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Perspective

Tenofovir Disoproxil Fumarate Induced Mitochondrial Damage and Enhanced Oxido-Nitrosative Stress in the Kidney

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DESCRIPTION

The oral prodrug of tenofovir, a type 1 Human Immunodeficiency Virus (HIV) reverse transcriptase inhibitor, is called Tenofovir Disoproxil Fumarae (TDF) (HIV-1). As of right now, the Food and Drug Administration (FDA) in the USA has only licensed one Nucleotide Analogue Reverse-Transcriptase Inhibitor (NRTI) for the treatment of HIV infection. However, long-term use of TDF can have substantial negative effects. Renal damage in HIV patients receiving TDF is becoming very common. Serious incidences of renal tubular toxicity linked to TDF exposure have been recorded in a large number of case reports and case series. An estimated 15% of people using tenofovir for 2-9 years get renal tubular impairment. Renal function reduction may be accompanied with tubular dysfunction.

The proximal tubule is the primary location of TDF toxicity, and in extreme situations, patients may experience acute kidney injury or fanconi syndrome, which is characterized by phosphaturia, glycosuria, bicarbonate wasting, tubular proteinuria, and aminoaciduria. Tenofovir's role as a proximal tubular toxin has been supported by a number of case reports, observational studies, and animal models.

As of right now, the data points to mitochondria as tenofovir's subcellular target organelles. Numerous investigations on people and animals have revealed damage, particularly to the mitochondria of the renal proximal tubule. The predominant abnormality on light microscopy was acute proximal tubule damage and the presence of intra cytoplasmic inclusions in the kidney biopsy samples from TDF-treated HIV patients. In proximal tubule mitochondria, electron microscopy revealed broad morphologic abnormalities, including distinct variations in size and form, disruption of cristae, swelling of the mitochondria, and intra-mitochondrial deposits.

Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) produced excessively as a result of mitochondrial damage are known to accumulate and cause oxidative and nitrosamine damage to lipids, proteins, and DNA. Adenosine Triphosphate (ATP) is necessary for the active reabsorption of filtered nutrients and ions by proximal tubular cells. Therefore, damage to the proximal tubular mitochondria can have two effects: increased ROS production, which leads to increased oxidative stress, and proximal tubular malfunction, which results in fanconi syndrome.

Being both a source of reactive species and a target for them, mitochondria are inextricably related to oxidative stress and mitochondrial dysfunction. The cell is equipped with a number of antioxidants and antioxidant enzyme systems to detoxify ROS created because of the harmful effects of ROS. According to reports, tissues only experience oxidative stress once the Antioxidant (AO) defense systems have been exhausted, leaving ROS to target cellular macromolecules like lipids, proteins, and Deoxyribonucleic Acid (DN).

To evaluate the oxidative damage to lipids (and other constituents) and proteins, respectively, two key criteria are lipid peroxidation and protein carbonyl content. Proteins that contain carbonyl groups undergo an irreversible change that frequently renders them inactive. In comparison to Protein Carbonyl Content (PCC) is said to be a more sensitive and early indicator of oxidative stress to tissues.

The primary ROS generated by the mitochondria, primarily from the electron transport chain, is Superoxide Anion (SA). The first line of defense against superoxide, the main ROS generated by the mitochondria, is Superoxide Dismutase (SOD), which catalysis the dismutation of superoxide radicals into hydrogen peroxide and molecular oxygen. Hydrogen peroxide produced by SOD is converted to water by glutathione peroxidase, peroxiredoxins, and catalase. Carbonic anhydrase, reduced glutathione, and glutathione reductase are a few of the antioxidants found in mitochondria. Glutathione in the mitochondria is regarded as the essential antioxidant for survival.

As a result of excessive superoxide anion production or a lack of

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SOD, highly reactive superoxide radicals can build up in the mitochondria. When these radicals are too abundant, they can combine with mitochondrial nitric oxide to form peroxynitrite, a Reactive Nitrogen Species (RNS) and a powerful oxidant that can change proteins to form 3-Nitrotyrosine (3 NT). Along with protein carbonyl content, 3 NT content is thought to be a marker of oxidative alteration of proteins.

To find out how chronic TDF administration affected the proximal tubular mitochondria, oxido-nitrosative stress parameters, and antioxidant system in the rat kidneys, we conducted the current investigation. According to the current study's findings, TDF administration causes serious harm to the proximal tubular mitochondria. Increased protein and lipid oxidation as well as the depletion of the antioxidant system, which includes reduced Glutathione (GSH), carbonic anhydrase, glutathione peroxidase, and glutathione reductive, were all associated with proximal tubular injury.