

## Short Communication

# $\beta$ -Thalassemia - Call for Restoration of Normal Vitamin E Status

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A recent review of  $\beta$ -thalassemia pathophysiology discussed several drugs (old and new) for treating anemia and concomitant iron overload [1], but an obvious consequence of the presence of unmatched  $\alpha$ -hemoglobin (Hb) in  $\beta$ -thalassemia red blood cells ( $\beta$ -thal RBCs) is systemic oxidative stress, first noted by reduced plasma vitamin E (vit E) levels and increased sensitivity of  $\beta$ -thal RBCs to H<sub>2</sub>O<sub>2</sub>-induced lysis in  $\beta$ -thalassemia subjects [2]. This led to numerous clinical trials in  $\beta$ -thal subjects of vitamin E supplementation (alone or combined

with other anti-oxidants, e.g., N-acetyl cysteine), ranging from 300 mg/day for 15 days to 600 mg/day for nine months, which produced improvements in  $\beta$ -thal RBC parameters of oxidant damage but not in Hb levels, dampening this “quick fix” approach [3]. This is not surprising given recent understandings of the complex changes to erythrocyte plasma membrane (including intracellular membranes of erythroid progenitor cells) caused by bound unmatched  $\alpha$ -Hb and consequent heme-dependent oxidative damage to both membrane lipids and proteins, affording an explanation for ineffective erythropoiesis (due to apoptosis/autophagy) and premature eryptosis [4]. Although the exact mechanisms by which aged RBCs are removed by the body reticuloendothelial system remain unclear, in the case of  $\beta$ -thal RBCs, oxidative damage to plasma membrane proteins is accepted as the primary etiology.

Nevertheless, a new appraisal for restoration of normal vitamin E status in  $\beta$ -thal patients is warranted. With availability of fluorescent-labelled Annexin V to detect presence of cell surface phosphatidylserine (PS), it was realized that PS on surface of circulating  $\beta$ -thal RBCs is responsible (in part) to the hypercoagulable state, platelet activation, thrombosis and pulmonary hypertension observed in  $\beta$ -thal subjects [1,4]. A limited number of clinical trials of vit E supplement (alone or together with N-acetylcysteine) on small cohorts of  $\beta$ -thal subjects showed improvement in parameters related to oxidative stress and hypercoagulopathy (Table 1). However, it is worth noting that upon cessation of vitamin E supplementation, all measured parameters (including plasma vit E) returned to pre-treatment levels within three

**Table 1:** Effects of vitamin E supplementation on hypercoagulation and oxidative stress status of  $\beta$ -thalassemia subjects.

Reference	Subject/Treatment	Result
Kasemsant et al. 1996 [8]	NSPLZ and SPLZ $\beta$ -thalassemia ( $\beta$ -thal)/Hb E (n = 7 each group). Vitamin (vit) E 485 U/day for 3 months.	<ul style="list-style-type: none"> <li>Pre-supplement parameters, median (range): NSPLZ and SPLZ <math>\beta</math>-thal/Hb E plasma vit E = 0.61 (0.52-1.66) and 0.60 (0.16-0.81) mg/L respectively; prothrombinase activity = 0.60 (0.41-0.72) and 0.81 (0.48-1.70) thrombin unit/10<sup>9</sup> cells.</li> <li>Post-supplement parameters, median (range): NSPLZ and SPLZ <math>\beta</math>-thal/Hb E plasma vit E = 14.21 (10.53-22.38) and 12.40 (5.04-23.80) mg/L respectively; prothrombinase activity = 0.33 (0.30-0.38) and 0.48 (0.38-0.65) thrombin unit/10<sup>9</sup> cells.</li> </ul>
Unchern et al. 2003 [9]	NSPLZ (n = 16) and SPLZ (n = 9) $\beta$ -thal/Hb E. Vit E 525 U/day for 3 months.	<ul style="list-style-type: none"> <li>Pre-supplement parameters, median (range): NSPLZ and SPLZ <math>\beta</math>-thal/Hb E plasma vit E = 34.9 (8.1-53.2) and 33.4 (5.4-45.0) mg/L respectively; platelet aggregation (induced by 2 <math>\mu</math>M ADP) = 48 (19-64) and 56 (37-64)% light transmission respectively.</li> <li>Post-supplement parameters, median (range): NSPLZ and SPLZ <math>\beta</math>-thal/Hb E plasma vit E = 127 (66-353) and 174 (111-238) mg/L respectively; platelet aggregation (induced by 2 <math>\mu</math>M ADP) = 51 (8-67) and 44 (18-57)% light transmission respectively.</li> </ul>
Yanpanitch et al. 2015 [10]	NSPLZ $\beta$ -thal/Hb E (n = 19). Vit E 400 U + N-acetylcysteine 200 mg/day for 12 months.	<ul style="list-style-type: none"> <li>Pre-supplement parameters, mean <math>\pm</math> SD: Red blood cell MDA<sup>a</sup> = 1,487 <math>\pm</math> 138 nmol/g Hb; procoagulation status: PF3-like activity<sup>b</sup>, RBC PS<sup>c</sup> and platelet PS<sup>c</sup> = A<sub>405 nm</sub> 1.24 <math>\pm</math> 0.10, 5.41 <math>\pm</math> 1.03% and 0.61 <math>\pm</math> 0.15%, respectively; platelet activation status: CD62 expression<sup>d</sup> and PAC1 expression<sup>e</sup> = 16.9 <math>\pm</math> 3.1 and 4.6 <math>\pm</math> 1.1% respectively.</li> <li>Post-supplement parameters, mean <math>\pm</math> SD: Red blood cell MDA<sup>a</sup> = 698 <math>\pm</math> 24 nmol/g Hb; procoagulation status: PF3-like activity<sup>b</sup>, RBC PS<sup>c</sup> and platelet PS<sup>c</sup> = A<sub>405 nm</sub> 0.67 <math>\pm</math> 0.06, 1.73 <math>\pm</math> 0.71% and 0.24 <math>\pm</math> 0.04%, respectively; platelet activation status: CD62 expression<sup>d</sup> and PAC1 expression<sup>e</sup> = 12.3 <math>\pm</math> 3.3 and 2.7 <math>\pm</math> 1.0% respectively.</li> </ul>
Haghpanah et al. [11]	NSPLZ (n = 20) and SPLZ (n = 20) $\beta$ -thal (n = 26). Vit E 10 U/kg/day (maximum dose of 400 U) for 3 months.	<ul style="list-style-type: none"> <li>Pre-supplement parameters, mean <math>\pm</math> SD: TOS<sup>f</sup> = 0.83 <math>\pm</math> 0.20 <math>\mu</math>mol H<sub>2</sub>O<sub>2</sub> Eqv/L; TAC<sup>g</sup> = 3.25 <math>\pm</math> 0.68 mmol Eqv/L.</li> <li>Post-supplement parameters, mean <math>\pm</math> SD: TOS<sup>f</sup> = 0.74 <math>\pm</math> 0.07 <math>\mu</math>mol H<sub>2</sub>O<sub>2</sub> Eqv./L; TAC<sup>g</sup> = 2.98 <math>\pm</math> 0.20 mmol Eqv./L.</li> </ul>

<sup>a</sup>Malondialdehyde (induced by hydrogen peroxide treatment). <sup>b</sup>Platelet PF3. <sup>c</sup>Surface phosphatidylserine. <sup>d</sup>Platelet surface P-selectin. <sup>e</sup>Platelet activated glycoprotein IIb/IIIa. <sup>f</sup>Blood plasma total oxidative stress. <sup>g</sup>Blood plasma total antioxidant capacity. NSPLZ: Non-splenectomized; SPLZ: Splenectomized.

months (in studies that carried out these experiments).

Although the clinical significance of these studies of vit E supplementation on the hypercoagulation status of  $\beta$ -thal patients may be questioned, it surely cannot be beneficial to the general health of a person to be under a state of constant hypovitaminosis E, regardless of current debates on whether vit E, in addition to its canonical function as a lipophilic antioxidant, might also have non-antioxidant properties, such as a direct regulator of gene expression or indirectly through modulation of metabolic pathways [5]. The ability to measure in urine, using gas or liquid chromatography-mass spectrometry, F2-isoprostanes, the biomarker of systemic oxidative stress provides a convenient non-invasive method for quantifying this stress condition [6,7] and a ready means to assess the efficacy of vit E supplementation (with or without other antioxidants) in alleviating oxidative stress in  $\beta$ -thal individuals.

Taken altogether, we advocate vitamin E supplementation of  $\beta$ -thalassemia subjects at a minimal level that restores plasma vitamin E level to the accepted normal level designated by the subject's country FDA together with determination of attenuation in systemic oxidative stress. This simple, available and non-toxic supplement should be beneficial to the overall health of the global  $\beta$ -thal population in particular those who live in regions with limited access to other relatively more expensive pharmacological interventions.

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