

Endocrine and metabolic disorders in adult patients with thalassemia major

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Abstract

Aim: Iron overload in tissues, despite current chelation therapies, is a major cause of organ dysfunction and serious complications in thalassemia major. Similarly, iron accumulation in endocrine tissues pave the way for various endocrinopathies. Previous reports regarding prevalence of endocrinopathies in thalassemia major varies significantly based on study population. In this study, we aimed to investigate the metabolic and endocrine disorders among the transfusion-dependent adult thalassemia major patients.

Materials and Methods: Data from transfusion-dependent adult thalassemia major patients with regular follow-up were retrospectively evaluated. Former records of the patients were examined to evaluate endocrine disorders, on the basis of laboratory test results.

Results: A total of 76 patients with a median age of 28 years, composed of 39 (51.3%) female and 37 (48.7%) male patients were included. Out of the entire cohort, 36.8% (n=28) had hypogonadism, 30.3% (n=23) had thyroid dysfunction, 28.9% (n=22) had a glucose metabolism disorder and 7.9% (n=6) had hypoparathyroidism. Hypogonadism was encountered in 38.5% (n=15) of females and in 35.1% (n=13) of males. Only one patient from each gender had hypergonadotropic hypogonadism, possibly related to iron overload, while the rest had hypogonadotropic hypogonadism. A positive history of delayed puberty was noted in 30.8% (n=12) of females and 24.3% (n=9) of males. Of the patients, 30.3% (n=23) had one, 18.4% (n=14) had 2, 10.5% (n=8) had 3, and 1.3% (n=1) had 4 different endocrine dysfunctions. Accordingly, 61.5% of the patients had at least one endocrine dysfunction while only 39.5% (n=30) had no endocrine dysfunction at all.

Conclusion: Survival time has been prolonged in patients with thalassemia major by virtue of effective transfusion and chelation therapies. As a consequence of prolonged survival, endocrine dysfunctions commonly strike adult thalassemia major patients, therefore, endocrine functions need to be evaluated at regular intervals during follow-up.

Keywords: Endocrinopathies; thalassemia major, Iron overload

INTRODUCTION

Thalassemia major, a chronic hereditary disease manifesting with hemolysis, is a cause of significant morbidity and mortality. Blood transfusions constitute an essential part of treatment. As a result of effective transfusions and improved quality of care, patients now pursue a longer survival (1,2). In turn, patients with thalassemia major are facing other concerns in the long-term, one of which is the iron accumulation due to the repetitive blood transfusions, despite chelation therapies. Iron accumulation in respective tissues causes serious complications such as heart failure, arrhythmias, infections and chronic liver disease (1,3,4).

Endocrine tissues and organs are also susceptible to iron

overload, which gives rise to various endocrinopathies such as hypogonadism, hypothyroidism and diabetes mellitus (DM) (5).

Endocrine dysfunctions are capable of ending up with severe morbidities and an inferior quality of life. There have been past research in this field so far reporting various figures for the prevalence of endocrinopathies; which were carried out on heterogeneous patient groups comprised of children, adolescents, and adults (5-8). In this study, we aimed to evaluate the prevalence of metabolic and endocrine disorders in a homogeneous group of transfusion-dependent adult thalassemia major patients and to assess the clinical characteristics of patients with endocrine dysfunctions.

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MATERIAL and METHODS

Patient selection

This study was conducted in concordance with the Declaration of Helsinki ethical guidelines and permission to use the relevant data in the study was granted by the hospital management. All transfusion-dependent adult thalassemia major patients who have been followed up regularly by the Department of Endocrinology and Metabolic Diseases of Akdeniz University Faculty of Medicine were included in the study.

Data acquisition

Demographic, biochemical and hormonal data of the patients were analyzed retrospectively. Viral serology (hepatitis B and hepatitis C) and presence of hepatomegaly and splenomegaly were recorded. Ongoing medical treatments, ongoing chelation therapies, intervals and annual amounts of transfusion, ferritin levels, hepatic and myocardial iron content as estimated by T2-weighted magnetic resonance imaging (MRI) were included. Hepatic and myocardial iron content was classified as either normal or as increased; patients with an elevated hepatic or myocardial iron content were considered to have iron overload.

Patient records were examined to evaluate metabolic and endocrine function on the basis of biochemical and hormonal test results. Glucose levels, and oral glucose tolerance test (OGTT) results, if available, were examined. Glucose metabolism disorders were diagnosed based on the recommendations of American Diabetes Association. Accordingly, patients with fasting blood glucose level < 100 mg/dL were considered to have a normal glucose metabolism. Patients with with fasting blood glucose level \geq 126 mg/dL or with random blood glucose level >200 mg/dL were considered to have DM. Based on OGTT results, corresponding patients were classified into one of the three groups: impaired fasting glucose (IFG) if fasting blood glucose level is within the range of 100-125 mg/dL, impaired glucose tolerance (IGT) if 2-hour glucose level is within the range of 140-199 mg/dL, and DM if their 2-hour glucose level is \geq 200 mg/dL (9). Hemoglobin A1c (HbA1c) was not used as diagnostic criteria, due to the fact that hemoglobin variants may affect HbA1c measurements (9). Based on past thyroid function test results and medication history, patients were classified as euthyroid, subclinical hypothyroidism, primary hypothyroidism or secondary hypothyroidism. Data on calcium, phosphorus, albumin, 25-hydroxy vitamin D, and parathyroid hormone (PTH) levels were analyzed to record whether patients have hypoparathyroidism or vitamin D deficiency. Delayed puberty was also based on medical records. Delayed puberty was defined as the absence of breast development up to the age of 13, incomplete puberty within 4 years after the onset of breast development, or no menstrual bleeding until the age of 16 in women (10). In men, delayed puberty was defined as no testicular growth up to 14 years of age or incomplete pubertal development within 5 years after testicular growth (10). For female patients, status of primary or secondary amenorrhea and

its etiology was recorded. In terms of gonadal functions, patients were classified into the subgroups of normal gonadal function, hypogonadotropic hypogonadism or hypergonadotropic hypogonadism. Basal growth hormone (GH) and insulin like growth factor-1 (IGF-1) levels were evaluated to determine whether there was a growth hormone deficiency. Likewise, adrenal insufficiency was inquired through basal hormonal tests on hypothalamic-pituitary-adrenal (HPA) axis and, if available, data on cortisol response to stimulation tests. Adrenal insufficiency was ruled out in patients with a basal cortisol level of 13 μ g/dL or higher (11). Dual-energy x-ray absorptiometry (DXA) results were reviewed for bone loss. Patients with a femoral neck, total femur or total vertebra Z-score below -2 were accepted to have a "low bone mass for chronological age" (12).

Statistical method

Data were analyzed using the SPSS version 17.0. Distribution of continuous variables and frequency of categorical variables was analyzed. Continuous variables were presented as median (minimum-maximum) and categorical variables as frequency and percentage. To investigate the relationships between categorical variables, Chi-square tests were used. Mann-Whitney-U tests were applied to analyze the relationships between continuous variables. A value of $p \leq 0.05$ was accepted as statistically significant.

RESULTS

Demographic data

A total of 76 patients with a median age of 28 composed of 39 (51.3%) female and 37 (48.7%) patients were included. Demographic features and key thalassemia major characteristics of the included patients are given in Table 1.

Out of entire cohort, 36.8% (n=28) had hypogonadism, 30.3% (n=23) had thyroid dysfunction, 28.9% (n=22) had a glucose metabolism disorder, and 7.9% (n=6) had hypoparathyroidism (Table 2). Hypogonadism was encountered in 38.5% (n=15) of female and in 35.1% (n=13) of male patients, respectively. One male and one female patient had hypergonadotropic hypogonadism, while the rest had hypogonadotropic hypogonadism. A positive history of delayed puberty was noted in 30.8% (n=12) of females and 24.3% (n=9) of males (Table 2).

50% (n=38) of all patients had undergone DXA measurements; and 80.8% of these patients had low bone mass for chronological age at either lumbar spine or femoral neck (Table 2). Of these patients, a low bone mass for chronological age was detected only at the lumbar spine in 34.2% (n=13), only at femoral neck in 5.3% (n=2) and both at lumbar spine and femoral neck in 60.5% (n=23).

None of the patients had fully-documented adrenal insufficiency or GH deficiency. In 71.1% (n=54) of the patients, basal cortisol levels were high enough to rule out adrenal insufficiency.

In the remaining patients, basal cortisol levels were either unavailable or did not suffice to definitely rule out a possible adrenal insufficiency, with no stimulation test performed. IGF-1 levels were normal in 59.2% of the patients (n=45) and were low in 21.1% of the patients (n=16) and unavailable in 19.7% (n=15). A stimulation test to search for GH deficiency was not carried out on the patients either in childhood or in adulthood.

Table 1. Demographic features and key thalassemia major characteristics of the patients

Age (median (minimum-maximum))	28 (18-58)
Gender	
Female (n,%)	39 (51.3)
Male (n,%)	37 (48.7)
Transfusion interval (days)	15 (7-30)
Annual amount of transfusion (units)	48 (12-96)
Organomegaly	
Hepatomegaly n (%)	51 (67.1)
Splenomegaly n (%)	19 (25)
Splenectomy n (%)	44 (57.9)
Unknown n (%)	6 (7.9)
Chelation regimen	
Deferasirox n (%)	35 (46.1)
Deferoxamine n (%)	12 (15.8)
Deferasirox and deferoxamine n (%)	19 (25)
Unknown n (%)	10 (13.2)
Viral hepatitis serology	
HCV positive n (%)	15 (19.7)
HBV positive n (%)	2 (2.6)
Iron content	
Normal n (%)	22 (28.9)
Increased n (%)	54 (71.1)
Hepatic iron accumulation	
Normal n (%)	26 (34.2)
Overload n (%)	50 (65.8)
Cardiac iron accumulation	
Normal n (%)	51 (67.1)
Overload n (%)	25 (32.9)
Ferritin (ng/mL)	2669 (455-12940)

Of all patients included in this study, 30.3% (n=23) had 1, 18.4% (n=14) had 2, 10.5% (n=8) had 3, and 1.3% (n=1) had 4 endocrine dysfunctions. Accordingly, 61.5% of the patients had at least one endocrine dysfunction while only 39.5% (n=30) had no endocrine dysfunction at all (Table 3).

Effect of age and sex on endocrinopathies

Males had a higher rate of low femoral bone mass for chronological age (68.2% vs 40%, p=0.05). Similarly, the ratio of males (82.4%) with a low bone mass for chronological age in both femur neck and lumbar spine was higher compared to females (47.4%) (p=0.032).

Table 2. Metabolic and endocrine functions of the patients

Metabolic and endocrine function	n (%)
Glucose metabolism	
Normal	54 (71.1)
DM	12 (15.8)
IFG	5 (6.6)
IFG + IGT	5 (6.6)
Thyroid functions	
Euthyroid	53 (69.7)
Hypothyroidism	23 (30.3)
Primary hypothyroidism	12 (15.8)
Secondary hypothyroidism	6 (7.9)
Subclinical hypothyroidism	5 (6.6)
Gonadal functions	
Normal	48 (63.2)
Hypogonadism	28 (36.8)
Hypogonadotropic hypogonadism	26 (34.2)
Hypergonadotropic hypogonadism	2 (2.6)
Delayed puberty	21 (27.6)
Secondary amenorrhea*	8 (20.5)
Primary amenorrhea*	6 (15.3)
Hypoparathyroidism	
None	70 (92.1)
Yes	6 (7.9)
Vitamin D deficiency	
None	11 (14.5)
Yes	65 (85.5)
DXA	
Low bone mass for chronological age	38 (50)
Normal bone mass for chronological age	9 (11.8)
Unevaluated	29 (38.2)
*In females	

Table 3. Number of endocrine dysfunction(s) found out in patients

Number of Endocrine dysfunction(s)	n (%)
0	30 (39.5)
1	23 (30.3)
2	14 (18.4)
3	8 (10.5)
4	1 (1.3)

Patients with hypogonadism were older than the patients with normal gonadal function (31 vs 24, respectively, p=0.026). Likewise, patients with thyroid dysfunction were older than patients with normal thyroid function (31 vs 25, respectively, p=0.027). Patients with at least one endocrinopathy were, in a similar manner, was older than the patients without endocrinopathies (31 vs 22,

respectively, $p=0.004$). No effect of gender was found on the frequency of endocrine dysfunction(s).

Among the individuals with iron overload, a low bone mass for chronological age in femur neck and in femur neck and lumbar spine together was more common (63.6% vs 28.6% and 76.9% vs 30%, $p=0.029$ and $p=0.013$, respectively). Furthermore, individuals with an iron overload also had a significantly higher rate of a glucose metabolism impairment (81.3% and 37.5%, $p=0.047$).

Mean ferritin level in patients with delayed puberty was significantly higher than that of the patients with no history of delayed puberty (2901 ± 391 ng/mL vs 2581 ± 378 ng/mL, $p=0.03$). Similarly, mean ferritin level in patients with hypogonadism was significantly higher than that of the patients with normal gonadal functions (3397 ± 391 ng/mL vs 2244 ± 378 ng/mL, $p=0.03$).

Endocrine dysfunctions were encountered more frequently in patients who had undergone splenectomy in comparison to those with no splenectomy (72.7 vs 34.6%, $p=0.001$). However, we failed to show any relationship, between endocrinopathies and duration and/or intensity of transfusion and chelation therapies.

DISCUSSION

Iron accumulation is a substantial problem in transfusion-dependent adult thalassemia major patients. As a result, endocrine and metabolic disorders are common, but past research reports various prevalence figures. A key factor in the variability of reported prevalence is the difference among patient groups included in various studies. Pediatric, adolescent and adult patients were included together in a substantial portion of the conducted studies (5,8,13-15). In our study, however, a homogenous group of adult transfusion-dependent adult thalassemia major patients were included and analyzed.

In our cohort, a majority of the patients had at least one endocrine dysfunction; only 39.5% had no endocrine dysfunction. In an Omani study, the ratio of patients with no endocrine dysfunction was 26.7% (16). Patients with normal endocrine functions in the study by De Sanctis et al, on the other hand, was as low as 16.5% (17). A possible reason for the higher percentage of patients with normal endocrine functions compared to the De Sanctis study might be that we had a younger patient population. In our study, 48.7% of the patients had one or two endocrine dysfunction and an additional 11.8% had three or more endocrine dysfunctions. Our results indicate a lower ratio of one or two endocrine dysfunction but a higher ratio of three or more endocrine dysfunction compared to the previously reported ratios for the inflicted patients. In literature, ratio of patients with one or two endocrine dysfunctions ranges from 66.8 to 77.2% and the ratio reported for three or more endocrine dysfunctions ranges between 6.7 and 7.5% (16,17).

Most common endocrine dysfunction reported in our study was hypogonadism, of which the majority was

hypogonadotropic hypogonadism. Former research in adult thalassemia major patients have also identified hypogonadism as the most common endocrine dysfunction, with a varying ratio of 36.3-78.4% (13,16,18,19). In further corroboration of our study, hypogonadotropic hypogonadism stands for the majority of these previously reported hypogonadism cases.

Hypothyroidism was reported ranging between 2.6-13.7% in adult thalassemia major patients previously (16,19-22). In our study, thyroid dysfunction was detected in one third of the cohort which stands for a higher ratio compared to the literature. In a study by Zervas et al, which included 200 thalassemia major patients, have identified no central hypothyroidism, 4% overt hypothyroidism and 12.5% subclinical hypothyroidism (22). Compared to their study, we report a higher frequency of primary hypothyroidism and a lesser frequency of subclinical hypothyroidism. Previous studies have reported quite lower, if at all, ratios of central hypothyroidism (17,22,23). On the other hand, we report a ratio of central hypothyroidism of 7.9%, suggesting central hypothyroidism indeed should not be overlooked among thalassemia major patients.

Hypoparathyroidism in our cohort was more prevalent than other endocrinopathies, but still at a comparable ratio to the figures described in the literature, such that, hypoparathyroidism in adult thalassemia major patients has been reported to vary from 2.7% to 17.1% (16-18,24).

A glucose metabolism disorder was determined in 28.9% of the patients in our study. In literature, adult thalassemia major patients have been reported to have diagnosed with DM within a ratio of 6-26.7% and have diagnosed with IFG/IGT within a ratio varying from 6 to 24% and our results are in line with the previous reports (16,18,19,21,25).

Unfortunately, a majority of our patients were lacking bone mineral density assessment. Nevertheless, in a notable portion of the patients for whom bone density measurement was available, bone mass was lower than expected for chronological age. As most of our patient were young adults, we preferred to evaluate whether they had "low bone mass for chronological age" based on the Z score of osteoporosis assessment. In previous adult studies, proportions as high as 92.7% have been reported for osteopenia and osteoporosis, in harmony with our results (18,19). Baldini et al reported osteopenia was more remarkable in femur neck while osteoporosis was more remarkable in lumbar spine (18). Prevalence of low bone mass in femur neck alone and in both femur neck and lumbar spine concurrently were higher in males in our study. Although there have been articles concluding prevalence of low bone mass is sex-independent in thalassemia patients, a study by Jensen et al, in addition to ours, has documented bone pathologies developing in thalassemia patients are more prevalent in males (5,26).

Patients with thyroid dysfunction, patients with hypogonadism, and patients with at least one other endocrine dysfunction were older than the patients

without endocrinopathies; suggesting an increased risk of developing endocrine dysfunctions with increased age. Similarly, Cunningham et al reported prevalence of hypothyroidism, treatment-requiring hypogonadism, hypoparathyroidism, DM and higher number of endocrinopathies increased with age (25). Consistent with our study, same study has not attributed any gender effect on the prevalence of endocrine dysfunctions.

In our study, patients with iron overload had more frequent abnormal OGTT results, as well as a lower femur neck or femur neck plus lumbar spine bone mass for chronological age. In addition, patients with delayed puberty and hypogonadism had higher levels of ferritin. Patients who underwent splenectomy were found to have a higher ratio of endocrine dysfunctions. Altogether, our results imply iron overload in the body may increase risk to develop endocrine dysfunctions. Belhoul et al have also previously reported thalassemia major patients with endocrinopathies such as DM, hypogonadism, hypothyroidism, and hypoparathyroidism had higher ferritin levels (14). Moreover, previous studies have, alike our study, blamed splenectomy for causing a higher risk of developing endocrine dysfunctions (14,27). The higher risk is basically attributable to the fact that following its removal, spleen, the organ normally acting as reservoir for iron, can no longer exert function in mitigating the toxic effects of iron (28).

Our study has certain limitations including its retrospective and single-center design. Another aspect of limitation to our study is the lack of a clear assessment on prevalence of adrenal insufficiency and GH deficiency in patients as in a considerable number of patients, the integrity of HPA and GH axes could not be examined. It is also worth pointing out, based on our review of medical records, that neither adrenal nor GH axis were checked properly during the childhood endocrine function tests.

Previous studies have shown that adrenal insufficiency and GH deficiency are not uncommon in both adult and pediatric thalassemia major patients as well. (29-32). Additionally, we failed to show any relationship, between endocrinopathies and duration and/or intensity of transfusion and chelation therapies, which may be due to the retrospective nature of this study and requires further prospectively designed studies to confirm these results.

CONCLUSION

Our study, bolsters the past data in concluding that endocrine dysfunctions are common among thalassemia major patients. Therefore, endocrine and metabolic functions of such patients should be regularly checked, keeping in mind the likelihood of more than one coexisting endocrine dysfunction.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

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