Oxidative Stress in Diabetic Patients with Sickle-Cell Anemia: A Warning Call for Endemic Areas

Sickle-cell disease (SCD) is an inherited condition in which red blood cells (RBCs) become less flexible and some become buckled into the characteristic sickle shape.[1] SCD has been known by its symptoms of bone pains and early death for over a century in Africa.[2] Sickle cells were first identified in a medical student from Grenada.[3]

In the presence of gene for sickle hemoglobin (HbS), valine, normally present at the sixth position from the amino terminus of the β chain of HbS is substituted by glutamic acid. SCD is acquired by inheriting abnormal genes from both parents. The combination from both parents can give rise to different forms of SCD; with most common at birth being homozygous sickle-cell (SS) disease, also called sickle-cell anemia, in which the HbS gene is inherited from both parents. Carrier state or sickle-cell trait (SCT) results from inheritance of an HbS gene from one parent and normal β-globin gene from the other.[1]

Major clinical manifestations in patients of SCD are due to two basic mechanisms – hemolysis and vasoocclusion. The lifespan of a RBC is decreased from a normal 120 days to 10–12 days in most patients with SS disease causing megaloblastic erythropoiesis, aplastic crisis, jaundice, and gall stones. Similarly, obstruction to normal flow of blood by stiff or sickled red cells can cause ischemic changes in the area supplied and depends on the type of vessel affected.[4]

On the other hand, oxidative stress is thought to exacerbate the symptoms of hemolytic anemias including sickle-cell anemia, thalassemia, glucose-6-phosphate dehydrogenase deficiency, and hereditary spherocytosis.[5] It has been reported that the oxidative stress is a major outcome of diabetes mellitus (DM) affecting red cell antioxidant enzymes, and this in turn can lead to reduced hemoglobin concentrations in diabetic patients.[6] It has also been documented that oxidative stress is an important feature of SCD and plays a significant role in the pathophysiology of hemolysis, vasoocclusion, and ensuing organ damage in sickle-cell patients.[7]

A comparative study conducted on healthy individuals (CONT), individuals with type 2 DM (T2DM) or SCT, and patients with both T2DM and SCT (T2DM-SCT), comparing vascular function, hemorheological profile, and biomarkers of oxidative stress, inflammation, and nitric oxide metabolism found that oxidative stress, advanced glycation end products, and inflammation (interleukin-1 β) were greater in patients with T2DM-SCT compared with the other groups. Blood viscosity was higher in individuals with TD2M, SCT carriers, and individuals with T2DM-SCT, and the values were further increased in the latter group, thus concluding that SCT should be viewed as a risk factor for further cardiovascular disorders in individuals with T2DM.[8] In another study, normoglycemic patients with SCD demonstrated impaired β-cell function with reduced insulin secretion even before oral glucose tolerance test was impaired.[9] To make the matter worse, another study has postulated a role of elevated oxidative products in the development of insulin resistance and high glucose levels in SCD patients.[10]

Thus, the cascade of diabetes leading to oxidative stress leading to hemolysis appears intermingled in patients with SCD will prove catastrophic in patients with SCD comorbid with DM and will particularly affect endemic areas. Recent epidemiological data predict that as per current trends, Africa, and more particularly sub-Saharan countries, will have the greatest increase in the number of people with T2DM, from 19.8 million in 2013 to 41.4 million in 2035.[11] As we know, in sub-Saharan African countries, SCT is highly prevalent.[12] This concomitant presence of T2DM and SCT in sub-Saharan region is bound to give warning call to the health authorities.

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Quick Response Code:

Website: www.ijabmr.org

DOI: 10.4103/ijabmr.IJABMR_104_18

How to cite this article: Mahajan R. Oxidative stress in diabetic patients with sickle-cell anemia: A warning call for endemic areas. Int J App Basic Med Res 2018;8:65-6.