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Short Communication

β-Thalassemia - Call for Restoration of Normal Vitamin E Status

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A recent review of β-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 α-hemoglobin (Hb) in β-thalassemia red blood cells (β-thal RBCs) is systemic oxidative stress, first noted by reduced plasma vitamin E (vit E) levels and increased sensitivity of β-thal RBCs to H_2O_2-induced lysis in β-thalassemia subjects [2]. This led to numerous clinical trials in β-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 β-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 α-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 β-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 β-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 β-thal RBCs is responsible (in part) to the hypercoagulable state, platelet activation, thrombosis and pulmonary hypertension observed in β-thal subjects [1,4]. A limited number of clinical trials of vit E supplement (alone or together with N-acetylcysteine) on small cohorts of β-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 β-thalassemia subjects.

Reference	Subject/Treatment	Result
Kasemsant et al. 1996 [8]	NSPLZ and SPLZ β-thalassemia (β-thal)/Hb E (n = 7 each group). Vitamin (vit) E 485 U/day for 3 months.	• Pre-supplement parameters, median (range): NSPLZ and SPLZ β-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/10^8 cells. • Post-supplement parameters, median (range): NSPLZ and SPLZ β-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/10^8 cells.
Unchern et al. 2003 [9]	NSPLZ (n = 16) and SPLZ (n = 9) β-thal/Hb E. Vit E 525 U/day for 3 months.	• Pre-supplement parameters, median (range): NSPLZ and SPLZ β-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 μM ADP) = 48 (19-64) and 56 (37-64)% light transmission respectively. • Post-supplement parameters, median (range): NSPLZ and SPLZ β-thal/Hb E plasma vit E = 127 (66-353) and 174 (111-238) mg/L respectively; platelet aggregation (induced by 2 μM ADP) = 51 (8-67) and 44 (18-57)% light transmission respectively.
Yanpanitch et al. 2015 [10]	NSPLZ β-thal/Hb E (n = 19). Vit E 400 U + N-acetylcysteine 200 mg/day for 12 months.	• Pre-supplement parameters, mean ± SD: Red blood cell MDA[a] = 1,487 ± 138 nmol/g Hb; procoagulation status: PF3-like activity[b], RBC PS[c] and platelet PS[c] = $A_{405\ nm}$ 1.24 ± 0.10, 5.41 ± 1.03% and 0.61 ± 0.15%, respectively; platelet activation status: CD62 expression[d] and PAC1 expression[e] = 16.9 ± 3.1 and 4.6 ± 1.1% respectively. • Post-supplement parameters, mean ± SD: Red blood cell MDA[a] = 698 ± 24 nmol/g Hb; procoagulation status: PF3-like activity[b], RBC PS[c] and platelet PS[c] = $A_{405\ nm}$ 0.67 ± 0.06, 1.73 ± 0.71% and 0.24 ± 0.04%, respectively; platelet activation status: CD62 expression[d] and PAC1 expression[e] = 12.3 ± 3.3 and 2.7 ± 1.0% respectively.
Haghpanah et al. [11]	NSPLZ (n = 20) and SPLZ (n = 20) β-thal (n = 26). Vit E 10 U/kg/day (maximum dose of 400 U) for 3 months.	• Pre-supplement parameters, mean ± SD: TOS[f] = 0.83 ± 0.20 μmol H_2O_2 Eqv/L; TAC[g] = 3.25 ± 0.68 mmol Eqv/L. • Post-supplement parameters, mean ± SD: TOS[f] = 0.74 ± 0.07 μmol H_2O_2 Eqv./L; TAC[g] = 2.98 ± 0.20 mmol Eqv./L.

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

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months (in studies that carried out these experiments).

Although the clinical significance of these studies of vit E supplementation on the hypercoagulation status of β-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 β-thal individuals.

Taken altogether, we advocate vitamin E supplementation of β-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 β-thal population in particular those who live in regions with limited access to other relatively more expensive pharmacological interventions.

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