Original Article

Glucose homeostasis in Egyptian children and adolescents with β-Thalassemia major: Relationship to oxidative stress

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ABSTRACT

Background: Oxidative stress in children with β-thalassemia may contribute to shortened life span of erythrocytes and endocrinal abnormalities. **Aim:** This study was aimed to evaluate glucose homeostasis in Egyptian children and adolescents with β-thalassemia major and its relation to oxidative stress. **Materials and Methods:** Sixty children and adolescents with β-thalassemia major were studied in comparison to 30 healthy age and sex-matched subjects. Detailed medical history, thorough clinical examination, and laboratory assessment of oral glucose tolerance test (OGTT), serum ferritin, alanine transferase (ALT), fasting insulin levels, plasma malondialdehyde (MDA) as oxidant marker and serum total antioxidants capacity (TAC) were performed. Patients were divided into two groups according to the presence of abnormal OGTT. **Results:** The prevalence of diabetes was 5% (3 of 60) and impaired glucose tolerance test (IGT) was 8% (5 of 60). Fasting blood glucose, 2-hour post-load plasma glucose, serum ferritin, ALT, fasting insulin level, homeostatic model assessment for insulin resistance index (HOMA-IR) and MDA levels were significantly elevated while TAC level was significantly decreased in thalassemic patients compared with healthy controls ($P < 0.001$ for each). The difference was more evident in patients with abnormal OGTT than those with normal oral glucose tolerance ($P < 0.001$ for each). We also observed that thalassemic patients not receiving or on irregular chelation therapy had significantly higher fasting, 2-h post-load plasma glucose, serum ferritin, ALT, fasting insulin, HOMA-IR, oxidative stress markers OSI and MDA levels and significantly lower TAC compared with either those on regular chelation or controls. HOMA-IR was positively correlated with age, serum ferritin, ALT, MDA, and negatively correlated with TAC. **Conclusions:** The development of abnormal glucose tolerance in Egyptian children and adolescents with β--thalassemia is associated with alteration in oxidant-antioxidant status and increase in insulin resistance. **Recommendation:** 1- Glucose tolerance tests, HOMA-IR, and MDA should be an integral part of the long-term follow-up of children and adolescents with β-thalassemia major. 2- Regular iron chelation and antioxidant therapy should be advised for thalassemic patients to improve glucose hemostasis.

Key words: β-thalassemic major, diabetes mellitus, insulin resistance, oxidative stress

Introduction

In Egypt, thalassemia is the most common hemolytic anemia with carrier rates ranging from 9 to 16%.[1] It constitutes 45% of the total hematological patients and 86% of chronic hemolytic pediatric patients attending the Hematology Clinic, Assiut Children University Hospital - Egypt. Thalassemia causes a severe hemolytic anemia in patients necessitating frequent transfusions leading to iron overload and endocrine complications. Diabetes is an important problem encountered in thalassemic patients.[2] The severity and type of glucose disturbances vary greatly in different studies. In addition, controversy about the etiology of this glycemia abnormality still exists.[3-5] Decreased or impaired β-globin biosynthesis in β-thalassemia leads to ineffective erythropoiesis and plays a crucial role in producing the role of oxidative stress in thalassemic patients.[6] Glucose homeostasis and its relation to oxidative stress has not

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been widely studied especially in Egyptian children and aldolescents with β-thalassemia major.

Aim of the study

This study was aimed to evaluate glucose homeostasis in Egyptian children and adolescents with β-thalassemia major and its relation to oxidative stress.

Materials and Methods

This cross-sectional contolled study was conducted on 60 children and adolescents with β-thalassemia major attending the Outpatients Clinics of Assiut University Children Hospital, Assiut, Egypt from February 2013 to September 2013. Another group of 30 age and sex-matched healthy subjects recruited from our hospital records and proven to be healthy after full clinical examination and laboratory investigations were enrolled as control group. Patients and controls were on a normal diet without vitamin supplementation. The patients were diagnosed as β-thalassemia major based on clinical and hematological characteristics [complete blood count (CBC) and hemoglobin electrophoresis.

Inclusion criteria

- Age >6 years <18 years
- They had received blood transfusion and chelation therapy with variable compliance
- Absence of cardiac, and renal disease.

Exclusion criteria

- Patients on antioxidants or on medication known to cause glucose intolerance
- Patients with hepatitis B or C virus infection
- Family history of diabetes mellitus in 1st degree relatives.

An informed consent was obtained from each patient or control subject or their legal guardians before enrollment into the study. The study was approved by the local ethical committee of Assiut Children University Hospital.

All cases were subjected to

1. Detailed history including age, sex, duration of illness, frequency of blood transfusion, type and duration of chelation therapy, and history of splenectomy
2. Clinical examination including
   - Anthropometrics measurements: The weight and height of the each subject was measured. Body mass index (BMI) was calculated as weight (kg) divided by square of the height (m^2)
   - Detailed local abdominal examination including liver size and spleen size
3. Laboratory investigations included
   - Complete blood picture (CBC)
   - Determination of alanine aminotransferase (ALT) as a marker of hepatic dysfunction
   - Glycometabolic status was assessed by performing oral glucose tolerance test (OGTT) that was done after 8 hours of fasting at 8.00 am. Glucose was ingested in a dose of 1.75 g/kg to a maximum of 75 g, and serial blood samples were obtained for the measurement of plasma glucose. Diagnosis of diabetes is established when a fasting plasma glucose >126 mg/dL or 2-h plasma glucose >200 mg/dL during OGTT. Impaired glucose tolerance test (IGT) is considered when 2-h OGTT plasma glucose concentration is >140 and <200 mg/dL[7]
   - Fasting serum insulin measurement was done by an auto-analyzer (DDC/immulite). Insulin resistance (IR) was calculated using the following equation: The homeostasis model assessment method: HOMA-IR = fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5[8]
   - Serum ferritin by an auto-analyzer (AxSYM Ferritin-Abbott laboratories, Abbott Park, IL, USA)
   - Plasma malondialdehyde (MDA) was assayed spectrophotometerically using thiobarbituric acid (TBA).[9] The final results were expressed as umol of MDA formed per liter of serum. Intra-assay and inter-assay imprecision were 3.24% and 5.78%, respectively[10]
   - Serum total antioxidants capacity (TAC) and total peroxides (TPs; organic and inorganic) were colorimetrically measured according to the methods described by Koracevic *et al.,*[11] and Harma *et al.*[12] Oxidative stress index (OSI) was the ratio of TP/TAC.[11]

Statistical analysis

Data analysis was carried out using Statistical Package for Social Sciences (SPSS, version 16). Simple statistics such as frequency, arithmetic mean, and standard deviation (SD) were used. For comparison of the two groups, Student's *t*-test was used for parametric data and the Mann-Whitney U-test was used for nonparametric data. Multiple groups were compared using the ANOVA test. Linear correlations were performed by Spearman's or Pearson's test. For all analyses, $P < 0.05$ provided statistical significance.

Results

- The prevalence of diabetes was 5% (3 of 60) and IGT was 8% (5 of 60) among thalassemic patients. The most relevant characteristics of patients are shown in [Table 1]
- Thalassemic patients had significantly higher fasting,

2-h post-load plasma glucose levels, serum ferritin, ALT, fasting insulin level, HOMA-IR, oxidative stress markers (OSI and MDA) and significantly lower TAC compared to controls [Table 2]

- No significant difference in fasting, 2-h post-load plasma glucose levels, serum ferritin, ALT, fasting insulin level, HOMA-IR, oxidative stress markers (OSI and MDA) and TAC between the splenectomized patients and non-splenectomized patients with thalassemia
- Patients with abnormal glucose tolerance test were older with longer disease duration. They had significantly higher fasting, 2-h postload plasma glucose, serum ferritin, ALT, fasting insulin, HOMA-IR, oxidative stress markers (OSI and MDA) levels and significantly lower TAC compared with those of normal OGTT [Table 3]
- Thalassemic patients not receiving or on irregular chelation therapy had significantly higher fasting, 2-h post-load plasma glucose, serum ferritin, ALT, fasting insulin, HOMA-IR, oxidative stress markers (OSI and MDA) levels and significantly lower TAC compared with either those on regular chelation or controls [Table 4]
- HOMA-IR was positively correlated with age, ferritin, ALT and MDA and negatively correlated with TAC [Figures 1-5]
- MDA was positively correlated with with serum ferritin ($r = 0.754$, $P \leq 0.001$), ALT ($r = 0.722$, $P \leq 0.01$), and negatively correlated with TAC ($r = -0.655$, $P \leq 0.001$)
- Serum ferritin was positively correlated with with age ($r = 0.812$, $P \leq 0.001$), duration of the disease ($r = 0.722$, $P \leq 0.01$), ALT ($r = 0.803$, $P \leq 0.001$) and negatively correlated with TAC ($r = -0.817$, $P \leq 0.001$).

Table 1: Demographic characteristics of thalassemic patients

Variable	Patients (*n*=60)
Age (years)	15.1±3.3
Sex (male/female)	22/38
Age at diagnosis (months)	8.3±2.2
Mean age at first blood transfusion (months)	9.7±2.04
Mean duration of blood transfusion (years)	8.452±3.7
Mean age at start of iron chelation therapy (years)	6.8±5.4
Number of patients on chelation therapy (none/irregular/regular)	12/28/20
Chelation duration (years)	8.2±3.1
Splenectomized/non-splenectomized	26/34

Table 2: Comparison between β- thalassemia patients and controls

	Patients with Thalassemia (60)	Healthy controls (30)	*P* value
Age (years)	15.1±3.3	14.2±2.1	NS
Body mass index (kg/m^2)	15.3±2.7	16.7±4.6	NS
Fasting plasma glucose (mg/dL)	106.7±33.1	88.3±13.1	<0.01
2-h postload plasma glucose (mg/dL)	139.6±78.3	104.2±15.3	<0.001
Serum ferritin (mg/L)	3011±2101	77.2±21.1	<0.001
ALT (U/L)	83.5±44.2	23.5±4.2	<0.001
Fasting Insulin(μIU/ml)	16.8±5.7	5.2±2.6	<0.001
HOMA-IR	4.37±1.16	1.13±1.13	<0.001
MDA (μmol/L)	1.742±0.06	0.565±0.08	<0.001
TP(mmol/L)	0.065±0.013	0.053±0.011	NS
OSI	4.215±0.22	2.217±0.25	<0.001
TAC (μmol/L)	1.299±0.06	2.301±0.24	<0.001

OSI: Oxidative stress index, MDA: Malondialdehyde, TAC: Total antioxidant capacity, TP: Total peroxide, ALT: Alanine aminotransferase

Table 3: Comparison between measured parameters in β- thalassemia patients with normal and abnormal glucose tolerance

	Patients with normal glucose tolerance test *n*=52	Patients with abnormal glucose tolerance test *n*=8	*P* value
Age (years)	14.2±2.4	15.6±1.2	NS
Body mass index (kg/m^2)	14.3±3.5	17.7±3.3	NS
Fasting plasma glucose (mg/dL)	87.5±9.21	138.3±76.1	<0.001
2-h postload plasma glucose (mg/dL)	106.6±14.3	244.2±112.3	<0.001
Serum ferritin (mg/L)	3296±2245	4584±2145	<0.001
ALT (U/L)	73.5±34.7	123.5±41.2	<0.001
Fasting Insulin(μIU/ml)	6.6±2.3	18.5±4.5	<0.001
HOMA-IR	1.42±1.10	6.31±2.12	<0.001
MDA (umol/L)	0.832±0.4	1.88±0.6	<0.01
TP(mmol/L)	0.065±0.011	0.073±0.013	NS
OSI	2.342±0.34	5.391±0.15	<0.001
TAC (umol/L)	3.345±0.17	1.403±0.32	<0.001

OSI: Oxidative stress index, MDA: Malondialdehyde, TAC: Total antioxidant capacity, TP: Total peroxide, ALT: Alanine aminotransferase

Discussion

The use of regular, frequent blood transfusions in thalassemia major has improved the span and quality of life of the patients, but it leads to chronic iron overload which frequently causes endocrine problems especially diabetes mellitus.[13,14] In the present study, the prevalence of diabetes was 5% (3 of 60) and IGT was 8% (5 of 60) among studied cases with β-thalassemia major. This prevalence was very high compared to the prevalence of type 1 DM in Egyptian children and adolescents (the prevalence of T1DM in Egypt is 0.13-0.4% according to the International Diabetes Federation[15]). In previous reports in children and adult, the occurrence of impaired glucose metabolism in transfusion-dependent thalassemic patients has been reported to range from 2.3 to 24% depending on the age of studied population, the duration of the blood transfusion, the amount of iron overload, and

Table 4: Comparisons between measured parameters in β- thalassemia patients according to the use of chelation therapy

Parameters	Regular chelation (*n*=20)	Irregular chelation (*n*=28)	No chelation (*n*=12)	Healthy controls (*n*=30)
Age (years)	13.7±3.6 *P*1>0.05	16.7±3.2 *P*1>0.05, *P*2>0.05	16.3±4.1 *P*1>0.05, *P*2- > 0.05, *P*3>0.05	14.2±2.1
Body mass index (kg/m^2)	15.4±2.8 *P*1>0.05	17.6±2.5 *P*1>0.05, *P*2>0.05	18.2±3.1 *P*1>0.05, *P*2<0.05, *P*3>0.05	16.7±4.6
Fasting plasma glucose (mg/dL)	88.4±6.11 *P*1>0.05	176.3±57.2 *P*1<0.01, *P*2<0.01	198.2±45.3 *P*1<0.001, *P*2<0.001, *P*3<0.05	82.3± 13.1
2-h post load plasma glucose (mg/dL)	108.5±11.2 *P*1>0.05	235.2±98.8 *P*1<0.01, *P*2<0.01	266.1±134.7 *P*1<0.01, *P*2<0.01, *P*3<0.05	104.2± 15.3
Serum ferritin (mg/L)	354± 136 *P*1<0.05	2131±986 *P*1<0.0001, *P*2<0.0001	4317± 1986 *P*1<0.001, *P*2<0.0001, *P*3<0.01	77.2±21.1
ALT (U/L)	71.4± 12.7 *P*1<0.05	122.5±22.9 *P*1<0.001, *P*2<0.05	134.5± 19.7 *P*1<0.001, *P*2<0.05, *P*3>0.05	23.5±4.2
Fasting Insulin (μIU/ml)	5.9±1.4 *P*1>0.05	15.4±3.4 *P*1<0.001, *P*2<0.001	18.2±1.7 *P*1<0.001, *P*2<0.001, *P*3>0.05	4.2±2.6
HOMA-IR	2.39±1.30 *P*1>0.05	5.43±3.17 *P*1<0.001, *P*2<0.01	7.68±2.19 *P*1<0.001, *P*2<0.001, *P*3>0.05	1.13±1.13
MDA (umol/L)	0.766±0.50 *P*1>0.05	2.57±1.60 *P*1<0.001, *P*2<0.01	2.99±1.80 *P*1<0.001, *P*2<0.001, *P*3>0.05	0.565±0.08
TP(mmol/L)	0.065±0.07 *P*1>0.05	0.087±0.06 *P*1<0.01, *P*2<0.01	0.091±0.05 *P*1<0.01, *P*2<0.01, *P*3>0.05	0.053±0.011
OSI	2.851±0.23 *P*1<0.05	4.80±0.15 *P*1<0.001, *P*2<0.01	5.645±0.15 *P*1<0.001, *P*2<0.01, *P*3>0.05	1.60±0.25
TAC (umol/L)	2.271±1.29 *P*1<0.05	1.811±0.46 *P*1<0.01, *P*2<0.01	1.612±0.33 *P*1<0.01, *P*2<0.05, *P*3>0.05	3.301±0.24

*P*1 significance vs. controls, *P*2 significance vs regular chelation, *P*3 significance vs irregular chelation, OSI: Oxidative stress index, MDA: Malondialdehyde, TAC: Total antioxidant capacity, TP: Total peroxide, ALT: Alanine aminotransferase

the dosage of iron-chelating therapy.[16-18] Diabetes mellitus still responsible for significant morbidity and mortality in thalassemic patients. Because not all of the patients with thalassemia major could be correctly diagnosed by fasting glucose alone, it is preferred to use OGTT rather than fasting blood glucose for the diagnosis of abnormal glucose tolerance in thalassemic patients.[17]

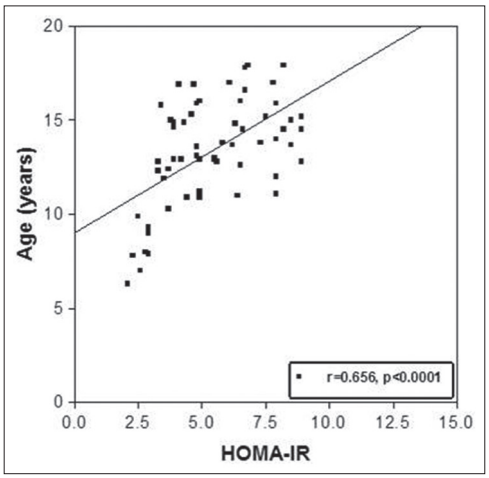

Figure 1: Correlation and linear regression between HOMA-IR and age in β-thalassemic patients

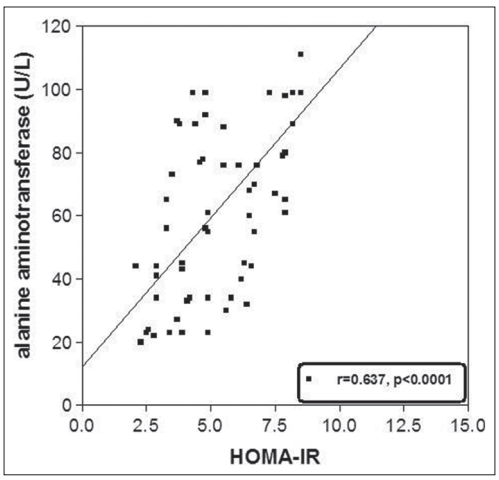

Figure 2: Correlation and linear regression between HOMA-IR and alanine tranferase in β-thalassemic patients

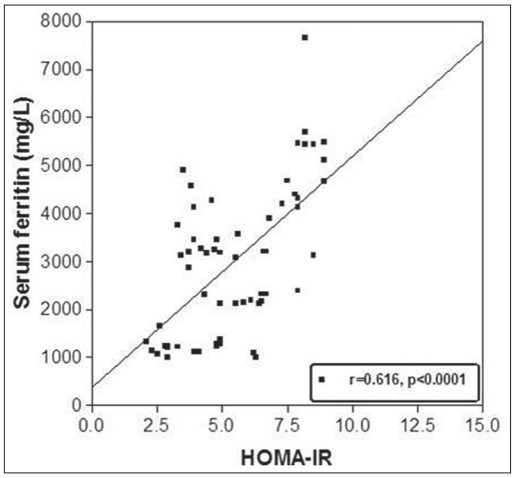

Figure 3: Correlation and linear regression between HOMA-IR and ferritin in β-thalassemic patients

In this study, fasting and 2 hours glucose, fasting insulin, HOMA-IR, ALT and serum ferritin levels showed significant

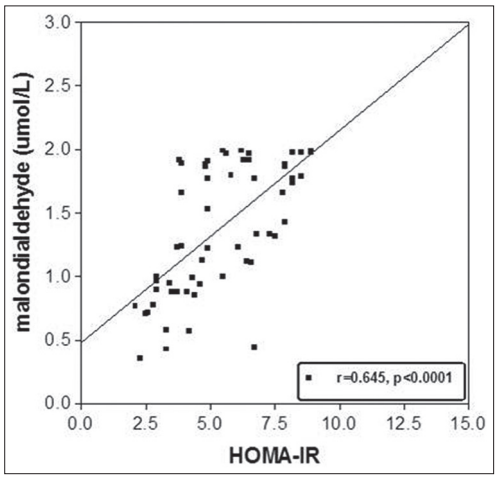

Figure 4: Correlation and linear regression between HOMA-IR and malondialdehyde in β-thalassemic patients

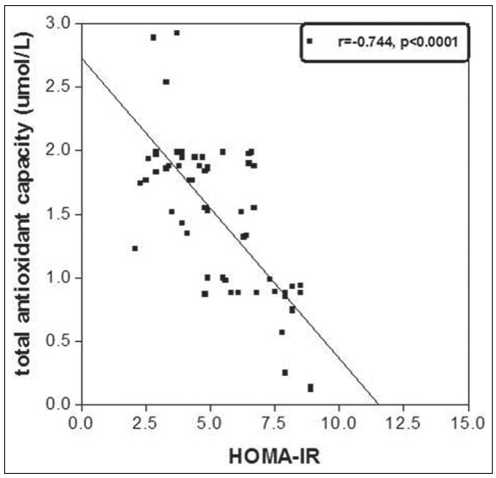

Figure 5: Correlation and linear regression between HOMA-IR and total antioxidant capacity in β-thalassemic patients

elevation in studied patients with β-thalassemia compared with healthy controls ($P < 0.001$). The increase was more evident in patients with abnormal OGTT than those with normal oral glucose tolerance. ($P < 0.001$). HOMA-IR as a marker of insulin resistance showed significant positive correlation with age, serum ferritin, and ALT levels suggesting that the degree of iron overload and hepatic dysfunction are responsible for the insulin resistance. This, in agreement with previous reports, demonstrated the increasing insulin levels and insulin resistance in β-TM patients with DM. These studies suggested that overt diabetes mellitus in β-TM patients is preceded by a long period of hyperinsulinemia and insulin resistance. Deterioration to IGT occurs when insulin resistance increases further and/or the compensatory insulin secretory response decreases.[19,20] The insulin resistance has been postulated to be at the level of the liver (due to iron deposition), where it may interfere with the insulin's ability to suppress hepatic glucose uptake, and also at the level of the muscle, where iron deposits may decrease the glucose uptake.[21] With advancing age a persistent insulin resistance along with the decrease in the circulating insulin levels (due to declining β-cell function), leads to the onset of glucose intolerance and frank diabetes mellitus.[21,22] However, even in the face of adequate chelation a significant amount of carbohydrate metabolism dysfunction occurs,[23] suggesting that the development of diabetes might be complicated by other factors.[24] Pancreatic autoimmunity demonstrated by islet cell antibodies,[22] liver abnormalities like cirrhosis, liver fibrosis,[25] genotype- IVS II nt 745,[26] family history of diabetes[21] are some of the factors postulated.

In the present study, oxidative stress markers (MDA and OSI) were significantly higher in children with β-thalassemia compared with the control. The difference was more evident in patients with abnormal OGTT than those with normal oral glucose tolerance. ($P < 0.001$). In addition, HOMA-IR correlated positively with MDA. This in agreement with previous reports that demonstrated that the increase in the oxdative stress markers and its relation to devopment of DM in patients with β-thalassemia.[27-29] These findings support the role of oxidative stess and development of DM in children with β-thalassemia. β-TM patients generated oxidative stress and rapid formation of marked amounts of free MDA.[30] The increased circulating MDA level may act as the persistent metabolic signal for insulin secretion and progression to insulin resistance.[29] Chronic oxidative stress is particularly dangerous for β-cells because pancreatic islets have the lowest levels of antioxidant enzyme expression, and β-cells have high oxidative energy requirements.[30] In addition, there is considerable evidence that increased free radicals impair glucose stimulated insulin secretion, decrease the gene expression of key β-cell genes, and induce cell death.[31] If β-cell functioning is impaired, it results in an underproduction of insulin, fasting hyperglycemia, and eventually, the development of diabetes.[29]

In the present study, the antioxidant defense was evaluated by measuring TAC in serum. The measurement of different antioxidant molecules separately is labor intensive, time consuming, and costly. Moreover, some investigators suggest that assessment of TAC of plasma may be more useful than measuring each antioxidants individually since their synergistic interaction could be determined.[32] In our patients with thalassemia, TAC was significantly lower in thalassemic patients compared with the controls. The difference was more evident in patients with abnormal OGTT than those with normal oral glucose tolerance. ($P < 0.001$). In addition, MDA, serum ferritin and HOMA-IR correlated negatively with TAC. The antioxidant status of our patients further emphasizes the role of oxidative stress as a significant determinant in appearance of DM among the studied thalassemic patients.

Pancreatic islets have the lowest levels of antioxidant enzyme expression. Moreover, thalassemic patients are in a state of enhanced oxidative stress due to iron overload with subsequent consumption of antioxidants trying to ameliorate increased oxidative stress parameters which have an important role in stimulation of insulin secretion and development of insulin resistance.[29]

In the present study, thalassemic patients not receiving or on irregular chelation therapy had significantly higher fasting, 2-h postload plasma glucose, serum ferritin, ALT, fasting insulin, HOMA-IR, oxidative stress markers (OSI and MDA) levels and significantly lower TAC compared with either those on regular chelation or controls. Aggressive regular chelation and antioxidant therapy should be used to cut the progression of the adverse effects of oxidative stress and to improve carbohydrate physiology in transfused β-TM patients.[33]

Conclusions

The development of abnormal glucose tolerance in Egyptian children and adolescents with β-thalassemia is associated with alteration in oxidant, antioxidant status, and increase in insulin resistance.

Recommendation

1-Glucose tolerance tests, HOMA-IR and MDA should be an integral part of the long-term follow-up of children and adolescents with β-thalassemia major. 2- Regular iron chelation and antioxidant therapy should be advised for thalassemic patients to improve glucose hemostasis.

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