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Commentary

Famine From Feast: Low Red Cell Vitamin C Levels in Diabetes☆

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Decreased oxygen delivery to tissues is an important downstream consequence of diabetic microvascular disease. Although endothelial dysfunction causing abnormal blood flow regulation is often considered the major factor in this regard, impaired oxygen delivery by erythrocytes may also play a role in both vascular and tissue damage. Erythrocytes in persons with diabetes with poor glycemic control have impaired deformability, leading to increased fragility and hemolysis (McMillan et al. 1978). Beyond anemia as a cause of poor oxygen delivery, decreased erythrocyte deformability in diabetes may also compromise capillary perfusion and thus impair delivery of oxygen to the tissues. The studies of Tu et al. (2015) in this issue of EBioMedicine add another potential factor to the abnormal red cell function in diabetes: high glucose concentrations cause erythrocyte vitamin C deficiency, which may then amplifies defects in erythrocyte structure and function due to diabetes alone.

This work was prompted by the astute "clinical" observation that mice unable to synthesize their own vitamin C, when placed on a vitamin C-deficient diet for 12 weeks, showed hemolysis. This was associated with increased osmotic fragility and conversion of many cells from biconcave discs to rounded spherocyte forms. The latter are less deformable and more prone to hemolysis than are normal erythrocytes (Waugh and Sarelius, 1996). Evaluation by gel electrophoresis of erythrocyte cytoskeletal proteins showed that vitamin C deficiency caused loss of more than 50% of β-spectrin, without changes in other cytoskeletal proteins. Both the decrease in β-spectrin and the osmotic fragility were partially reversed after 10 days of ascorbate repletion. Since β-spectrin is required for normal cytoskeletal structure and function, it seems likely that its loss or damage accounted for the observed shape changes and sensitivity to hemolysis. This brings up the question of how ascorbate deficiency caused loss of β-spectrin. Although this was not investigated in the studies of Tu et al. (2015), it could relate to the previous observation that susceptible amino acid residues (e.g., cysteines, histidines, methionines) in β-spectrin are more readily oxidized than those of other erythrocyte cytoskeletal proteins, even to the point of undergoing non-enzymatic cleavage of peptide bonds (Arduini et al. 1989). This would suggest that the antioxidant function of vitamin C is necessary to preserve β-spectrin and thus cytoskeletal integrity in erythrocytes.

Although vitamin C deficiency to the point of scurvy is no longer common in developed countries, it is well established that persons with diabetes in poor glycemic control have low plasma and leukocyte vitamin C levels, measured as the fully reduced form, ascorbate (Cunningham et al. 1991; Ginter et al. 1978). Thus, it was logical for Tu et al. (2015) to assess the impact of hyperglycemia and diabetes on erythrocyte vitamin C. Indeed, they found that the ascorbate content of erythrocytes from diabetic subjects varied inversely with the degree of hyperglycemia to which they were exposed. This relationship was not due to changes in plasma ascorbate levels, but rather to the fact that erythrocytes from both mice and humans take up vitamin C as the two-electron oxidized form of the vitamin, dehydroascorbate. This occurs by facilitated diffusion on GLUT-type glucose transporters (Vera et al. 1993). High but still physiologic extracellular glucose levels compete with even very low concentrations of dehydroascorbate for uptake and this decreases intracellular dehydroascorbate available for conversion to ascorbate. Most cells take up ascorbate directly on one of the two isoforms of the Sodium-dependent Vitamin C Transporter, SVCT. However, mature erythrocytes lack this transporter (May et al. 2007). The ability of glucose to impair dehydroascorbate uptake into erythrocytes makes them unique in that they may be prone to significant intracellular vitamin C deficiency in diabetes.

Perhaps most important, erythrocyte ascorbate deficiency due to diabetic hyperglycemia may accentuate or even account for known abnormalities in diabetic erythrocytes. It was shown over 2 decades ago that β-spectrin in erythrocytes from both type 1 and type 2 diabetics is oxidized and associated with decreased deformability (Schwartz et al. 1991). Although β-spectrin was not found to be decreased in diabetic erythrocytes in that study, quantification by normalization to β-actin was not carried out. The finding in the study by Tu et al. (2015) that sensitivity to hemolysis was inversely correlated with erythrocyte ascorbate content and more pronounced in diabetic subjects with poor glycemic control suggests that deficient intracellular ascorbate could have played a causative role in the changes in diabetic erythrocytes. This is supported by the parallel observation that erythrocyte β-spectrin (but not α-spectrin) was also decreased in proportion to the hemoglobin A1C, a measure of glycemic control.

There are implications from this study by Tu et al. (2015). First the erythrocyte, because of its unique glucose-sensitive mechanism of vitamin C uptake, may be more susceptible to intracellular ascorbate deficiency than other cell types in which ascorbate is taken up directly.

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Second, erythrocyte ascorbate deficiency decreases cytoskeletal β-spectrin, which in turn likely accounts for decreased deformability and susceptibility to hemolysis. Third, the hyperglycemia of diabetes decreases erythrocyte ascorbate, deficiency of which could contribute to decreased erythrocyte fragility in poorly controlled diabetes.

The work opens up several areas for future studies, such as whether the loss of β-spectrin due to ascorbate deficiency is due to oxidative damage, whether it contributes to the observed increased osmotic fragility of erythrocytes deficient in ascorbate, and most important, whether erythrocyte ascorbate deficiency accounts for increased deformability and lysis seen in diabetes. If so, then this study could prompt further clinical studies of the impact of vitamin C supplements on erythrocyte fragility in diabetes.

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