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Status of Thyroid Function and Iron Overload in Adolescents and Young Adults with Beta-Thalassemia Major Treated with Deferoxamine in Jordan

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***Abstract*—**Thyroid dysfunction is one of the most frequently reported complications of chronic blood transfusion therapy in patients with beta-thalassemia major (BTM). However, the occurrence of thyroid dysfunction and its possible association with iron overload in BTM patients is still under debate. Therefore, this study aimed to investigate the status of thyroid functions and iron overload in adolescent and young adult patients with BTM in Jordan population. Thirty six BTM patients aged 12-28 years and matched controls were included in this study. All patients have been receiving frequent blood transfusion to maintain pretransfusion hemoglobin concentration above 10 g dl^{-1} and deferoxamine at a dose of 45 mg kg^{-1} day^{-1} (8 h, 5-7 days/week) by subcutaneous infusion. Blood samples were drawn from patients and controls. The status of thyroid functions and iron overload was evaluated by measurements of serum free thyroxine (FT4), triiodothyronine (FT3), thyrotropin (TSH) and serum ferritin level. A number of some hematological and biochemical parameters were also measured. It was found that hematocrit, serum ferritin, hemoglobin, FT3 and zinc, copper mean values were significantly higher in the patients than in the controls ($P < 0.05$). On other hand, leukocyte, FT4 and TSH mean values were similar to that of the controls. In addition, our data also indicated that all of the above examined parameters were not significantly affected by the patient's age and gender. Deferoxamine approach for removing excess iron from our BTM patient did not normalize the values of serum ferritin, copper and zinc, suggesting poor compliance with deferoxamine chelation therapy. Thus, we recommend the use of a combination of deferoxamine and deferiprone to reduce the risk of excess of iron in our patients. Furthermore, thyroid dysfunction appears to be a rare complication, because our patients showed normal mean levels for serum TSH and FT4. However, high mean levels of serum ferritin, zinc, copper might be seen as potential risk factors for initiation and development of thyroid dysfunctions and other diseases. Therefore, further studies must be carried out at yearly intervals with large sample number, to detect subclinical thyroid dysfunction cases.

***Keywords*—**beta-thalassemia major**,** deferoxamine**,** iron overload, triiodothyronine, zinc.

I. INTRODUCTION

BETA-thalassemia major (BTM) is a common health problem in the Middle East, Africa, the Indian subcontinent, and Southeast Asia. BTM is a hereditary severe anemia resulting from defects in beta-globin synthesis [1], [2].

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This disease is commonly associated with the shortened erythrocyte lifespan and excessive destruction of erythrocytes. Therefore, blood transfusion is needed every 2 to 5 weeks, to maintain a pretransfusion hemoglobin level above 10 g/dl, as a life saving for BTM patients [2]. However, frequent blood transfusion can lead to iron overload which may accumulate in key organs such as liver, heart, and endocrine glands of BMT patients due to the lack of physiological pathway for iron excretion [3], [4], [5]. This massive accumulation may cause organ dysfunction and failure, and ultimately death [2].

Endocrine dysfunctions have been reported in children, adolescents and young adults suffering from BTM, including thyroid dysfunction due to transfusion-related iron overload [2], [6], [7]. The thyroid gland secretes two important thyroid hormones termed thyroxine (T4) and triiodothyronine (T3), which play a very important role in controlling metabolic activity in children and adults, and affecting the function of every organ system [9]. The thyroid gland mainly produces T4 which has little effect on the body's metabolic rate. On other hand, only 20 % of T3, the more active hormone, is produced by thyroid gland, whereas the remaining 80% of T3 is formed by deiodination of T4.

Due to the association of iron overload with organ dysfunction in transfusion-dependent BTM patients, successful iron chelation therapy is essential for the optimal management of this disease. To date, deferoxamine (DFO) is the most commonly used iron chelation compound in transfusion-dependent BTM patients [7], [10], [11], [12]. To comply completely with

DFO therapy, BTM patients must undergo parenternal doses of approximately 45 mg kg^{-1} day^{-1} of DFO therapy for up to 8-12 hours a day and 5-7 nights a week [13]. Results of several studies showed that the combination of blood transfusion and DFO therapy has dramatically reduced the risk of iron overload-induced toxicity, and allow for normal growth and sexual development in BTM patients, and thus increase life span of BTM patients especially among those patients who were able to cop with this type of therapy [7], [11], [12]. Beside the chelation of iron, DFO can also act as a chelator for other metals such as zinc (Zn), copper (Cu) and cobalt [14]. Zn and Cu are important antioxidant elements that requires in trace amount as cofactors for some metalloenzymes to be functional such as Zn-Cu superoxide dismutase, and thus play key roles in maintaining cellular

homeostasis [15], [16]. Zinc is also required for thyroid metabolism and structure; and may play role in conversion of T4 to T3 in humans. On other hand, zinc deficiency may lead to reduction in concentrations of T3 in plasma [17], [18].

Furthermore, according to previous and recent data, it appears that the long term survival remains poor in BTM patients due to poor adherence to the regular subcutaneous infusions of DFO therapy [19], [20], [21]. The key reason for poor compliance is most likely due to the fact that DFO therapy needs to be daily administered parenterally with night-long infusion (8–10 h for 5-7 days each week). Thus, based on existing data, the effectiveness of DFO treatment among BTM patients who received regular transfusion is still under debate. Therefore, this study was carried out to investigate the status of thyroid functions and iron overload in adolescents and young adults with BTM treated with DFO. Accordingly, we report here for the first time some hematological and biochemical parameters in BTM patients, such as hematocrit, serum ferritin levels, hemoglobin levels and white blood cells, Zn, Cu, and the serum thyroid hormones (T4 and T3) and thyrotropin (TSH).

II. MATERIALS AND METHODS

A. Study Patients

Thirty six patients with BTM were included in the study. Their mean age was 17 years (range from 12 to 28 years). The diagnoses of BTM were made based on the clinical, hematological and hemoglobin electrophoresis profiles and the results of β-goblin chain synthesis at Thalassaemia Unit at Princess Rahma Educational Hospital, Irbid, Jordan. In addition, thirty six healthy individuals of matched age and gender were also included as controls. None of these individuals had history of anemia, abnormal complete blood counts and abnormal hemoglobin electrophoresis results.

Before this study was commenced, ethical approval was obtained by the Institutional Review Board of Princess Rahma Educational Hospital. Medical histories such as clinical and transfused records of all 36 BTM patients were obtained from the hospital files. Informed consent was provided for each patient and healthy control who participated in this study. All patients and controls were interviewed and filled out standardized questionnaires during this study. In addition, all patients and controls were tested and found free from HBV, HCV and HIV. None of the studied patients are undergo of splenectomy or other supplement treatment.

All patients were received regular blood transfusion after the age of one year old, usually given regularly every 2-4 weeks, to maintain a pretransfusion hemoglobin level above 10 g dl^{-1}. None of the subjects was treated with vitamin E and/or vitamin C supplementations before the study. All patients were also started on subcutaneous infusion of DFO as chelating agent (45 mg kg^{-1} day^{-1}, for 8–10 h on 5-7 days each week) at age of two or three years old prior to presentation to us.

B. Blood collecting

Five ml of venous blood sample was drawn into heparin from each BTM patient before the transfusion and from each healthy control. Three ml were centrifuged at 3000 rpm for 10 min at room temperature. The serum samples were stored at 4°C until needed for analysis of zinc, copper, ferritin and thyroid hormone levels. The remaining two ml were used for studying some hematological parameters such as hematocrit, hemoglobin levels and leukocyte counts as described below.

Blood analysis

The hemoglobin levels and leukocyte counts were examined using Automate blood cell counter. Serum ferritin levels were measured using commercial analytical kits from Sigma (St. Louis, Mo, USA) according manufacture procedure.

C. Thyroid hormones

The serum free T3 (FT3), free T4 (FT4) and TSH were measured by radioimmunoassay method as described previously [22]. Their values were reported as pg/ml, pg/ml and μIU/ml, respectively for serum FT3, FT4, and TSH.

D. Zinc and Copper measurement

Measurement of serum Zn concentration was performed using Zn reagents from Randox Laboratories (UK) following the manufacturer's instructions. Absorbance was spectrophotometerically monitored at a wavelength of 560 nm in a Biosystem BTS 310 Photometer UV-VIS (Suyog Diagnostics Pvt. Ltd., India). The serum Cu concentration was also determined spectrophotometerically at a wavelength of 580 nm using 4-(3,5-dibromo-2-pyridylazo)-N-ethyl-N-sulfopropylanine assay from Audit Diagnostics (Carrigtwohill, Ireland) according to the manufacturer's instructions. The zinc and copper levels were reported in μg/dl.

E. Statistical analyses

Analysis was conducted using Statistical Package for Social Science for Windows version 11.0 (SPSS, Chicago, IL, USA). Means and standard deviations were calculated and student's t-test was used to compare the two groups. P-values less than 0.05 were considered statistically significant.

III. RESULTS

A total of 36 BTM patients receiving multiple blood transfusions were enrolled in this study. The patients have an age range from 12 to 28 years, with average age of 17 ± 6.4 years. They were divided into two groups according to their age. The first group includes adolescent patients aged 11 to 17. The second group includes young adults aged 18 to 28. Seventeen patients (47%) were male, and nineteen patients (53%) were female. As shown in Tables 1 and 2, hemoglobin concentration and hematocrit value in our patients were significantly lower than that of the controls ($p < 0.05$), as anticipated. By contrast, no significant change in the number of leukocytes was observed between the BTM patients and control group.

To evaluate the effectiveness of DFO treatment on removal of excess iron in our patients, the serum ferritin level was measured in these patients and used as iron index (Tables 1

and 2). The mean level of serum ferritin was significantly higher in patients than the controls of both genders ($p < 0.05$). Our data also indicate that there was no significant difference in mean level of serum ferritin between the female with BTM (2412 ± 750 µg/L) and male with BTM (2699 ± 858 µg/L). Similarly, there was no significant difference in the hematocrit value between the female and male in both BTM patients and controls (Table 1). On other hand, hemoglobin concentration in male BTM patients was similar to that of female BTM patients. Our data also reveal that the mean level of serum ferritin was lower in adolescent BTM patients aged 11 to 17 (2441 ± 764 µg/L) than adult BTM patients aged 18 to 28 (2683 ± 880 µg/L). However, this finding was not statistically significant (Table 2). On other hand, the hematocrit concentration was higher in adolescent BTM patients than adult BTM patients, but this difference was also not statistically significant. In contrast, hemoglobin concentration in adolescent BTM patients was similar to that of adult BTM patients.

TABLE I
THE HEMATOLOGICAL DATA OF BETA-THALASSEMIA MAJOR PATIENTS TREATED WITH DFO ACCORDING TO GENDER

Parameter	Male		Female	
	Control (n=19)	Patients (n=19)	Control (n= 17)	Patients (n=17)
Hematocrit (%)	36 ± 3.1	25 ± 5.6*	37 ± 2.5	30 ± 4.3*
Ferritin (µg/L)	72 ± 32	2699 ± 858*	67 ± 25	2412 ± 750*
Hemoglobin (g/dl)	13.1 ± 0.8	8.4 ± 1.1*	11.4 ± 1.1	8.5 ± 0.6*
Leukocytes x 10^6/L	10.98 ± 2.16	9.22 ± 3.17	10.37 ± 2.22	10.5 ± 1.76

Values are presented here as mean values ± standard deviation
* Statistically significant when compared to control group at $p<0.05$

TABLE II
THE HEMATOLOGICAL DATA OF BETA-THALASSEMIA MAJOR PATIENTS TREATED WITH DFO ACCORDING TO AGE GROUPS

Parameter	Age group (Controls)		Age group (Patients)	
	11-17 (n=20)	18-28 (n=16)	11-17 (n=20)	18-28 (n=16)
Hematocrit (%)	36.8 ± 3.6	34.1 ± 5.7	29.0 ± 2.19*	26.5 ± 7.43*
Ferritin (µg/L)	70.6 ± 28	68.4 ± 20	2441 ± 764*	2683 ± 880*
Hemoglobin (g/dl)	12.6 ± 1.3	11.8 ± 1.2	8.54 ± 0.81	8.37 ± 1.02
Leukocytes x 10^6/L	10.56 ± 2.31	10.42 ± 3.26	9.44 ± 2.67	10.2 ± 2.46

Values are presented here as mean values ± standard deviation
* Statistically significant when compared to control group at $p<0.05$

Furthermore, our current results also indicate that the mean level of serum TSH did not differ between the BTM patients and controls. Similarly, the mean level of serum FT4 was found to be similar in both BTM patients and controls (Table 3 and 4). However, the mean level of serum FT3 significantly increased in our patients compared to the controls of both genders. In addition, the mean levels of serum Cu and Zn were also significantly higher in BTM patients than the controls ($P < 0.05$). Considering these data by sex, Table 3 also reveals that the mean level of serum TSH did not differ significantly between males BTM patients (1.90 ± 1.19 µIU/ml) and female BTM patients (1.78 ± 0.63 µIU/ml). Similarly, the mean levels of both serum T3 and T4 in male BTM patients were similar to female BTM patients. Considering these data by age group, Table 4 indicates that the mean level of serum TSH of our patients was lower in adolescents aged 11 to 17 (1.52 ±0.80 µIU/ml) than adults aged 18 to 28 (2.30 ± 1.09 µIU/ml), but this finding was not statistically significant (Table 4). In addition, the serum FT3 and FT4 levels in adolescents were similar to that of adults.

IV. DISCUSSION

The roles of DFO as iron chelation therapy to improve normal growth and sexual development in BTM patients, and reduced the risk of iron overload-induced toxicity have received much attention because of the report that organ dysfunctions are present in high quantities in BTM patients receiving frequent blood transfusion [6], [7], [8]. To the best of our knowledge this is the first report of investigation of the status of thyroid function and iron overload in adolescent and young adult patients with BTM in Jordan population. In accordance to what is reported in the literature, serum ferritin levels must be maintained below 1000 µg/L, which can be tolerated by organs of patient [23]. However, contrary to what is reported in the literature, our present study reveals that our patients treated with DFO had clinically significant amount of serum ferritin (> 2400 µg/L). This can be explained by suboptimal use of DFO due to poor compliance with this therapy. This notion is consistent with previous studies which reported that poor compliance is more common in BTM patients treated with DFO chelation therapy than patient treated with DFP chelation therapy or combination of DFP and DFO [19], [20], [21]. Thus, our data reveal that DFO treatment appeared to be not effective at decreasing or

normalizing serum ferritin concentrations during continued blood transfusions as evident by high serum ferritin level. In addition, multiple and chronic blood transfusion may contribute to the rise in iron index as reported by Kassab and colleagues [24]. According existing data, serum ferritin represents only 1% of total iron pool, and inflammation (e.g. hepatitis) and liver damage usually induce an increase in serum ferritin level [23]. Thus, we can not also exclude the possibility that inflammation may contribute to such increase, because liver inflammation is more common in BTM patients. Therefore, adherence to DFO chelation therapy must be monitored carefully and systematically. In addition, iron level should be maintained within safe limits to avoid progressive organ damage. Taken together, it is possible to suggest that the high iron index might be seen as a potential risk factor for future initiation and development of thyroid dysfunction and other complications in our BTM patients.

TABLE III
SERUM THYROID HORMONES AND THYROID-STIMULATING HORMONE [A], COPPER AND ZINC LEVELS IN THE CONTROL AND BETA-THALASSEMIA MAJOR PATIENTS ACCORDING TO GENDER

Parameter	Male		Female	
	Control (n=19)	Patients (n=19)	Control (n= 17)	Patients (n=17)
TSH µIU/ml	2.15 ± 0.62	1.90 ± 1.19	2.63 ± 1.05	1.78 ± 0.63
FT3 pg/ml	2.01 ± 0.29	2.97 ± 0.92*	1.80 ± 0.32	2.98 ± 0.69*
FT4 pg/ml	10.6 ± 2.1	9.8 ± 2.6	10.5 ± 1.8	10.2 ± 2.9
Copper µg/dl	106.70 ± 14.22	171.1 ± 46.0*	108.23 ± 15.36	188.7 ± 53.5*
Zinc µg/dl	111.35 ± 12.4	199.2 ± 54.2*	114.23 ± 15.5	212 ± 58.8*

Values are presented here as mean values ± standard deviation
* Statistically significant when compared to control group at $p<0.05$
[a] FT3: free triiodothyronine; F T4: free thyroxine; TSH: thyroid-stimulating hormone.

TABLE IV
SERUM THYROID HORMONES AND THYROID-STIMULATING HORMONE , COPPER AND ZINC LEVELS IN THE CONTROL AND BETA-THALASSEMIA MAJOR PATIENTS ACCORDING TO AGE

Parameter	Age group (Controls)		Age group (Patients)	
	11-17 (n=20)	18-28 (n=16)	11-17 (n=20)	18-28 (n=16)
TSH µIU/ml	2.25 ± 0.81	2.47 ± 0.92	1.52 ± 0.80	2.30 ± 1.09
FT3 pg/ml	1.95 ± 0.20	1.86 ± 0.48	3.13 ± 0.86*	2.86 ± 0.78*
FT4 pg/ml	10.5 ± 1.9	10.5 ± 2.1	10.0 ± 2.8	9.6 ± 2.9
Copper µg /dl	108.70 ± 13.34	104.90 ± 17.26	175.7 ± 4 7.8*	172.1 ± 4 9.6*
Zinc µg /dl	110.22 ± 11.88	115.11 ± 16.24	199.7 ± 4 4.2*	218.5 ± 68 .8*

Values are presented here as mean values ± standard deviation
* Statistically significant when compared to control group at $p<0.05$

Our current data also indicate that the mean level of serum TSH of our BTM patients was within the references range (0.4 – 5.0 □IU L^{-1}). Our data clearly suggest that thyroid dysfunction appears to be a rare complication in Jordanian adolescents and young adults suffering from BTM. This is also clearly evident by normal serum levels of FT4, and despite the fact that our patients showed significant increased iron index. Similar observation was made by different groups of investigators [25], [26]. They reported no correlation between ferritin plasma levels and thyroid functional status. Thus, it can be suggested that these observations raise the possibility that additional factors may be contributing to the incidence of the thyroid dysfunction in BTM patients. Conversely, results from other studies indicated that individuals suffering from BTM should not be exposed to excess iron due to increased sensitivity to its toxicity effects on thyroid functions, and the thyroid gland appears to fail before the central components of the axis [27], [28].

Zn, Cu and Fe are trace metals that play vital roles as cofactors for a variety of proteins. Besides iron, there are evidences that Zn, Cu can pose a significant threat to human health and well-being [4], [8], [29], [30], [31], [32]. Abnormal levels and metabolism of Zn, Cu and Fe has been found to cause several chronic pathogenesis, such as endocrine dysfunctions, diabetes and diabetic complications and others. Moreover, Cohen et al. (2002) reported that DFO can also act as chelator for both Zn and Cu [18]. Thus, we anticipate that Zn and Cu levels could be closely similar to the controls. However, our study reveals that there were significantly increased in mean levels of serum Zn and Cu in our patients compared to the controls. These findings indicate that Zn and Cu deficiencies in our BTM patients are rare and it appears that Zn and Cu supplementations are not required. These findings also support the above notion that DFO treatment appears to be not effective as evident by high Zn and Cu. In previous studies, Bashir (1995) and Oktekin and Gokmen (2000) reported that zinc and copper levels are significantly increased in patient treated with DFO [30], [31]. Similarly, in

recent study, Mehdizadeh et al. (2008) showed that mean serum zinc level was significantly higher in the thalassemic group, and no relationship between serum zinc level and serum ferritin level, DFO dose, initiating time of blood transfusion, and chelation therapy was observed [32]. These results are compatible with our results. By contrast, low plasma Zn and Cu levels have been found in patients treated with DFO [33]-[35]. In addition, a slight reduction in plasma zinc was observed over time in BTM patients receiving frequent blood transfusion and treated with DFP, and also no significant correlation between Zn and thyroid gland functions was observed [18], [36]. These results might differ from ours probably because of differences in the manner, degree of compliance and doses and/or type of chelation therapy. Based on these findings, there are wide discrepancies in existing studies regarding the status of Zn and Cu levels in BTM patients treated with DFO. Thus, the reasons for such increase in mean levels of serum Zn and Cu in our study are still unclear. However, a number of explanations can be proposed for such increase. High serum Zn and Cu levels are probably due to the impairment of Zn and Cu metabolism and utilization in tissues in the pathogenesis of these patients. It is also possible that the decrease rate of glomerular filteration of Zn and Cu in chronic hemolysis may contribute to such increase in these two metals. However, we did not evaluate our patients for the presence of renal dysfunctions. Thus, this necessitates further study to investigate the renal dysfunctions in our BTM patients. Moreover, additional factors may also contribute to the increase in Cu and Zn, including an increase in Zn and Cu absorption via the gastrointestinal tract, different transfusion rates, types and doses of chelation therapies, age of patients, nutrition status, psychological and health problems, such as depression, metabolic and endocrine complications.

As mentioned above, frequent blood transfusions for BTM patients usually lead to overload the body organs with excess iron which, in turn, may cause wide of range complications including thyroid dysfunction and others. Together, our findings combined with previous findings point to the critical need to monitor iron, Zn and Cu levels during DFO chelation therapy to avoid further complications that might be appeared due to accumulation of excess iron, Zn and Cu in key organs such as thyroid gland, heart, liver and others. To solve this issue, first we might recommend that the dose of DFO therapy must be changed to the needs of our patients to maintain concentrations of these metals below those associated with iron-induced toxicity or closer to the normal levels. Second, we might recommend the use of alternative chelation therapy, such as combination of deferoxamine and deferiprone. Because, recent data revealed that DFO can remove mainly extracellular iron and only a small fraction of the intracellular iron, and intensive combined chelation therapy (deferiprone and DFO) reduce iron overload and may reverse some cases of primary hypothyroidism, either subclinical or compensated, and may prevent progression to overt hypothyroidism [7], [37].

Another interesting finding of the present study is that FT3 level was significantly high in our BTM patients compared to the controls. It was also seen that in zinc deficiency study by Kralik et al. (1996), the activity of 5-deiodinase to convert T4 to T3 was reduced by 67%, which may be shown as evidence of the relation between zinc and thyroid functions [15]. Thus, it may be accepted as evidence that high zinc level stimulates the conversion of T4 to T3 via increase of 5-deiodinase activity. Taken together, our findings combined with previous findings suggest that the rise in zinc level might explain the increase in high FT3 levels that have been seen in our patients.

Despite of the fact that blood transfusion and suboptimal use of DFO can contribute to elevated serum ferritin level in our patients, available studies clearly indicated that serum ferritin data are not normally distributed in most populations. In addition, it has been recently suggested that iron absorption is increase in patients with severe BTM due to increase intestinal iron absorption [38]. Thus, the elevated serum ferritin level is not due solely to blood transfusion and suboptimal use of DFO, but other factors might also contribute to such increase. Furthermore, we are also aware that a limitation of this study is the small number of BTM patients and the use of blood tests for thyroid functions. It is important to mention that blood tests for thyroid functions are not highly accurate. Therefore, using only blood thyroid levels as the diagnostic criteria for thyroid dysfunctions leave many people with low and/or mild forms of hypothyroidism that remain undiagnosed or undiscovered. It has been reported that in all cases of hypothyroidism, symptoms occur slowly over time and may vary from subclinical to overt hypothyroidism which is associated with an increased risk of cardiovascular disease [7]. Thus, it is anticipated that the rate of thyroid dysfunctions increases steadily with advancing age. However, our current data show that all of the above examined parameters (e.g. serum levels of FT3, FT4, TSH and ferritin) were not significantly affected by the patient's age and gender. This was probably due to the small sample size and/or approaches used to measure these parameters. Taken together, it is not possible to draw a final conclusion, and thus the question regarding the status of thyroid function and iron overload in BTM patients with chronic blood transfusion and DFO treatment remains unclear.

V. CONCLUSION

In conclusion, our data indicate that DFO monotherapy approach was not effective at decreasing or normalizing serum ferritin, Cu and Zn concentrations in our patients during continued blood transfusions as evident by high serum levels of ferritin, Cu and Zn, suggesting poor adherence to DFO chelation therapy. Therefore, adherence to DFO chelation therapy must be monitored carefully to maintain iron, Zn and Cu levels within safe limits to avoid progressive organ dysfunctions and damage. Our data also reveal for the first time that FT3 level was higher in our BTM patients; and high zinc along with excess iron might contribute to high level of FT3. Even though, our BTM patients had no any clinical signs

of thyroid dysfunction, high serum levels of iron, Cu and Zn might be seen as potential risk factors for future initiation and development of thyroid dysfunction as well as other organ dysfunctions in our patients. Thus, careful monitoring of ferritin and TSH, FT4 and FT3 levels at regular intervals is recommended. Furthermore, DFP dose increase or combined DFO and DFP chelation therapy might be considered for our patients with substantial high serum ferritin, Zn and Cu levels. In addition, further studies must be carried out at yearly intervals with large sample size, to detect subclinical thyroid dysfunction cases and to confirm the above speculations.

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