Journal of
Advanced Veterinary Research
Volume 3 (2013) 52-56

Editorial

Involvement of Free Radicals in Diseases of the Urinary System

Mahmoud R. Abd Ellah*

Department of Animal Medicine, Faculty of Veterinary Medicine, Assiut University 71526, Egypt

Free radicals are identified as molecules having one or more unpaired electrons in their outer orbits, the name radicals means unstable. Free radicals gain the stability by attracting electrons from neighboring molecules as proteins, enzymes, lipids or amino acids (Abd Ellah, 2013a). They are highly reactive substances produced continuously during metabolic processes and participating mainly in physiological events such as immune response, metabolism of unsaturated fatty acids, and inflammatory reactions. The most important free radicals include superoxide anion ($O_2^{\cdot -}$), hydroxyl radical (·OH), and hypochlorous acid (Stohs, 1995; Abd Ellah, 2010). Generally, sources of free radicals are oxidative phosphorylation through the mitochondrial electron transport chain, cytochrome P_{450} enzymes, oxidase enzymes like NADPH oxidases. Furthermore, capillaries of the glomerular and tubular cells, circulating leucocytes and platelets represent important sources for production of free radicals (Wardle, 2005). It has long been recognized that reactive oxygen species (ROS) are harmful for cells, mainly because they leads to structural and functional impairments of lipids, proteins, and nucleic acids (Freeman and Crapo, 1982; Mantle and Preedy, 1999).

Role of antioxidants in renal diseases

The cells contain a variety of antioxidants mechanisms that play a central role in the protection against ROS (Pár and Jávor, 1984; Halliwell, 1991). The antioxidant system is classified into two major parts: the first one is the antioxidant enzymes, which include superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px), and ancillary enzymes (glutathione reductase (GR), glutathione S-transferase, and glucose 6-phosphate dehydrogenase. The second class of antioxidants is vitamins including alpha-tocopherol, ascorbate, and beta-carotene (Halliwell, 1994; Abd Ellah, 2010). Both the enzymatic and non-enzymatic antioxidants become overwhelmed during oxidative stress, due to excessive generation of ROS.

Chain breaking antioxidants include vitamin E, C and beta-carotene represent the second line of defense that protects different tissues against oxidative stress. Vitamin E is located both intracellularly and extracellularly; one of its functions is to improve the oxidative status and to remove lipid peroxy radicals formed during the process of increased oxidative stress (Cristol *et al*., 1997). On the other hand, vitamin C has sparing effect on vitamin E, as it helps recycling of α-tocopherol from its oxidized form to native form. The role of ascorbic acid and vitamin E in relieve of renal diseases has been established by many studies; decreased of ascorbic acid and vitamin E levels in sera of uremic patients were reported by Giardini *et al*. (1984) and Frei *et al*. (1989). Also, decreased oxidative stress and relieve of renal cell injury were observed after supplementation of vitamin C (Frei *et al*., 1989). Supplementation of vitamin E suppresses oxidative stress and retards kidney failure (Gorgum *et al*., 1999). Furthermore, dietary treatment with vitamin E diminished renal functional and structural changes in experimental glomerulopathy in rats (Trachtman *et al*., 1996).

Oxidative stress and renal diseases

Cellular release of free radicals is controlled by the defense mechanism in the form of antioxidants. Over production of free radicals and/or decrease the antioxidants defence mechanisms are the main predisposing cause for the occurrence of oxidative stress (Abd Ellah, 2013b). Furthermore, neutrophils get attracted to the site of inflammation undergo a 'respiratory burst' resulting in excessive

*Corresponding author: M.R. Abd Ellah.

E-mail address: mrushdi@aun.edu.eg

ISSN: 2090-6277/2090-6269, www.advetresearch.com

production of oxygen free radicals (Paller and Hedlund, 1988). In many experimental studies, the participation of reactive oxygen species (ROS) in glomerular damage was confirmed by measuring the products of oxidant injury and antioxidants levels in renal tissue and urine (Wojcicka and Beltowski 2001). Many toxic chemicals induce nephrotoxicity through the generation of ROS as suggested by Somani *et al*. (2000). Also, tissue deposition of immune complexes can induce an acute inflammatory response resulting in tissue injury. Many research studies had been reported that oxidative stress mediates a wide range of renal injuries, which ranging from acute renal failure (Paller *et al*., 1998; Baliga *et al*., 1999; Shah, 2001), rhabdomyolysis (Vanholder *et al*., 2000), obstructive nephropathy (Klahr, 2001), hyperlipidemia (Wanner *et al*., 1997; Sakatsume *et al*., 2001) and glomerular damage (Kitamura and Ishikawa, 1999) to chronic renal failure (Handelman *et al*., 2001). Studies in models of acute renal failure (ARF) have generated evidence that ROS production occurs during ischemia/reperfusion (Greene and Paller 1991).

Reactive oxygen species are involved in the pathogenesis of toxic, ischemic, immunologically mediated renal injury (Baude and Ardaillou 1993) and chronic renal failure (CRF). The increased production of ROS in CRF may be related to metabolic consequences of the uremia such as decreased production of NADPH (Yawata and Jacob, 1975) and GSH-Px activity (Schiavon *et al*., 1994) and lowered vitamin E level (Yalcin *et al*., 1989). The potential consequences of increased generation of ROS in CRF are accelerated atherosclerosis (Green *et al*., 1983) and increased RBCs rigidity, which may shorten erythrocyte life span and contribute to renal anemia (Kikuchi *et al*., 1982 and (Delmas-Beauvieux *et al*., 1995). Some studies considered oxidative stress in CRF as an important source of patient morbidity and mortality, through their involvement in the pathogenesis of malnutrition (Galle, 2001, Maggi *et al*., 1994; Galle *et al*., 2003), anaemia (Taccone-Gallucci *et al*., 1999), and increased risk of cancerogenesis (Vamvakas *et al*., 1998).

Studying the status of the oxidative stress in animals is lacking. In one study, vitamin antioxidants such as vitamin E, C and β-carotene levels were measured in blood of camels suffered from cystitis (Abd Ellah *et al*., 2012), the authors reported decrease serum vitamin C level in camels with chronic cystitis compared with those suffered from acute cystitis, and decreases in serum α-tocopherol and β-carotene levels in both acute and chronic cystitis affected camels, which indicated the excessive production of free radicals that assimilate available vitamin C (Tappe, 1968).

Dogs with renal azotaemia were reported to have a higher intra-erythrocytic CAT activity. However, glutathione content and plasma malondialdehyde (MDA) level were unaltered (Buranakarl *et al*., 2009).The antioxidant vitamin E ameliorates the effects of glomerular disease. Dietary treatment with the antioxidant vitamin E attenuated renal functional and structural changes in experimental glomerulopathy (Trachtman *et al*., 1996). It was demonstrated that and vitamins A, C, and E have a protective role against LPO of erythrocytes in patients with CRF.

Auto-transplantation method in canine is a good model to evaluate the problems of ischemia– reperfusion (I/R) injury. The reperfusion injury caused by oxidative stress is relieved by antioxidant supplementation. In a renal transplantation model, ascorbic acid alone was reported to play a role in attenuating I/R injury and assisted in the recovery of the renal function (Lee *et al*., 2006).

Lipid peroxidation in renal diseases

There are some predisposing factors for the formation of lipid peroxidation in tissues. One of these factors is the increased destruction of cells especially in renal ischemia, which associated with overproduction of free radicals. Another important factor is the decrease of antioxidants, which become evident with the progress of the diseases. The presence of the two factors or one of them may result in lipid peroxidation. In addition, cell membrane contains high amount of polyunsaturated fatty acids, which combine with free radicals to form lipid peroxide derivatives. The production of free radicals may cause the progress of the renal injury to acute renal failure, especially after ischaemic renal injury as reported by Mark *et al*. (1984); Ratych and Bulkley (1986); Greene and Paller (1991) and Rao Srinivasa *et al*. (1996). In patients with chronic renal failure, increased production of free radicals had been reflected by increased peroxidation of erythrocyte membranes (Morosetti *et al*., 1987; Ginevri *et al*., 1989; Toborek *et al*., 1992).

Lipid peroxidation had been reported in patients with acute renal failure, which occurred during myohemoglobinuria (Abheri *et al*., 2010) that was explained by the increased iron in the renal tissues, which react with free radicals and predispose to the formation of toxic radicals.

Conclusion

The present review threw the light on previous researches that aimed to study the response of the oxidant and antioxidants balance to different diseases of the urinary system. Studying the oxidative stress in diseases of the urinary system in animals are lacking compared with similar researches in human. Further studies are required to elucidate the oxidative status in urinary system diseases in relation to the productive and reproductive capacity of different animal species.

References

Abd Ellah, M.R., 2010. Involvement of free radicals in animal diseases. Comparative Clinical Pathology 19, 615–619.

Abd Ellah, M.R., 2013a. Involvement of free radicals in parasitic infestations. Journal of Applied Animal Research DOI:10.1080/09712119.2012.739093.

Abd Ellah, M.R., 2013b. Role of free radicals and antioxidants in mastitis. Journal of Advanced Veterinary Research 3: 1-7.

Abd Ellah, M.R., Gaber, F.Kh., Neveen, A.E., 2012. Serum lipoproteins, antioxidants and urine biochemical constituents in camel cystitis. Comparative Clinical Pathology 21, 515-519.

Abheri, D.S., Anisur, R.M., Ghosh, A.K., 2010. Free Radicals and Their Role in Different Clinical Conditions: An Overview. International Journal of Pharmacological Sciences and Research 1, 185-192.

Baliga, P., Ueda, N., Walker, P.D., Shah, S.V., 1999. Oxidant mechanism in toxic acute renal failure. Drug Metabolism Reviews 31, 971–997.

Baude, L., Ardaillou, R., 1993. Involvement of reactive oxygen species in kidney damage. British Medical Bulletin 49, 621–629

Buranakarl, C., Trisiriroj, M., Pondeenana, S., Tungjitpeanpong, T., Jarutakanon, P., Penchome, R., 2009. Relationships between oxidative stress markers and red blood cell characteristics in renalnazotemic dogs. Research in Veterinary Science 86, 309–313.

Cristol, J.P., Bosc, J.Y., Badiou, S., Leblanc, M., Lorrho R., 1997. Erythropoitein and oxidative stress in haemodialysis: Beneficial effects of vitamin E supplementation. Nephrology Dialysis Transplantation 12, 2312-2317.

Delmas-Beauvieux, M.C., Peuchant, E., Dumon, M.F., Receveur, M.C., Le Bras, M., Clerc, M., 1995. Relationship between red blood cell antioxidant enzymatic system status and lipoperoxidation during the acute phase of malaria. Clinical Biochemistry 28, 163–169.

Freeman, B.A., Crapo, J.D., 1982. Biology of disease: free radicals and tissue injury. Laboratory Investigation 47, 412–426.

Frei, B., England, L., Ames, B.N., 1989. Ascorbic acid is an outstanding antioxidant in human blood plasma. Proceedings of the National Academy of Sciences 6, 6377- 6381.

Galle, J., 2001. Oxidative stress in chronic renal failure. Nephrology Dialysis Transplantation 16, 2135-7.

Galle, J., Seibold, S., Wanner, C., 2003. Inflammation in uremic patients: what is the link?. Kidney and Blood Pressure Research 26, 65-75.

Giardini, O., Lubrano, R., Galluci, T., 1984. Effects of alpha tocopherol administration on red blood cell membrane lipid peroxidation in haemodialysis patient. Clinical Nephrology 21, 174-177.

Ginevri, F., Ghiggeri, G.M., Candiano, G., Oleggini, R., Bertelli, R., Piccardo, M.T., Perfumo, F., Gusmano, R., 1989. Peroxidative damage of the erythrocyte membrane in children with nephrotic syndrome. Pediatric Nephrology 3, 25–32.

Gorgum, M., Erdogan, D., Abban, G., Turkozkan, N., Elbeg, S., 1999. Effects of vitamin E on Adriamycin- induced nephrotoxicity at the ultrastructural levels in guinea pigs. Nephron 82, 155-163.

Green, D., Stone, N.J., Krumlovsky, F.A., 1983. Putative atherogenic factors in patients with chronic renal failure. Progress in Cardiovascular Diseases 26, 133–144.

Greene, E.L., Paller, M.S., 1991. Oxygen free radicals in acute renal failure. Mineral and Electrolyte Metabolism 17, 124- 132.

Halliwell, B., 1991. Reactive oxygen species in living systems: Source biochemistry, role in human disease. American Journal of Medicine 91, 14–22

Halliwell, B., 1994. Free radicals antioxidants, human disease: Curiosity cause or consequence. Lancet 344, 721–724

Handelman, G.J., Walter, M.F., Adhikarla, R., Gross, J., Dallal, G.E., Levin, N. W., Blumberg, J.B., 2001. Elevated plasma F2-isoprostanes in patients on long-term hemodialysis. Kidney International 59, 1960–1966.

Kikuchi, Y., Koyama, T., Koyama, Y., Trozawa, S., Arai, T., Hori-Moto, M., Kakiuchi, Y., 1982. Red blood cell deformability in renal failure. Nephron 30, 8–14.

Kitamura, M., Ishikawa, Y., 1999. Oxidant-induced apoptosis of glomerular cells: intracellular signaling and its intervention by bioflavonoid. Kidney International 56, 1223–1229.

Klahr, S., 2001. Urinary tract obstruction. Seminars in Nephrology 21, 133–145.

Lee, J.I., Son, H.Y., Kim, M.C., 2006. Attenuation of ischemia-reperfusion injury by ascorbic acid in the canine renal transplantation. Journal of Veterinary Science 7, 375–379.

Maggi, E., Belazzi, R., Falaschi, F., Frattoni, A., Perani, G., Finardi, G., Gazo, A., Nai, M., Romanini, D., Bellono, G., 1994 Enhanced LDL oxidation in uremic patients: an additional mechanism for accelerated atherosclerosis?. Kidney International 45, 867-883.

Mantle, D., Preedy, V.R., 1999. Free radicals as mediators of alcohol toxicity. Adverse Drug React. Toxicological Reviews 18, 235–252.

Mark, S.P., John, R.H., Thomas, F.F., 1984. Oxygen free radicals in ischaemic acute ranel failure in the rat. Journal of Clinical Investigations 74, 1156 - 1164.

Morosetti, M.E., Tozzo, C., Strolighi, L., Casciani, C.U., 1987. Red blood cell lipid peroxidation in hemodialysis chronic renal failure. Clinical Nephrology 27, 238–241.

Paller, M.S., Hedlund, B.E., 1988. Role of iron in postischemic renal injury in the rat. Kidney International 34, 474 – 480

Paller, M.S., Weber, K., Patten, M., 1998. Nitric oxide-mediated renal epithelial cell injury during hypoxia and reoxygenation. Renal Failure 20, 459–469.

Pár, A., Jávor, T., 1984. Alternatives in hepatoprotection: cytoprotection- influences on monooxidase system-free radical scavengers a review). Acta Physiologica Hungarica 64, 409–423.

Rao Srinivasa, P.V.L.N., Dakshinamurti, K.V., Saibaba, K.S.S. Vijayabhaskar, M., 1996. Evidence for oxidant injury in patients with postdiarrhoeal acute renal failure. Indian Journal of Clinical Biochemistry 11, 66 - 69.

Ratych, R.E., Bulkley, G.B., 1986. Free radical mediated postischaemic reperfusion injury in the kidney. Journal of Free Radical Biology and Medicine 2, 311 - 319.

Sakatsume, M., Kadomura, M., Sakata, I., Imai, N., Kondo, D., Osawa, Y., Shimada, H., Ueno, M., Miida, T., Nishi, S., Arakawa, M., Gejyo, F., 2001. Novel glomerular lipoprotein deposits associated with apolipoprotein E2 homozygosity. Kidney International 59, 1911–1918.

Schiavon, R., Guidi, G.C., Biasioli, S., De Fanti, E., Targa, L., 1994. Plasma glutathione peroxidase activity as an index of renal function. European Journal of Clinical Chemistry and Biochemistry 32, 759–765.

Shah, S.V., 2001. Role of iron in progressive renal disease. American Journal of Kidney Diseases 37 (Suppl. 2), S30–S33.

Somani, S.M., Husain, K., Whitworth, C., Trammell, G.L., Malafa, M., Rybak, L.P., 2000. Dose-dependent protection by lipoicacid against cisplatin-induced nephrotoxicity in rats: antioxidant defense system. Pharmacology and Toxicology 86, 234-241.

Stohs, S.J., 1995. The role of free radicals in toxicity and disease. Journal of Basic Clinical Physiology and Pharmacology 6, 205–228.

Taccone-Gallucci, M., Lubrano, R., Meloni, C., Morosetti, M., Manca di Villahermosa, S., Scoppi, P., Palombo, G., Castello, M., Casciani, C., 1999. Red blood cell membrane lipid peroxidation and resistance to erythropoietin therapy in hemodialysis patients. Clinical Nephrology 52, 239-45.

Tappel, A.L., 1968. Will antioxidant nutrients slow aging processes. Geriatrics 23, 97–105.

Toborek, M., Wasik, T., Drozdz, M., Klin, M., Magner-Wrobel, K., Kopieczna-Grzebieniak, E., 1992. Effect of hemodialysis on lipid peroxidation and antioxidant system in patients with chronic renal failure. Metabolism 41, 1229–1232.

Trachtman, H., Chan, J.C., Chan, W., Valderrama, E., Brandt, R., Wakely, P., Futterweit, S., Maesaka, J., Ma, C., 1996. Vitamin E ameliorates renal injury in an experimental model of immunoglobulin a nephropathy. Pediatric Research 40, 620–626.

Vamvakas, S., Bahner, U., Heidland, A., 1998. Cancer in end-stage renaldisease: potential factors involved. American Journal of Nephrology 18, 89-95.

Vanholder, R., Sever, M.S., Erek, E., Lamiere, N., 2000. Rhabdomyolysis. Journal of the American Society of Nephrology 11, 1553–1561

Wanner, C., Greiber, S., Krämer-Guth, A., Heinloth, A., Galle, J., 1997. Lipids and progression of renal disease: role of modified low density lipoprotein and lipoprotein(a). Kidney International 52 (Suppl. 63), S102–S106.

Wardle, E.N., 2005. Cellular oxidative process in relation to renal disease. American Journal of Nephrology 25, 13 -22.

Wojcicka, G., Beltowski, J., 2001. Oxidative stress in glomerulonephri- tis. Postepy higieny medycyny doswiadczalnej 55, 855–869.

Yalcin, A.S., Yurtkuran, M., Dilek, K., Kilinc, A., Taga, Y., Emerk, K., 1989. The effect of vitamin E therapy on plasma and erythrocyte lipid peroxidation in chronic hemodialysis patients. Clinical Chimistry Acta 185,109–112.

Yawata, Y., Jacob, H., 1975. Abnormal red cell metabolism in patients with chronic uremia: Nature of the defect and its persistence despite adequate hemodialysis. Blood 45, 231–239.