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How important is oxidative stress-mediated erythrocyte damage to diabetic complications?

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Dear Editor,

Nowadays it is well established that oxidative stress accompanies diabetes mellitus and may participate in its progress and its assosiated complications. In particular, the prevalence of increased reactive oxygen species (ROS) is thought to contribute to micro and macrovascular complications such as retinopathy, cataracts, atherosclerosis, nephropathy and chronic kidney disease. Based on our experiences, using glutathione peroxidase-1 knockout (GPx1-/-) mice, we suggest that ROS such as H2O2 play an important role in mediating diabetic complications such as diabetic nephropathy and atherosclerosis (1, 2). In addition, it is becoming increasingly clear that oxidative stress may shorten the life span of ethrythrocytes from diabetic patients and thereby impact on diabetic complications such as nephropathy(3). Indeed, the higher fragility of erythrocytes from diabetic patients may lead to a loss of red blood cell (RBC) function, increased eryptosis (apoptosis of the erythrocyte) and removal from the circulating blood through macrophage phagocytosis. Ultimately, the oxidative stress mediated destruction of the RBC could further contribute to the erythropoietin (EPO)-mediated anemia known to accompany diabetic nephropathy and further enhance renal damage.

In a recently published study in Int J Endocrinol. Metab. by Varashree and Gopalskrishna (4) the authors investigated the levels of oxidative stress (malondialdehyde (MDA), measured as thiobarbituric acid reactive substances) and the proteolytic activity in erythrocytes of diabetic patients. Their results, showing increased MDA levels and increased proteolytic activity in erythrocyte lysates prepared from diabetic patients, although correlative, draws further attention to the status of RBCs in a diabetic milieu. Red blood cells are particularly vulnerable to oxidative damage as a result of several factors, most notably the high content of polyunsaturated fatty acids within their membrane, their high iron content, and their role as oxygen transporters with a high exposure to oxygen free radicals. The results of the study by Varashree and Gopalskrishna show that erythrocytes of diabetic patients are more susceptible to oxidant-mediated damage, most likely as a result of decreased antioxidant defences in diabetic RBCs. Indeed, it has been shown

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that antioxidant defences decline in diabetic patients with significant reductions in total antioxidant capacity and the ratio of GSH/GSSG in erythrocytes (3). Of interest, the reduction in antioxidant defence declines even further in diabetic patients with the additional burden of chronic kidney disease, and is associated with increased RBC apoptosis (3). Collectively, these data are suggestive of a correlation between oxidative events within RBCs and some of the complications associated with diabetes, although to discern the direction of the cause-effect relationship is impossible at this stage.

In addition, the paper of Varashree and Gopalskrishna (4) points to a further interesting phenomenon in diabetic RBCs, namely the enhanced activity of proteolytic enzymes that degrade oxidatively modified proteins. Proteolytic enzymes within the RBC are suggested as a second line of defence against oxidative damage, coming into play once the oxidative event has occurred, and as a way of limiting further damage caused by modified proteins (5, 6). At the outset, although suggestive of increased oxidative damage to RBCs in diabetes, the findings of Varashree and Gopalskrishna imply that diabetic RBCs are better able to cope with the increased oxidative burden. This may appear counter-intuitive; however, an earlier study suggests that the ability to detoxify oxidatively modified proteins is lost in patients with greater than 9% glycated haemoglobin levels as diabetes progresses (7). Primary studies into erythrocyte protein-degradation pathways identified the involvement of an ATP-independent mechanism (5). Further investigations into the nature of these proteolytic enzymes might therefore show the relevance in limiting oxidative damage in diabetic RBCs. It would also be important to establish the relevance of these findings in diabetic complications, particularly where anemia may enhance diabetic outcomes such as nephropathy.

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