut-off value (12 g/dl). Approximately half of these patients are not on chelating therapy and even those who are (47%) started at a late age, mean 8.15 (6.2) years. The mean Ferritin level, the main indicator for monitoring chelating therapy, was significantly higher than the cut-off value which is the upper limit of the ferritin normal range (6.9-282 ng/ml).

Of the 13 female patients, 3 had absence of menarche (30%) and have not experienced any

menstrual cycle despite being above 16 years old. Two of the three adult females had zero concentration of estradiol. Three out of 30 in the case group were receiving hormone replacement therapy, one was receiving growth hormone therapy and two were receiving testosterone supplements. In the case group 50% has had the spleen removed and over half were on iron chelating therapy: neither splenectomy nor chelating therapy had any association with hypogonadism (P>0.05). None of the thalassemic patients, or the control group, suffered from diabetes mellitus.

Discussion

In this study, hypogonadtrophic hypogonadism (HH) or secondary hypogonadism related to the hypothalamus and pituitary glands was 47% among Palestinian patients, compared to 9.6% in the control group. This agrees with the literature in which HH in thalassaemia ranges from 40 to 72%.[6,9,11,17,18] Adult females present hypogonadism in the form of total absence of spontaneous menarche (primary amenorrhea): this applied to30% of female participants with thalassaemia, as confirmed by the total absence of estradiol (0.0 pg/ml), while the other form is lack or irregular menses (secondary amenorrhea). Hypogonadism can be in the form of sexual infantilism in males: this applied to65% of male participants with thalassaemia which is in agreement with a study[17], but in disagreement with another[19]. In this study, we found high ferritin levels in our patients with hypogonadism and women with secondary amenorrhea compared to the other patients, supporting the implication of iron overload as one of the main causes which progressively damages the pituitary gland and the hypothalamus[20, 21]. The mean hemoglobin level of 8.1 g/dl is also considerably below the recommended range of 12 g/dl for females and 13 g/dl for males[22]. Our results showed inadequate, irregular and late initiation as well as poor compliance to chelation therapy which, subsequently, resulted in increased iron overload reflected by high levels of serum ferritin. Despite significantly high levels of ferritin among case group patients, yet of these only46% suffered from hypogonadism with no significant difference between serum ferritin level and development of hypogonadism (P> 0.05). Although hypogonadism is the most encountered endocrinopathy among thalassemic patients, still, the relationship between ferritin level and hypogonadism is controversial issue in which certain studies managed to establish association like that conducted by Vogiatzi et al. while others like Chern*et al*. did not find any statistically significant relationship between the two variables.[11, 18] One plausible explanation to the absence of relationship between extremely high ferritin levels and hypogonadism is the effect of age on serum ferritin. The older the patient the more prone to hypogonadism as a result of chronic iron overload.[18]In our case, serum ferritin seemed to be a poor predictor for hypogonadism in young-aged thalassemic patients. In this study, hypogonadism affected both sexes with higher percentage in males (82%) indicating that males are more prone to hypogonadism.

Another common complication was that thalassemic patients were found to be suffering from growth retardation - short stature and underweight compared to their normal healthy counterparts (P<0.05) which is an indication of poorly-transfused patients. This is in agreement with many studies such Najafipour*et al*., Mostafavi*et al*. and Aydinok*et al*. who found short stature in up to

91% of their patients.[4, 6,23] Underweight and short stature are due to growth retardation which is common in thalassemic patients. The growth retardation could be attributed to chronic anemia caused by inadequate transfusion, hypoxia, and other endocrine disorders which could be due to iron overload causing failure of puberty and consequent growth retardation.[6,24] Yet, there was no significant statistical relationship between hypogonadism and underweight and short stature ($P>0.05$).

Although hypothyroidism is the another common complication with a range from 0 to 19.4% and even to as high as 52%, the prevalence of subclinical hypothyroidism among Palestinian cases was 6.7% compared to zero cases in the control group.[25-27] FT3 and FT4 were significantly lower and TSH was significantly higher in the case group, suggesting a general tendency to hypothyroidism. These different reports could be due to targeting overt hypothyroidism and ignoring subclinical cases, and differences in the age groups studied. Hypothyroidism is affected by factors like chelation therapy protocol and type of chelating agent.[28] Also, frequency of transfusion therapy protocol with its subsequent iron overload is another risk factor of hypothyroidism. Again, and similar to hypogonadism, hypothyroidism has no significant relationship with ferritin level ($P>0.05$), thus ruling out increased ferritin level as a risk factor ($P<0.05$), which is in agreement with other studies like Shamshiraz*et al*.[29]

None of the subjects participating in the study, cases and controls, had any clinical history of diabetes mellitus (DM). The prevalence of DM ranges from 0% to 24% depending on factors like age, amount of transfused blood, level of ferritin, compliance to chelation therapy, family history of DM and impaired pubertal status.[7, 30-33]

In the absence of any genetic investigation and depending on early start of blood transfusion (0.4 (0.3) yr), about 83% (25/30) of cases were β-thalassemia major, whilethe remaining 5 cases were β-thalassemia intermedia as they started transfusion at later stage in life. Moreover, if the frequency of blood transfusion reflects the severity of case, then 23% (7/30) of the cases were severe as they are transfused twice a month and 50% (15/30) are transfused once a month, both of which are β-thalassemia major. The 5 β-thalassemia intermedia are less severe as their transfusion frequency ranges from once a month to once every three months. Despite the high frequency of blood transfusion, anaemia is still insufficiently corrected. Poor compliance with chelation therapy (47%) and the relatively late age at start of therapy (8.1 (6.2) yr) explain the iron overload, which is the main determinant of endocrinopathies and patient survival. Even those on chelation therapy face irregularities, mainly due to inaccessibility of iron chelating medications. Other causes include patients' discomfort and unpunctuality caused by lack of awareness of the consequences of not adhering to chelation therapy. Kidson-Gerber *et al*. mentioned that the use of oral chelation therapy increased rate of compliance.[1]

Finally, splenectomy was not established as a significant risk factor for hypogonadism despite the assumption that splenectomized patients are more vulnerable to endocrine gland damage resulting from exposure to free radicals. Also, this study showed that patients

with blood transfusion frequency of one month or less are not associated with splenectomy (P=0.05).

In conclusion, we recommend early (pre-pubertal), regular, accessible and affordable ironchelation therapy and a protocol for early detection and prevention of iron overload which leads to cell damage in various endocrine glands.

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تقييم وظائف الغدد التناسلية والغدة الدرقية لمرضى الثلاسيميا المعتمدون على نقل الدم في فلسطين

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الملخص

الثلاسيميا هو اضطراب الهيموغلوبين الموروثة. يعد هذا المرض مشكلة صحية في فلسطين وبالتالي أصبح الفحص قبل الزواج لمرض الثلاسيميا إلزامي. إن الهدف من هذه الدراسة هو تحديد عوامل انتشار ومخاطر قصور الغدد التناسلية والغدة الدرقية التي تعتمد على نقل الدم بين مرضى β-الثلاسيميا في فلسطين. أجريت دراسة مستعرضة في الفترة 2010-2011 التي شملت مرضى β-الثلاسيميا في أربع مناطق فلسطينية. تم اختبار ستين شخصا (< 14 سنة)، 30 حالة و31 من الأصحاء كعينة ضابطة، لاختبارات وظائف الغدد التناسلية وشملت هرمون التستوستيرون الحر، استراديول، هرمون (LH) وهرمون (FSH) في حين أن هرمونات الغدة الدرقية شملت (TSH)، T3 وT4 الحرة.

كان انتشار قصور الغدد التناسلية في المجموعة حالة 47٪ مقارنة مع 9.6٪ في مجموعة المراقبة التي هي ذات دلالة إحصائية (P<0.005). لم يعانِ أيا من حالات β-الثلاسيميا من ارتفاع الغدة الدرقية العلني باستثناء حالتين تحت- الإكلينيكي (6.7٪)، في حين كانت المجموعة الضابطة خالية تماما من الغدة الدرقية. مرضى β-الثلاسيميا أقصر بكثير وأخف وزنا من عناصر العينة الضابطة (P<0.05). مستوى معدل الهيموغلوبين في المجموعة البحثية (8.1 (1.1) غ/دل) هو أقل بدلالة إحصائية من قيمته في المجموعة الضابطة (12 غ/ دل). مستوى معدل الفيريتين (4260 نانوغرام/ مل) هو أعلى بكثير من الحد الأعلى (282 نانوغرام/مل). حوالي 47٪ من مجموعة البحثية لا يتناولون العلاج و53٪. قد أزالوا الطحال ومع ذلك، لم يكن لاستئصال الطحال والعلاج أي ارتباط إحصائي مع قصور الغدد التناسلية (P> 0.05). ارتفاع معدل قصور الغدد التناسلية والاضطرابات ذات الصلة تكشف عن عدم كفاية الرعاية الصحية للمرضى. هذا يضع قدما الأولوية لمتابعة مستمرة وحثيثة لمرضى β-الثلاسيميا في فلسطين.

الكلمات الدالة: β- الثلاسيميا، قصور الغدد التناسلية، قصور الغدة الدرقية، فلسطين.