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Oxidative Stress - a key factor in the development of Diabetic Nephropathy

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----------ABSTRACT----------

Diabetes mellitus (DM) is a chronic disease spreading all around the world and has become one of the reasons for many deaths. It is a disease in which body is not able to produce or use insulin properly. Prolonged high blood sugar level leads to various complications like diabetic nephropathy (DN), diabetic retinopathy (DR), diabetic neuropathy and foot and skin complications. In modern treatment approach to diabetes, there is a quest for better and newer medication to improve the quality of living of diabetic patients. Oxidative stress has been closely linked with the pathogenesis of diabetic complications especially diabetic nephropathy (DN). In the current work, an attempt is been made to explore the initiation, generation and role of various Reactive Oxygen Species (ROS) in the development of diabetic nephropathy. The antioxidants effect on various clinical trials, in-vitro and in-vivo models are compiled in the present review for deeper understanding. Furthermore, this work will aid researchers for better understanding of antioxidants and diabetic nephropathy.

Keywords *- Diabetes mellitus, Diabetic nephropathy, Reactive Oxygen Species*

I. INTRODUCTION

The most rapidly growing epidemic of 21st century is diabetes and its complications. About 25% - 40% of diabetic patients are developing renal impairment [1]. Nowadays both structural and functional abnormalities occur in diabetic renal disease. Structural changes includes mesangial expansion, thickening of basement membrane, podocyte cell (glomerular epithelial) loss within glomeruli and hypertrophy.

Various clinical trials such as UKPD/DCCT/ADVANCE and ACCORD have revealed that diabetic microvascular complications especially nephropathy is due to poor metabolic control which further results in hyperglycaemia [2-4]. Apart from strict metabolic control, anti-hypertensive agents is the most effective treatment for diabetic nephropathy especially those that target the renin angiotensin system (RAS) [5-7].Additionally, studies have been done by many scientists indicating a link between the extent of glycemic control in diabetic patients and further development and progression of complications. The diabetic control and complications trial (DCCT) revealed that macrovascular and microvascular complications can be successfully delayed in both type -1 and 2 di abetic by strict glycemic control [8-9]. United Kingdom prospective diabetics study (UKPDS) also showed that risk of diabetic neuropathy and retinopathy can be controlled through intensive glycemic control in diabetic patient of type-1 and type-2 [10,11]. Through above two studies one can say that initiation and development of DN can be prevented by strict glycemic control. Thus, therapies are needed that specifically prevent DN and also have strict glycemic control. In several studies it has been reported that induction of oxidative stress by metabolism of dyslipidemia and hyperglycemia plays an important role in development of vascular complications [12-16]. DN has also shown the increase of

reactive oxygen species (ROS). Few recent studies have clearly showed that glucagon-like peptide-1 (GLP-1) and insulin prevent the progression of DN by neutralizing oxidative stress [17]. Many experimental models of diabetic nephropathy protective efficacy are being observed when treated with antioxidant [18, 19].

II. General Pathway of Oxidative Stress in Diabetic Neuropathy

Four major biochemical pathway leads to development of inappropriate hyperglycaemic complications. (1) The Polyol pathway, in which sorbitol is formed from glucose and further metabolized to fructose, Reactive Oxygen Species (ROS) and advanced glycation end products are also formed via these pathway, (2) The Protein Kinase C also known as PKC pathway, in which glucose is converted into glyceraldehyde-3-phosphate and results in formation of Diacylglycerol (DAG). Elevation of DAG intracellular activate PKC and then further activate NADPH oxidase to induce ROS, (3) The hexosamine pathway, glucosamine intermediates are formed from fructose-6-Phosphate, (4) Advanced glycation end-products (RAGE), interaction of AGEs with the receptors of advanced glycation end products (RAGE) results in ROS activation. [20-26].

An imbalance between the production of reactive-oxygen species and local antioxidants represents oxidative stress. High oxidative stress is known to cause the development and progression of diabetes and its complications [27]

There are a number of enzymatic and non-enzymatic sources of ROS within the diabetic kidney. These include advanced glycation, autooxidation of glucose, polypol pathway flux, transition metal cytalysed fenton reactions, nitric oxide synthase (NOS), peroxidase, nicotinamide adenine dinucleotide phosphate (NAD (P) H) oxidase and peroxidase [20].Free radical such as hydroxyl (OH), superoxide (O2−) peroxyl (RO_2) and superoxide (O2−) are liberated within the kidney. Additionally, non-radical species such as hypoochlorous acid (HOCL) and hydrogen peroxide (H_2O_2) are also released. Reactive nitrogen species from similar pathways are also produced such as nitrogen dioxide (NO2) and nitric oxide whereas non-reactive nitrogen species such as nitrous oxide (HNO_2), peroxynitrite ($ONOO^-$) and alkyl peroxynitrates (RONOO) are liberated [28]. From the above, few radicals such as O2−, NO, H_2O_2 and ONOO− are most widely investigated species in Diabetic nephropathy.

Molecularly, ROS in glomerular mesangial and tubular epithelial cells are activated by AGE, high glucose and cytokines [29]. High glycemic level activates glycolytic pathway and ROS are activated in mitochondria by stimulating NADPH and activating protein kinase C (PKC) [30]. Free radicals are formed in diabetic subjects through other processes such as glucose oxidation, oxidative degradation of glycated proteins and non-enzymatic glycation of proteins. These excessive free radical damages cellular proteins, nucleic acids, membrane lipids and finally cell death occurs [31]. Apart from that, vascular endothelium abnormalities are also caused by free radicals [32]. ROS indirectly damage endothelial cells by stimulating expression of several genes involved in inflammatory pathway [33]. In glomerular mesangial cell high ROS up regulates extracellular matrix (ECM) and TGF –β1 expression [34]. Through various studies it is evident that antioxidants can effectively suppress high glucose induced fibronectin and TGF−β1 up−regulation [35]. NF-κB Monocyte chemo attractant protein (MCP)-1 expression is also activated by ROS [36]. Various cell-stress associated stimuli are further activated by NF-κB such as vasoactive agents, growth factors, cytokines and oxidative stress [37]. Wolf and ziyadch, reported that TGF –β1 is the main cause for the accumulation of extracellular matrix and development of renal hypertrophy. In various

experimental models of diabetic nephropathy high expression of TGF –β1 is evidenced [38, 39, 40 and 41].

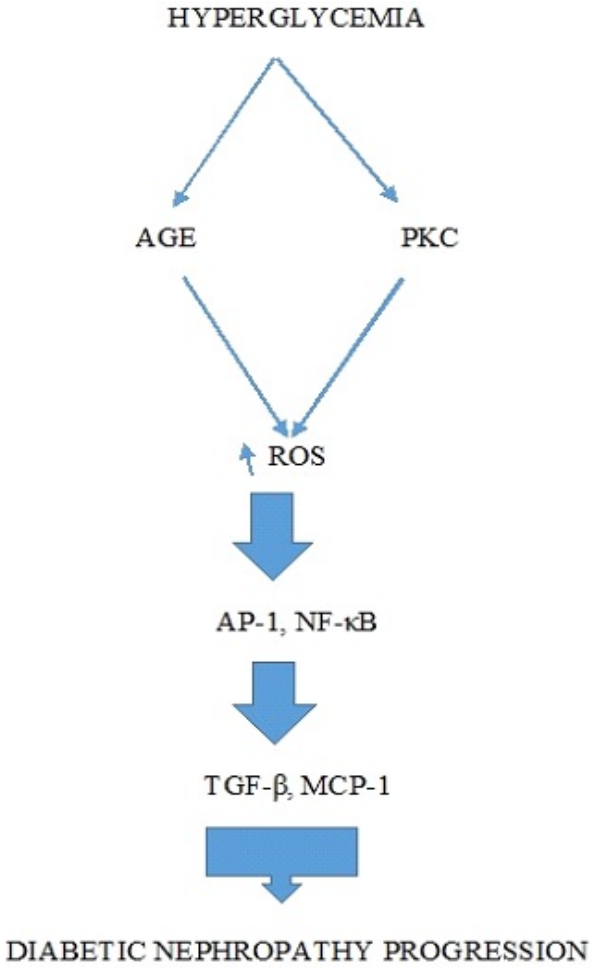

Figure-1. The link between ROS and diabetic nephropathy. PKC, Protein kinase C; AGE, Advanced Glycation End Products; ROS, Reactive Oxygen Species; AP-1,Activator Factor-Kappa-B; NF-κB, Nuclear Factor Kappa-B; TGF-β, Transforming growth factor – beta; MCP-1, Monocyte chemotactic Protein-1.

III. ROLE OF ANTIOXIDANTS IN DETOXIFYING ROS

Excess ROS is being produced during metabolism and respiration in human beings and to maintain homeostasis mammals have evolved numerous antioxidant systems. Superoxide dismutase is an important antioxidant enzyme which exists in three cellular forms namely manganese SOD (MnSOD, SOD1), Copper zinc superoxide dismutase (CuZn SOD, SOD2) and extracellular SOD (SOD3). In different cellular compartments these enzymes neutralize superoxide radicals to hydrogen peroxide and water. In diabetic micro vascular disease the decrease in expression of these enzymes and their related activity is reported in several previous studies [42]. Study done in experimental models of type−2 diabetic nephropathy, the overexpression of CuZnSOD provided protection against end organ damage [43]. Newly, multiple CuZnSOD gene variants have shown link with the progression of diabetic

nephropathy in humans [44]. Others studies in which knockout mice have been used, revealed a relative contribution of MnSOD in development of diabetic nephropathy [45]. MnTBAP one of the MnSOD mimetics prevents ROS induced injury but its in-vitro results were not so promising [46].According to Mollsten A et al, in humans, strengthening antioxidant MnSOD, specific polymorphisms of MnSOD gene are linked with the progression of diabetic nephropathy [47].

Surprisingly, GPx−1 deficient mice showed no increment in the risk of any diabetic complications especially diabetic nephropathy [48] which may be due to redundancy to other isoforms of GPx in kidney. Risk of nephropathy was not observed when podocyte specific knockout of selenoproteins were done in experimental models of diabetes which explains that functional GPx is not at all essential for protection of nephropathy [49]. Catalase over-expression provides protection against nephropathy in diabetics' type-2 experimental models [50].

An organosulphur compound lipoic acid, a cofactor for many enzymes also termed as "lipoate" in physiological systems. Number of studies was done demonstrating the advantages of treatment of α-lipoic acid in both human clinical patients and experimental models [51] with diabetic complications including diabetic nephropathy in particular [52]. Numerous other antioxidants such as the vitaminsthiamine and benfotiamine [53], thioredoxen [54], metallotiamine [55] and turine (an amino acid) [56] may play protective role against diabetic nephropathy.

Decrease in microalbuminuria has been reported by *S-E. Bursell et al w*hen diabetic patients were administrated with Vitamin-C alone and in combination with Vitamin-E. A small scale size and short duration study revealed that type-1 diabetic patients showed restoration of renal function when dose of 1,800 IU/day of Vitamin-E was administrated [57]. In opposite to that, four year longstudy by HOPE (Heart Outcomes Prevention Evaluation) in which about 3,600 diabetic patients were screened and results showed that Vitamin-E supplementation (400 IU/Day) did not act as a protective shield against cardiovascular disease [58]. Besides, some of the patients in the study already displayed microalbuminuria. In various other studies, utility of Vitamin-C and E against diabetic nephropathy showed unclear results.

IV. CONCLUSION

Good glycemic control is the best rule for the prevention, development and progression of diabetic nephropathy. Although ROS plays a role of initiator in diabetic nephropathy which further simplifies therapeutic targets, however, in-vitro and in-vivo studies particularly individual renal cell types are essential for further interpretation. Unfortunately, few disappointing results have been observed in various human studies with several antioxidants. Overall, ROS formation during diabetic nephropathy is pathogenic and leads to various other complications and to target these ROS formation, new generation antioxidant therapies need to be discovered.

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