Increased Reactive Oxygen Species Induced by Toxic Heavy Metals as an Initiator of CKDu

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For more than two decades, many people in the North Central Province of Sri Lanka are affected by chronic kidney disease of uncertain etiology (CKDu) . The main risk factors of this disease are identified as heavy metals (arsenic, cadmium and lead), pesticide exposure, heat stress and dehydration, fluoride content and hardness of water. To identify molecular mechanisms of renal injury by these factors, we carried out a comprehensive literature survey. According to literature, heavy metals like arsenic initiate toxicity through generation of excessive Reactive oxygen species via two mechanisms. The first mechanism is inducing enzyme complexes to increase reactive oxygen species formation. The second mechanism is via inhibiting antioxidant enzymes. To take an insight into which mechanism has the highest impact, we regenerated an existing mathematical model of redox system in the body. Since experimental data show an increase of superoxide level with heavy metal exposure, we increased superoxide concentration ten times in the simulation. Further, to simulate the inhibition of enzymes, enzyme levels were decreased ten times. Both changes increased reactive oxygen species levels such as hydroxyl ion and lipid peroxidation. In addition, increasing the superoxide level showed high impact rather than decreasing the antioxidant enzymes levels. The reason for increase of superoxide could be the ability of heavy metals to interact in activation of enzyme complexes such as NADPH oxidase, mitochondrial transport chain enzyme complexes I and III. The reason for depletion of antioxidants like Glutathione and antioxidant enzymes such as Superoxide dismutase and Catalase would be the ability of heavy metals to complex with thiol groups in these molecules. The outcome of both mechanisms was an accumulation of higher amount of reactive oxygen species inside the cell. These reactive oxygen species induced oxidative stress activates cellular pathways which lead to cellular toxicity.

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