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Oxidative Stress Parameters in Beta-Thalassemia

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Abstract: **Evaluation of the effect of the antioxidants lack on the level of oxidative stress and to find out if there is any increased susceptibility to atherogenesis.**

Patients and methods: Twenty Egyptian patients with β-thalassemia and twenty healthy controls were recruited from the outpatient clinic of Clinical Genetics Department, National Research Centre. Twenty healthy Egyptian were used as controls. This study was approved by the Ethics Committee.

Results: In beta-Thalassaemia patients had significant decrease in mean of Paraoxonase1, Arylesterase, Reduced Glutathione and Catalase ($p<0.01$) activities along with significant increased malondialdehyde (MDA) ($p<0.01$) level. Cholesterol, HDL-cholesterol, LDL-cholesterol levels were found to be significantly lower ($p<0.01$, $p<0.05$ and $p<0.01$ respectively), while the triglyceride level was found to be significantly higher ($p<0.01$) in patients with Beta-Thalassemia major than in the controls.

Conclusion: Beta-Thalassaemia patients are mainly exposed to higher oxidative stress of reactive oxygen intermediates due to iron overload hence, they had decreased antioxidants level(Paraoxonase 1, arylesterase , reduced glutathione and catalase) along with hypertriglyceridaemia, hypocholesterolemia ,low HDL-cholesterol levels and also increased malondialdehyde level. so that all these factors contributing to the development of atherosclerosis.

Keywords: **b-Thalassaemia- oxidative stress- atherosclerosis –Paraoxonase 1- arylesterase- reduced glutathione- catalase- malondialdehyde .**

1. INTRODUCTION

Beta (**β**)-thalassemia is the most widespread autosomal recessive hereditary disease, and it is characterized by reduced (β^+) or no (β^0) **β** globinchain synthesis**1**–5. Clinical appearances of this disorder include microcytosis and hemolytic anemia that requires regular blood transfusion **2,5**. The disorder can lead to irreversible damage to organs and tissues due to iron accumulation.

Beta thalassemia exists in different forms depending upon the beta globin chains deficit. The most severe form is beta thalassemia major which occurs as a result of inheritance of two beta globin chain mutations either in homozygous or compound heterozygous states. Patients with beta thalassemia major need repeated blood transfusions for survival due to severe anemia. The beta globin chain deficit for beta-thalassemia trait (minor) is 50%, while that for beta-thalassemia major is 100% and 50–80% for beta-thalassemia intermediate **6,7 (Elizabeth and Ann., 2010 and Shazia et al., 2012)**. Transfusion therapy in β- erythrocytes, iron overload, and depletion of antioxidants in tissues (e. g. blood circulation) promote oxidative stress. This implies the possible alteration of redox status in thalassemic patients. **Kassab- Chekir et al, 2003& Das et al., 2004 and Jetawattana., 2005)** appear after about 2-4 thalassemia major patients requires adequate iron chelation treatments to avoid its progressive accumulation in several organs, evoking subsequent tissue damage and, eventually, death. Although lifelong blood transfusions combined with adequate chelation therapy have significantly improved the survival of β-thalassemia major patients, cardiac complications remain the main cause of mortality in both

β-thalassemia major and intermedia (Modell et al ., 2000 &Aessopos et al., 2004 & 2005 and Stoyanova et al., 2012). In addition, arterial and venous thromboembolic events in β-thalassemia major patients have been reported (Panigrahi and Agarwal., 2007and Stoyanova et al., 2012). Several pathogenic factors contribute to these complications, including, adhesion of thalassemic erythrocytes in microvessels (Hovav et al., 1999 and Stoyanova et al., 2012).

Many studies have shown that reactive oxygen species are generated in increased amounts in thalassemic red cells. Conditions such as rupture of employed based on many factors such as age of the patients and severity of the disease. The symptoms vary from relatively mild anemia to life-threatening anaemia 14-17 (Phumala et al, 2003& overnight fasting state. Samples were stored at - months of age 18,19 (Ghone et al., 2008 and Bhagat et al., 2012). The production of free radicals associated with excessive iron-loading is increased in these patients (Canatan et al., 2001and Arıca et al ., 2012). In recent years, the relationship between the increase in blood lipid levels and atherosclerotic diseases was shown in the performed researches (Ginsberg., 1994& Gotto., 1994& Daniels et al ., 2008 and Arıca et al ., 2012).

2. SUBJECTS AND METHODS

The present research was carried out in the Department of Clinical Genetics Department, National Research Centre. The Institutional Ethical Committee clearance was obtained . Twenty thalassemic patients (n=20), their age range between 6 months to 30 years participated in this study. Mean age of participants in case group was 12.91 ± 8.47 (mean±SD) The control group consisted of 20 healthy participants matched sex and age. twenty normal Controls healthy persons (n=20) aged 5 to 30 years were used as control. The mean age of control was found to be 16.50 ± 8.28 . β- thalassemia patients were previously diagnosed by ultimately molecular characterization of β-Thalassemia, hemolytic state assessment, complete blood picture(CBC) analysis and hemoglobin electrophoresis. The blood samples were obtained following an β-thalassemia were found to be significantly lower than those of the control group ($p<0.001$), 70 o C until analysis. The all parameters measurement was carried out by using Shimadzu UV-1601 spectrophotometer. The estimation of paraoxonase1 activity was done according to the method of Menys et al., 2006, arylesterase by Kuo et al., 1995 method, reduced glutathione by Samuel et al., 2010 method, catalase by Carter et al., 2004 method,Malondialdehyde as an indicator of lipid peroxidation according to the method of Uchiyama and Mihara.,1978 and lipid profile (cholesterol by Roeschlau et al., 1974 , triglycerides by NÜssel.,1975., HDL and LDL by Gordon et al., 1977 .

Descriptive results were reported as mean (standard deviation).A P value of <0.05 was considered as statistically significant.

3. RESULTS

Results revealed that a predominance age from 10 to 20 years in beta-thalassemia patients. Fig.1. 18 of beta thalassemia patients had positive family history (90%) and 2 patients had negative family history (10%) Fig.2.

Table 1, paraoxonase1, arylesterase, reduced glutathione and catalase levels in patients with while the malondialdehyde levels were found to be higher ($p<0.01$). As seen in Table 2, cholesterol, LDL cholesterol($p<0.01$) and HDL-cholesterol($p<0.05$) levels in patients with **β-thalassemia** were found to be significantly lower than those of the control group, while the triglyceride levels were found to be higher ($p<0.01$).

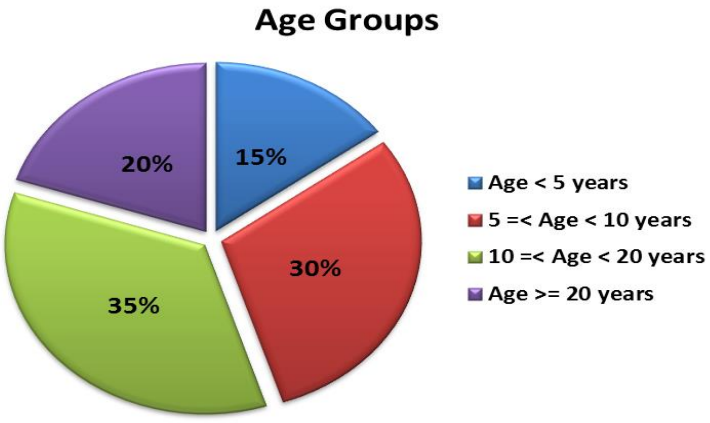

Fig.1: Age distribution in β-thalassemia patients. Showing a predominance age from 10 to 20 years

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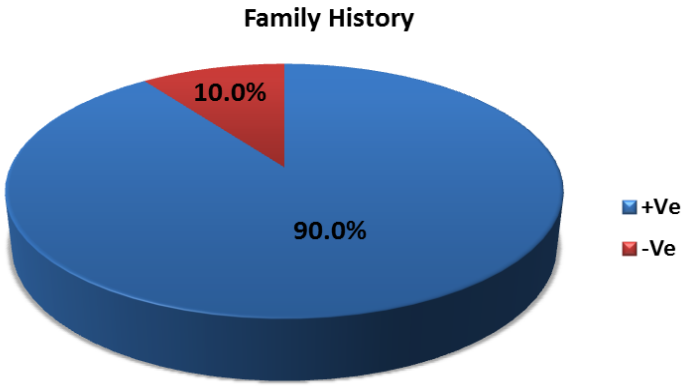

Fig.2: Family history in beta-thalassemia patients. Showed elevated ratios of positive family history confirming the autosomal recessive inheritance of the disease

4. DISCUSSION

Patients with β-thalassemia are mainly exposed to oxidative stress due to iron overload. Therefore evaluation and maintenance of antioxidant defense can be useful in protecting β-thalassemia patients from more serious complications of the disease (Laksmitawati et al., 2003& Kassab-Chekir et al., 2003& Dhawan et al., 2005 & Şimşek et al., 2005& Swaminathan et al., 2007 and Ghone et al., 2008).Oxidative modifications within the arterial wall that may initiate and/or contribute to atherogenesis likely occur when the balance between oxidants and antioxidants shifts 56,57(Halliwell and Gutteridge, 1999 and Stocker and Keaney, 2004).

In the present study found a predominance of age from 10 to 20 years in β-Thalassemia patients. beta thalassemia patients had a similarly affected family member (90.0%). while, El-Kamah et al., 2009 58 found that , Positive family history in 34.4% of thalassemia intermedia and thalassemia major. The current results revealed that, oxidative stress parameters in beta thalassemia patients revealed significantly higher Paraoxonase1 and aryl -esterase levels than the controls (P<0.001). These findings denoted that these patients suffered from the effect of increased oxidative stress. Livrea et al. 1998 and Barrano et al., 2000 Cakmak et al., 2009 reported that BTM patients had decreased paraoxonase and arylesterase activities. Aydin et al., 2012 results showed that there was a highly significant decrease in serum PON1 and serum TAC levels in BTT compared with controls. Selek et al., 2007 and Aydin et al., 2012 noted decreased levels of serum PON1 activity and increased oxidative stress in β-thalassaemia minor. Durrington et al., 2001 showed that there was a highly significant decrease in serum PON1 and serum TAC levels in BTT compared with controls. This study, also demonstrated that there was no statistical significant difference in Paraoxonase1 and Arylesterase levels (p>0.05) between male and female patients in beta-thalassemia patients. In the present study, catalase (CAT), responsible for detoxification of hydrogen peroxide in the cells and glutathione (GSH), an antioxidant which prevents damage to the cellular components were measured in beta thalassemia patients. Catalase and glutathione reductase revealed significantly higher catalase and glutathione reductase levels than the controls (P <(0.001 These values of serum catalase and glutathione reductase in beta-thalassemia patients were 3.7 and 3 times respectively lower than in healthy controls. These results are similar to those of Ruchaneekorn et al., 2010 and Attia et al.,2011. where low activity of catalase and glutathione reductase was detected, the decrease of these enzymes activities were 2.75 and 3 times respectively lower than in the healthy controls.

Malondialdehyde (MDA) which is the end product of the primary reactions that lead to the significant oxidation of such polyunsaturated fatty acids in cellular membranes and, thus, serves as a reliable marker of oxidative stress was detected Irmak et al., 2003 and Yildirim et al., 2011.

In the current study, the values of MDA in beta-thalassemia patients, were significantly higher than in healthy controls (P<0.001). This is in agreement with Das et al., 2004 and Ghone et al., 2008 ,who reported a significant increase (p<0.001) in the level of serum MDA in patients with beta thalassemia major as compared to controls. Abd el-maksoud et al., 2009, similarly reported significantly increased MDA in studied groups (p< 0.001). Naithani et al., 2006 and Walter et al., 2006, explained the significant increase in MDA in their thalassemic patients to be due to excess unpaired α -hemoglobin chains which are more prone to denaturation and oxidation. The reported increased plasma malondialdehyde

(MDA) level, as measured by the thiobarbituric acid reaction substance (TBARS) methods, in β-thalassemia patients Elalfy et al., 2013, is an indicator of an increase in lipid peroxidation and the ongoing oxidative stress in beta-Thalassemia patients, which is a factor of increased parthenogenesis and coronary heart disease.

Aviram et al., 2000; Labib et al., 2011 and Aydin et al., 2012, found that PON1 is mostly responsible for the antioxidant activity of HDL, to inhibit HDL oxidation and to preserve the anti-atherogenic function of HDL.

Increasing evidence suggests that the oxidative modification of low-density lipoprotein (LDL) is the key step in the sequence of events leading to atherogenesis-related vascular alternations Steinberg et al., 1989; Berliner et al., 1996 and Selek et al., 2007 hence, lipid profile for all studied patients was evaluated including : Cholesterol, High density Lipoproteins (HDL) and Low density Lipoproteins (LDL), their levels in controls were more significantly higher than beta-thalassemia patients ($P<0.01$in all).While(except) Triglycerides Levels in controls were significantly lower than beta-thalassemia patients ($P<0.01$). So that they suffer from decreased Cholesterol, (HDL) and (LDL) while they suffer from increased Triglycerides than in healthy controls. These results are in agreement with Maioli et al ., 1997 who concluded that cholesterol, HDL-cholesterol, and LDL cholesterol levels were found to be lower in beta-thalassemia patients than those of healthy individuals. On the other hand, Bordbar et al., 2012, reported highly significant decreases in LDL-C, HDL-C and TC levels in BTT subjects compared with controls. The decrease in LDL-C and TC levels appears to have a protective effect against atherosclerosis. However, the modification of LDL in the arterial wall, particularly by oxidation, appears to be more important than the level of LDL-C in the development of atherogenesis. This hypothesis is supported by the assumption of Haghpanah et al., 2010, who stated that at any level of serum cholesterol, there is a wide variation in the incidence of coronary heart disease, and oxidation is crucial to the cellular uptake of LDL in the first stages of atherosclerotic plaque formation (Aydin et al., 2012). Low levels of LDL-C in BTT subjects have been found also in a study of Madani et al., 2011.

Goldfarb et al., 1991, reported that in patients with βTM, the total cholesterol, HDL-cholesterol, LDL-cholesterol levels were decreased and triglyceride level was increased. However, the differences were not statistically significant. Whereas another study reported that the levels were the same in Thalassemia patients and the control group (Cakmak et al., 2009). Lipid abnormality has been frequently reported in thalassemia, but its pathophysiology is not totally clear(Meral et al., 2000; Calandra et al., 2004 and Patne et al., 2012). In this study, we observed low total serum cholesterol, low HDL-cholesterol and low LDL cholesterol with elevation of triglycerides in beta thalassemia major patients, as compared to control subjects. These results are in agreement with previous reports with regarding the above altered serum lipid pattern (Hartman et al., 2002 and Patne et al., 2012) in patients with beta thalassemia major. In our study the HDL cholesterol in thalassemic patients had very low values. Studies suggest that risk for myocardial infarction is high when HDL cholesterol is low (Patne et al., 2012; Brewer et al., 2003). The later may highlight the importance of total-to-HDL cholesterol ratio for the evaluation of blood lipids and the prevention of atherosclerotic disease. It has also been reported that the total cholesterol-to-HDL cholesterol ratio predicts coronary heart disease risk regardless of the absolute LDL- and HDL-cholesterol. Thalassemic patients are at much higher coronary risk than their matched controls, because of the low HDL cholesterol production, even if they are within normal values of total cholesterol (Giardini et al., 1978 and Patne et al., 2012). In addition, Patne et al., 2012 observed that total serum phospholipids, their fractions and cholesterol were significantly lower among patients with thalassemia major. Increased concentrations of TG were observed in most published studies on lipid profiles of thalassemic patients (Patne et al., 2012).

5. CONCLUSION

The current study highlighted the state of oxidative stress found in beta thalassemia patients. The low level of cholesterol, high density lipoproteins and low density lipoproteins and high level of triglyceride indicates the increased incidence of atherogenesis in beta thalassemia patients. This study recommends the administration of antioxidants in beta thalassemia patients to ameliorate the symptoms and improve the quality of life in these patients.

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