Egyptian Journal of Medical Research (EJMR)

Assessment Of Serum Level Of Selenium And Manganese In B-Thalassemia Major Patients In Beni-Suef University Hospital

Mohamed Hussein Meabed and Esraa Abdelal Shafey

Pediatric department, Faculty of Medicine, Beni-suef University, Egypt.

Abstract:

B- thalassemia major (β-TM) is one of the most common inherited single gene disorder .Children with Thalassemia frequently have poor growth and delayed pubertal development. Selenium and manganese are factors responsible for growth and puberty disorders in thalassemic patients.

Assessment of serum levels of selenium and manganese in patients with thalassemia in Pediatric Haematology Clinic in Beni Suef University Hospital. Blood was taken from 50 pediatric patients with b thalassemia major, and 50 normal children as controls all were subjected to full history taking and full examination and investigation was done in the form of CBC, serum Ferritin , serum Selenium and Manganese .

Patients with β- thalassemia major have high serum manganese level as compared to normal controls with P value of (0.000), while serum selenium level is insignificant as compared to normal controls with P value of (0.119)

Keywords: Thalassemia –Selenium – Manganese.

1. Introduction:

Thalassemia refers to a group of autosomal recessive genetic disorders that result from globin chain production which is seen in nearly all races (Marengo et al, 2017).Thalassemia is grouped into 2 major forms, namely, α- and β-thalassemia based on defects in such globin genes (1). β-TM mainly appears at the 2nd 6 months of life in the form of severe hemolytic anemia. The commonest therapeutic tool involves regular blood transfusions. Nevertheless, this management increases Fe overload where this excess Fe can't naturally be excreted from the body , resulting in Fe that causes delayed growth and sexual maturation, arrhythmia, hepatic destruction (fibrosis& cirrhosis), diabetes, hypogonadism , hyperparathyroidism, and thyroid disorders. In contrast, the blood transfusion complications as the transmission of HBV, HCV can be increased as another problem experience by Thalassemic patients (2).

Thalassemic patients have poor growth, abnormal puberty, in addition to abnormal

immune functions & decreased bone mineral Acquisition. The mechanism of these co-morbidites is typically explained by the toxic impacts of transfusion-related Fe overload. Severe nutritional deficiencies in fat &water-soluble vitamins along with vital essential minerals were documented. Decreased circulating level of nutrients has been detected in spite of seemingly sufficient dietary intake. This disconnection between intake and circulating level indicates that Thalassemic patients might have increased requirements for particular nutrients as a result of either poor nutrient absorption, elevated loss, or higher nutrient turnover. (**3**).

The iron overload accounts for oxidative stress as a result of the overproduction of free radicals, abnormal level of trace elements in serum along with antioxidant enzymes. (4).

Selenium (Se) is one of the crucial trace elements required for optimal health and development of humans as well as other mammals. This micronutrient is best detected for its peculiar biological roles in redox balance and might become one of the promising chemopreventive agents against many cancers. In addition, it plays a role in anti inflammatory and antiviral activities, prevention of heart disease, and decreasing progression of neurodegenerative disorders and AIDS. Both Se deficiency and excess may result in severe disorders. (5).

Also, Manganese (Mn) is trace essential element that participates in several enzymatic reactions. It acts as a central compound of a lot of metallo enzymes and as an activator for some metal-enzyme complexes. In addition , it is needed for human diet; however, its excess causes toxic impacts on human health .(6).

2. Subjects and Methods:

The study was conducted on 50 patients proved to have β-TM by clinical examination and Hb electrophoresis (Group 1) and 50 age &gender matched healthy controls (Group 2).. Both patients and controls were recruited from Pediatric hematology outpatient clinic or inpatient ward of paediatric department, Beni-suef university hospital

Inclusion criteria:

1) Patients with TM proved to have β-TM by clinical examination and Hb electrophoresis.

2) Age between 5 -15 years.

3) Patients with frequent blood transfusion.

4) Of both sexes.

exclusion criteria :

1) Other types of haemolytic anaemia.

2) Patients with other comorbidities that could affect nutritional state of the patient as cerebral palsy and other neurological diseases, CRF and cardiac disease.

3) Patients with symptoms suggesting of GIT diseases causing persistent vomiting or diarrhea or malabsorption.

All patients were subjected to:

All patients were subjected to:

1) Full history taking including :

a) Age.

b) Sex.

c) Family history of similar conditions and +ve consanguinity.

D) Frequency of blood transfusion.

E) Iron chelation therapy type, dose and compliance.

F) Nutritional history.

G) age of the 1st time blood transfusion .

H) History of splenectomy.

2) Full clinical examination including:

a) General examination.

b) Abdominal examination.

C) Neurological examination .

3) Investigations:

A) Laboratory:

a- CBC.

b- Serum ferritin.

C- serum Se .

d- serum Mn .

Statistical methods

All statistical calculations were done using computer programs Microsoft Excel (Microsoft Corporation, NY, and USA) & SPSS (Statistical package for the social science version 20) statistical programs (SPSS Inc., Chicago, IL, USA). Data were statistically described in terms of mean ± SD, frequency and percentages. Descriptive statistics were done for quantitative data as mean ± SD for quantitative parametric data, while it was done for qualitative data as number and percentage.

- When appropriate,the qualitative variables will be described in the form of frequency and percentages.

- Pearson correlation will be used to correlate quantitive variables fulfilling normal distribution.

- P value(which is either non-significant(NS) if>0.05,significant(S)

If<0.05,or highly significant (HS) if<0.01 will be calculated.

3. Results:

The study was conducted on 50 patients proved to have β-TM by clinical examination and hemoglobin electrophoresis (Group 1) and 50 age matched healthy controls (Group 2). Both patients and controls were evaluated by assessment of serum level of selenium and manganese.

Table (1): Comparison between cases and controls as regard demographic data

	Controls	**Cases**	**P**	**Sig.**
Age	9.8600 ± 2.26788	9.9400± 2.56674	.869	NS
Weight	55.9600 ± 28.45545	32.5800± 12.70078	.001	HS
Height	62.7000± 22.88414	26.0000± 14.58263	.001	HS

P-value > 0.05 (Non-significant)

Table (1): shows no significant differernce between patients and controls AS Regard age , AND showS Height AND Weight in patients was significantly lower than in controls

Table (2): Comparison between patients and controls as regard consanguinity

			Group		**P**
			Cases	**Controls**	
Consanguinity	Negative	Count	17	44	.002
		%	34.0%	88.0%	
	Positive	Count	33	6	
		%	66.0%	12.0%	

Table (2): This table shows significant difference between patient and control groups as regard consanguinity with p value (.002). with positive consanguinity higher at cases group

Table (3): Comparison between cases and controls as regard laboratory data :

	Controls	**Cases**	**P**
Tlc	8.2210± 2.23370	7.4412± 2.31714	.090
Hb	10.5360± .95975	4.1020± 1.15608	.000
Plt	347.4600± 100.08511	431.5600± 191.34765	.007
Serum Ferritin	66.0800± 33.16923	972.6940± 677.33732	.000
Serum Manganese	85.8800± 11.60162	99.8600± 8.31524	.000

Serum Selenium	34.5200± 35.11104	45.9800± 37.73403	.119

RBCs count And Hemoglobin levels were significantly lower in patients than controls . WBCs show insignificant difference between patients and controls , Platelets count was significantly higher in cases than in control . serum Ferritin was significantly higher in patients than controls. serum manganese was significantly higher in cases than in control with mean (99.8600± 8.31524) (34.5200± 35.11104) respectively with p value (0.000) . serum selenium shows insignificant difference between patients and controls with mean (45.9800± 37.73403) (34.5200± 35.11104) respectively with P value (0.119).

Table (4): Frequency of clinical parameters among patients group

		Frequency	**Percent**
Mongoloid facies	yes	41	82%
	no	9	18%
Hepatomegaly	no	30	61.2
	yes	19	38.8
Splenomegaly	yes	43	86%
	No	7	14%
Splenectomy	no	42	84 %
	yes	8	16 %
Compliance to TTT	no	10	20 %
	yes	40	80 %

This table shows 82 % of cases has mongoloid features , 38.8% has hepatomegaly ,86 % has splenomegaly , 16 % has splenectomy , 20% noncompliance to treatment.

Table (5): Comparison between TM patients with and without splenectomy as regard clinical and laboratory data

	Splenectomy (N=8)	**No Splenectomy (N=42)**	**P**
Body Weight (Kg)	30.6250± 12.65969	32.9524± 12.82709	.640
Height (Cm)	23.0000± 18.78449	26.5714± 13.84962	.531
Tlc_	6.6625± 1.94050	7.5895± 2.37339	.305
Hb	4.7875± 1.10381	3.9714± 1.13143	.067
Plt	785.2500± 179.87516	364.1905± 95.78946	.000
Serum Ferritin	1418.7500± 1350.85621	887.7310± 436.50232	.041
Serum Manganese	101.3750± 11.14755	99.5714± 7.80289	.579
Serum Selenium	40.7500±45.59370	46.9762± 36.61167	.673
Transfusion Intervals (Wks)	5.1250±1.45774	5.4048± 3.20867	.811

This table shows insignificant difference as regard body weight between pateints with splenectomy and others with no splenectomy with p value 0.6 , Height shows insignificant difference between pateints with splenectomy and others with no splenectomy with P value 0.5 , WBCs count shows insignificant difference between both groups with p value 0.3 , hemoglobin level is slightly higher in patients with splenectomy but insignificantly .with p value 0.06, platelets count is higher in patients with splenectomy than in patients with no splenectomy with mean (785.2500± 179.87516) (364.1905± 95.78946) respectively with p value 0.000. Serum ferritin is significantly high in patients with splenectomy than in patients with no splenectomy with P value 0.04 .Serum manganese and selenium shows in insignificant difference between both groups with P value (0.57)(0.67) respectively .transfusion intervals shows insignificant difference between both groups with P value 0.811 .

Table (6): Comparison between males and females in patients group as regard clinical and laboratory data

	Males (N=30)	**Females (N=20)**	**P**
Body Weight (Kg)	33.1000± 12.09260	31.8000± 13.84729	.727
Height (Cm)	25.9000± 15.29785	26.1500± 13.82703	.953

Tlc_	7.1887± 2.37365	7.8200± 2.23503	.351
Hb	4.2100± 1.12843	3.9400± 1.20717	.424
Plt	444.8000± 221.75093	411.7000± 136.67175	.554
Serum Ferritin	1055.5567±816.58366	848.4000± 371.91417	.294
Serum Manganese	99.1000± 8.39273	101.0000± 8.27806	.434
Serum Selenium	48.9000± 40.15346	41.6000± 34.31495	.508
Transfusion Intervals	5.2667± 3.28983	5.5000± 2.54434	.790

This table shows insignificant difference between male and female patients as regard body weight ,height ,CBC parameters, serum ferritin ,serum manganese ,serum selenium and transfusion intervals

Table (7): Comparison between patients adherent to treatment and patients not adherent to treatment as regard clinical and laboratory data :

	Adherent (N=40)	**Non-Adherent (N=10)**	**P**
Body Weight (Kg)	31.9688± 12.31963	33.6667± 13.64681	.655
Height (Cm)	28.9375± 13.04072	20.7778± 16.05342	.057
Tlc_	7.6800± 2.47916	7.0167± 1.99241	.336
Hb	4.1594± 1.23415	4.0000± 1.02842	.645
Plt	434.5625± 194.56385	426.2222± 190.93780	.884
Serum Ferritin	657.2813± 165.83770	1533.4278± 867.20684	.001
Serum Manganese	97.1875± 5.61356	104.6111± 10.22188	.002
Serum Selenium	46.2188± 37.29891	45.5556± 39.58345	.953
Transfusion Intervals (Wks)	5.2813± 2.85380	5.5000± 3.29438	.807

This table shows insignificant difference between patients compliant to treatment and those noncompliant to treatment as regard body weight ,while height show significant difference between both groups CBC parameters like TLC , Hb level and platelets show insignificant difference between both groups. serum ferritin level shows significant difference between both groups with P value 0.001 . serum manganese level shows significant difference between both groups with P value (0.002) .serum selenium level shows insignificant difference between both groups , transfusion intervals show insignificant difference between both groups .

Table (8): Correlations between serum manganese, selenium and other clinical and laboratory parameters

		Serum Manganese	**Serum Selenium**
Serum Manganese	R	1	-.022-
	P		.881
Serum Selenium	R	-.022-	1
	P	.881	
Age	R	.083	-.130-
	P	.568	.368
Age Of First Blood Transfusion	R	**.405****	-.153-
	P	**.004**	.289
Transfusion Intervals	R	.188	.178
	P	.192	.216
Bw_	R	-.126-	.198
	P	.383	.168
Length_	R	-.168-	**.508****
	P	.245	**.000**
Tlc_	R	.108	.072
	P	.457	.617
Hb	R	.076	.036
	P	.600	.806
Plt	R	.077	-.206-
	P	.594	.151
Serum Ferritin	R	**.290***	-.105-
	P	**.041**	.469

This table show positive strong correlation between serum manganese level and age of first blood transfusion . also there is positive strong correlation between length of the patients and serum selenium level .the level of serum selenium and the level of serum ferritin show weak positive correlation together .

Table (9) Frequency of neuropsychiatric manifestations in thalassemia patients

		Frequency	Percent
Neuropsychiatric Manifestations In	Absent	31	62.0
	Present	19	38.0

Neuropsychiatric manifestations in the form of fatigue, depression, cognitive changes, numbness, and parathesia in the lower limbs were detected in 19 patients (39.8%) and absent in 31 patients (62%), while these manifestations were absent in control group.

4. Discussion:

β-Thalassemia is an inherited Hb disorder resulted from impairement of the β-globin chain synthesis and resulting in chronic hemolytic anemia. This might cause oxidative stress and tissue injury as a result of Fe overload, abnormal antioxidant enzymes, in addition to other essential trace elements. (7). Trace elements and minerals are needed for the optimal growth development, as well as metabolic function of the living organism. They regulate vital biological processes via finctioning as centers for stabilizing structures of proteins and enzymes, serving as cofactors for enzymes, and changing the ionic nature of membranes within a specific range. (8)

In our study The height of patients was significantly lower than controls . this was in agreement with (9). and with (10) the patients height with mean of (139.3 ± 26.2) which was significantly decreased in comparison with mean of (147.8 ± 27.7) with p value of (0.04) .Our study revealed that RBCs count and Hb levels were significantly decreased in patients in comparison with controls. serum Ferritin was significantly elevated in patients in comparison with controls . This was in accordance with (11) that showed that patients had significantly decreased mean pre-transfusion Hb. There was no significant difference in serum ferritin level between female and male. This is due to chronic anemia , repeated transfusions demonstrate high ferritin level.

In our study Platelets count was significantly increased in cases in comparison with in control .this may be due to active erythropoiesis resulted from chronic anemia.

In our study 82 % of cases has mongoloid features this was in consistency with (12) , that said mongoloid features in the TM patient group yielded statistically significant difference in comparison with those in the control group

In our study platelets count is higher in patients with splenectomy in comparison with in patients with no splenectomy . Hb level is slightly increased in patients with splenectomy .this was in agreement with (13) that showed that Splenectomy improves anemia, but doesn't decrease Fe load; more patients were found to be on regular iron chelation after doing splenectomy

In our study: serum ferritin level showed significant high level in group of patients non compliant to treatment and relatively low level in patients complaiant to treatment.... This is due to drug effect as chelating agent reduces level of ferritin and consequently its complicatons.

In our study . serum Mn was significantly elevated in cases in comparison with in control This was in harmony with (14) that found also that Mn serum level is higher in β-TM patient serum when compared to healthy and also in the study of (15), high levels of Mn were detected for TM patients while the Mn levels of the control group were below the detection limit of the method. This might be due to the fact that some trace elements like Mn, Fe or K+ show higher intracellulary level in comparison with extracellulary. Haemolysis of RBCs due to chronic hemolysis promotes the release of intracellulary trace elements.

heavy metal like iron and are often present in the diet as well as in the environment. They are needed in small amounts for good health; However, they become toxic in large concentrations. The toxicity of Mn has been proved to be a major threat and many health risks are related to its toxicity

In our study serum Se showed insignificant difference between patients of thalassemia major and controls .This was in agreement with (16) study which showed no differences between the patients of β-TM and the control groups for Se .but there was decreased activity of GPx and TrxR activities that are Se dependent enzyme , it is believed that the low GPx and TrxR activities may be due to of Se deficiency, but we could not find any differences in Se levels between the TM patients and the control group in the current study.

On the other side (4) study detected a significant reduction in the plasma level of Se in TM patients in comparison with controls.

These differences between the studies might result from different dietary intakes of Se.

In our study Chelators seem to be ineffective on Se level in TM patients. This also was proved in the study of (4)

In our study There was no correlation between Se and Mn in patients of TM.

In our study Neuropsychiatric manifestations in the form of fatigue, depression, cognitive changes, numbness, and parathesia in the lower limbs were detected in 19 patients (39.8%), This was in agreement with (9) that showed that (33%) has neuropsychatric manifestations .

that might be explained by vitamin B12 deficiency, chronic anemia, high Mn level, hypoxia, Fe overload, the occurrence of thromboemboli, the usage of DFO, and the impact of the chronic nature of the disease itself.

5. Conclusion:

This study showed that patients with β- TM have high manganese level as compared to normal controls with P value of (0.000), whereas they have insignificant difference as regard Se level with P value of (0.67).

6. References:

1. Muncie Jr, H. L., & Campbell, J. S. (2009). Alpha and beta thalassemia. *American family physician*, *80*(4), 339-344.
2. Tari, K., Valizadeh Ardalan, P., Abbaszadehdibavar, M., Atashi, A., Jalili, A., & Gheidishahran, M. (2018). Thalassemia an update: molecular basis, clinical features and treatment. *International journal of biomedicine and public health*, *1*(1), 48-58
3. El Missiry, M., Hamed Hussein, M., Khalid, S., Yaqub, N., Khan, S., Itrat, F., ... & Faulkner, L. (2014). Assessment of serum zinc levels of patients with thalassemia compared to their siblings. *Anemia*, *2014*.
4. Shazia, Q., Mohammad, Z. H., Rahman, T., & Shekhar, H. U. (2012). Correlation of oxidative stress with serum trace element levels and antioxidant enzyme status in Beta thalassemia major patients: a review of the literature. *Anemia*, *2012*.
5. Akbaraly, T. N., Hininger-Favier, I., Carriere, I., Arnaud, J., Gourlet, V., Roussel, A. M., & Berr, C. (2007). Plasma selenium over time and cognitive decline in the elderly. *Epidemiology*, 52-58
6. Martinez-Finley EJ, Gavin CE, Aschner M, Gunter TE (2013): Manganese neurotoxicity and the role of reactive oxygen species.Free Radic Biol Med 62:65–75
7. Model, B., & Berdoukas, V. (1984). The clinical approach to thalassemia. *London: Grune & Stratton*, 140-150.
8. Hambidge, M. (2003). Biomarkers of trace mineral intake and status. *The Journal of nutrition*, *133*(3), 948S-955S.

9. Sherief, L. M., El-Salam, A., Sanaa, M., Kamal, N. M., Almalky, M. A., Azab, S. F., ... & Gharieb, A. F. (2014). Nutritional biomarkers in children and adolescents with beta-thalassemia-major: an Egyptian center experience. *BioMed research international*. Article ID 261761, 7 pages.
10. Helen Bornaun, Dedeoglu, R., Oztarhan, K., Dedeoglu, S., Erfidan, E., Gundogdu, M., ... & Cengiz, D. (2016). Detection of early right ventricular dysfunction in young patients with thalassemia major using tissue Doppler imaging. *Iranian journal of pediatrics, 26*(3).
11. Ammar, S. A., Elsayh, K. I., Zahran, A. M., & Embaby, M. (2014). Splenectomy for patients with β-thalassemia major: long-term outcomes. *The Egyptian Journal of Surgery*, *33*(4), 232.
12. *Sachdev, S. (2000*). Quantum criticality: competing ground states in low dimensions. *Science, 288*(5465), 475-480.
13. El Beshlawy, A., El Tagui, M., Hamdy, M., El Ghamrawy, M., Azim, K. A., Salem, D., ... & Pennell, D. J. (2014). Low prevalence of cardiac siderosis in heavily iron loaded Egyptian thalassemia major patients. *Annals of hematology*, *93*(3), 375-379.
14. Mohkam, M., Shamsian, B. S., Gharib, A., Nariman, S., & Arzanian, M. T. (2008). Early markers of renal dysfunction in patients with beta-thalassemia major. *Pediatric nephrology*, *23*(6), 971-976.
15. *Alter B. Nathan D, Orkin S, Ginsburg D and Look T. (2002):* The hemoglobinopathies in hematology of infancy and childhood , 6th edition, Philadelphia Health Sciences, 385-389.
16. Genc, G. E., Ozturk, Z., Gumuslu, S., & Kupesiz, A. (2016). Mineral levels in thalassaemia major patients using different iron chelators. *Biological trace element research*, *170*(1), 9-16.