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Modulation of Oxidative Stress in Chronic Kidney Disease Patients with Different Physiopathological Conditions

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ANNOTATION

Oxidative stress is an imbalance between the production of oxidants and antioxidants in the body, which can be involved in the onset and / or development of chronic kidney disease, causing the disease to progress to other complications such as: diabetes, atherosclerosis or hypertension. Hemodialysis is characterized by an increase in oxidative stress due to the loss of antioxidants during dialysis. The aim of this work is to present the modulation of oxidative stress in chronic kidney disease patients with different physiopatological conditions.

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INTRODUCTION

Utilization of molecular oxygen by aerobic organisms inevitably results in the formation of a number of oxygen-containing reactive species that are collectively known as reactive oxygen species (ROS). ROS play important roles in both physiology and pathophysiology of aerobic life (Li et al., 2016).

The excessive production of these molecules causes metabolic abnormalities called oxidative stress which has been defined by Himmelfarb as a disturbance in the balance between oxidant production and antioxidant mechanisms within cells, tissue, or a whole organism (Himmelfarb, 2009).

Oxidative stress is implicated in the pathologic pathways of various conditions, such as diabetes mellitus, atherosclerosis, inflammation, and progression of chronic kidney disease (CKD) to end-stage renal disease (ESRD) (Liakopoulos et al., 2017) which is a public health problem that has become a major cause of morbidity and mortality (Datta et al., 2010 ; Krata et al., 2017).

Chronic kidney disease (CKD) is currently defined either as kidney damage, confirmed by kidney biopsy or markers of damage, or as the presence of a glomerular filtration rate (GFR) of <60 ml/min/1.73 m2, each for a period greater than 3 months (Karamouzis et al., 2008).

The oxidative stress is very common in CKD; it is present even in the early stages, gradually increases along with renal impairment, and is further exacerbated by hemodialysis (HD) procedures (Liakopoulos et al., 2017).

Recent studies have shown the presence of a link between the alteration of oxidative stress statues and CKD. The aim of this study is to determine the alteration of oxidative stress in ESRD patients in several pathological cases.

MATERIAL AND METHODS

Our work was carried out in the Laboratory of Chemistry, Physics and Materials Biology, at the Department of Natural Sciences, Higher School Professors of Technological Education, Skikda, Algeria.

All patients included in this study were informed of the different analyses established and agreed to participate.

KEYWORDS:
Antioxidant,
Chronic kidney disease,
Hemodialysis,
Oxidative stress,
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Study Population

A total of 15 subjects were included in the study with a mean age of 40 to 70 years. They were divided into two groups. The first group was composed of 11 male patients (CKD group), with a diagnosis of Chronic Kidney Disease receiving hemodialysis (HD) at the dialysis center of the EPH – Collo, Algeria (Public Hospital Establishment), with an eGFR of 6 mL/min/1.73m2 (the value corresponds to an end-stage renal disease).

The second group (control group) was composed of 4 persons. None of them suffered from any acute or chronic disease.

Biochemical Analysis

Blood parameters

Uremia, serum creatinine (Creat), glycemia (Gly), hemoglobin (Hgb) and hematocrit (Hct) were measured by automated methods at the hospital laboratory.

Measurement of reduced glutathione (GSH)

The plasma samples (0.8ml) were initially deproteinized using 0.2 ml of salicylic acid(0.25%). 1ml of Tris (0.4M)-EDTA (0.02M) buffer was added to the supernatant recovered after centrifugation then it was treated with 10µl of 5-5'dithiobis (2-nitrobenzoic acid (DTNB) and the absorbance was read at 412nm.

Statistical Analysis

All values are expressed as the mean ± SEM. Statistical comparisons between the two groups were made by Student test using the Prism program (version 5, Graph Pad Software Inc., San Diego, CA, USA). Significance was considered present when probability values were <0.05.

RESULTS

Biochemical analysis

Blood parameters

Blood urea concentration was highly significantly greater in CKD group as compared to control group (1.14 ± 0.12 g/l vs 0.27 ± 0.04 g/l) (p<0.001). Serum creatinine concentration was highly significantly greater in CKD groups as compared to control group (84.51 ± 5.42mg/l vs 7 ± 0.58 mg/l).

On the other hand, hemoglobin levels were significantly lower in CKD group in comparison with the control group (9.77±0.46 g/dl vs13.18±0.95g/dl). Hematocrit concentration was significantly lower in CKD group as compared to control group (29.54±1.42% vs 40.37±2.80%). Concerning the glycemia levels there was no significant difference between control group and CKD group (Table 1).

Measurement of reduced glutathione (GSH):

There was no significant change in Glutathione levels in CKD patients compared to control group (774 ± 60.38 µmol/l vs 861.8 ± 19.57 µmol/l) (Figure 1).

Discussion

The main findings of our study were that the plasma GSH levels were not significantly changed in CKD patients in final stage compared to control group. Despite of a tendency to be lower and a bigger SEM in CKD group. A bigger sample of CKD patients could have made different results. Other studies showed that plasma concentration of the antioxidant uric acid was lower in dogs with CKD than in the control group, the difference was not statistically significant (Silva et al., 2013). Also the results for plasma uric acid concentration in human patients with kidney disease are conflicting, probably owing to the use of different methodologies (Clermont et al., 2000; Erdogan et al., 2002). The lower level of plasma albumin observed in the dogs with CKD could have contributed to their lower TAC. According to Terawaki et al., albumin exerts an important antioxidant role in CKD related oxidative stress (Terawaki et al., 2004). The lower antioxidant capacity did not promote the expected increase in TBARS. On the contrary, lipid peroxidation in the plasma was lower in the dogs with CKD than in the control group. The lower production of superoxide in the dogs with CKD may have contributed to reduced formation of TBARS. Although TBARS measurement is a commonly reported method of detecting MDA, it is insufficiently sensitive and is affected by interference from related species or overestimation due to stressing conditions during sample manipulation (Del Rio et al., 2005).

A study by Gerardi et al., showed that the total plasma antioxidant capacity of HD patients is remarkably increased compared to values measured in the controls. The finding is paradoxical, since the occurrence of oxidative stress in these patients should lead to a consumption of antioxidants, and

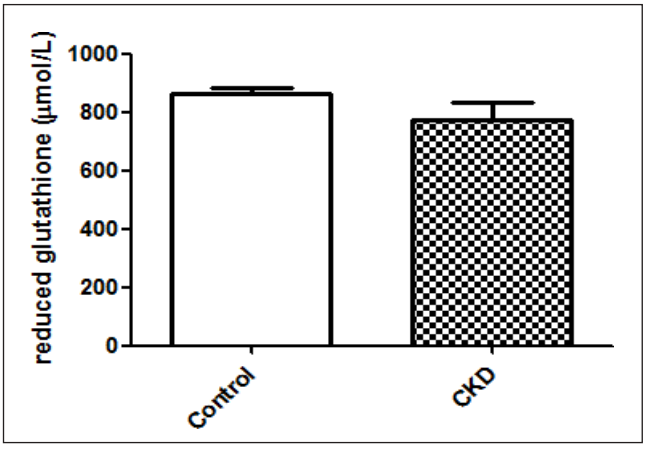

Fig. 1: Reduced glutathione levels in plasma

Table 1: Blood parameters of the studied groups

Blood parameters	*Hct (%)*	*Hgb (g/dL)*	*Gly (g/L)*	*Urea(g/L)*	*Creat (mg/L)*
Control	40.37 ± 2.80	13.18 ± 0.95	0.75 ± 0.03	0.27 ± 0.04	7 ± 0.58
CKD	29.54 ± 1.42*	9.77 ± 0.46*	0.73 ± 0.06	1.14 ± 0.12**	84.51 ± 5.42**

*p<0.01 versus control group
**p<0.001 versus control group

thus a decrease in the total antioxidant potential would be anticipated (Gerardi et al., 2002).

Although the antioxidants levels were not changed, there is a growing evidence showing that CKD patients are characterized by enhanced oxidative stress, even in early stages. Oxidative stress increases in later stages of CKD and becomes more severe in end-stage renal disease patients undergoing maintenance patients (Boudouris et al., 2013). Hemodialysis is characterized by excessive oxidative stress for several reasons. Firstly, conditions or comorbidities that usually accompany HD patients like dyslipidemia, hypertension, metabolic syndrome, old age, and atherosclerosis trigger prooxidant activity (Liakopoulos et al., 2017). Secondly, altered dietary restrictions and preferences may exaggerate the depletion of antioxidant defense mechanisms, such aslow levels of vitamins C and E (mainly because of dietary restrictions of vegetables and fruits, malnutrition, and loss of vitamins during HD procedure), reduced selenium levels,and reduced function of the GSH-scavenging mechanism (Simmons et al.,2005).

It is well known that oxidative stress is a major contributor to several conditions which predispose to CKD, such as diabetes, hypertension, and atherosclerosis promoting indirectly the progression of renal damage. In kidney failure, accumulation of ROS or reduction in antioxidant systems can be observed (Modlinger et al., 2004). Specifically, accumulation of ROS, especially O2- , leads to NO inactivation and deficiency, which is a critical antioxidant that protects kidney function by increasing renal blood flow, enhancing pressure natriuresis, regulating tubuloglomerular function, and preserving fluid and electrolyte homeostasis. NO deficiency and high levels of plasma O2- are considered critical promoters of oxidative stress. Several in vivo studies highlighted that CKD is a state of NO deficiency: hypertensive animal models showed increased levels of O2- in the endothelium and kidneys; animals with NO deficiency developed salt retention, hypertension, albuminuria, and glomerulosclerosis; and oral intake of the NO precursor molecule L-arginine in nephrectomized rats increased estimated glomerular filtration rates (eGFR) and improved glomerular function (Haugen et al., 1999). Chen et al. showed that plasma levels of O2- were significantly increased in maintenance hemodialysis patients compared to healthy controls (Chen et al., 1998).

In addition, the loss of antioxidants during dialysis procedures and accumulation of oxidative products. It has been suggested that the HD procedure promotes the formation of O2- , a powerful prooxidant reactive oxygen molecule (Chen et al., 1998).Another study showed a direct increase in ROS plasma levels after each HD session (Liakopoulos et al., 2017). During HD, blood exposure to dialyzer membranes and dialysate trigger activation of complement factors, platelets and polymorphonuclear white blood cells (PMNs), and subsequently ROS production, within minutes after initiation of HD sessions (Canaud et al., 1999). PMN stimulation was reported as a significant OS biomarker that is progressively increased along with the stages of CKD and is more pronounced in HD (Sela et al., 2005). Maher et al. reported that within 30 minutes of HD initiation, lipid peroxidation products increase and hypothesized that complement factor activation or production of free fatty acids induced by heparin might be the pathophysiologic mechanisms underlying these effects. Loughrey and collaborators, recruited 15 patients on regular HD and 15 ESRD patients with eGFR< 15 ml/min that were managed with supportive care without renal replacement therapy. Compared to the ESRD group, HD patients presented significantly higher levels of lipid peroxidation markers (MDA) and reduced plasma concentrations of antioxidants (vitamin C, GSH-Px, and selenium), indicating that OS is further exacerbated by the HD procedure (Loughrey et al., 1994).

The development of oxidative stress in CKD is thus entwined with the progression of the disease, both as a cause and as a consequence of CKD (Kao et al., 2010). Impaired mitochondrial function and enhanced mitochondrial ROS have been proposed as one of the causes of elevated oxidative stress in CKD. Impaired mitochondrial function might also be the cause of the lower energy metabolism displayed by many CKD patients (Galvanet al., 2017). A study comparing conservative treatment and hemodialysis in CKD patients found that the mitochondrial respiratory system was dysregulated in CKD, and this dysregulation was associated with enhanced oxidative stress (Granata et al., 2009).

However, oxidative stress may contribute to endothelial dysfunction and can also aggravate atherosclerosis and leads to the development of cardiovascular disease or various malignancies in ESRD patients (Shang et al., 2016).In addition, high levels of oxidized low-density lipoprotein (LDL) have been reported. This increase in oxidized LDL can favor the atherosclerotic process and seems not to be theconsequence of higher susceptibility to oxidation of circulating LDL particles from renal patients, as they showed sensitivity to copper-induced oxidation similar to those obtained from matched controls (Diepeveen et al., 2008). Zalba et al., showed that oxidative stress represents an emerging threat to patient cardiovascular outcome in end-stage renal disease and it is reasonable to consider that oxidative stress (probably due to the contribution of both stimulation of NADPH oxidase and inhibition of SOD) is already present at the earlier stages of CKD, and thus it is a potentially important mechanism of atherosclerosis from the beginning of the renal disease process (Zalba et al., 2006).

Galli and collaborators, (Galli et al., 2001) reported abnormally enhanced NADPH oxidase-mediated production in neutrophils from haemodialysis patients, it is likely that phagocytic NADPH oxidase overactivity may represent an early alteration that is maintained throughout the evolution of kidney disease. The exaggerated activity of NADPH oxidase in phagocytic cells from patients with stages 1–2 CKD might be the result of a state of pre-activation of these cell types. In fact, it has been shown that pre-activated monocytes from patients with CKD exhibit enhanced ROS production and increased release of cytokines upon stimulation (Sardenberg et al., 2004). On the other hand, *in vitro* experiments show that advanced oxidation protein products (AOPP) activate NADPH oxidase in human mononuclear cells (Witko-Sarsat et al., 2003).

According to other studies, an increased production of ROS in the kidney can initiate or accelerate the development of hypertension (Welch et al., 2006) by increasing renal vasoconstriction (Just et al., 2008), renin release (Welch et al., 1983), renal afferent nerve activity (Chan et al., 2006),contraction

of afferent arterioles to increased renal perfusion pressure (myogenic response) or to ANG II (Kawarazaki et al., 2012), endothelin-1 (ET-1) and thromboxane prostanoid receptor (TP) activation (Wang et al., 2004).

ROS also cause dysfunction of glomerular cells and proteinuria (Yalavarthy et al., 2007). Increased O2-. in the kidney leads to vascular dysfunction and disrupts water and sodium (Na+) homeostasis (Harrison et al., 2007). Vascular O2-. reacts with endothelium-derived NO and directly promotes vasoconstriction (Lob, 2011).

In diabetes, the over-production of ROS in the kidney is implicated in renal inflammation, affecting renal structure and function and subsequently leading to ESRD. Hyperglycemia-induced ROS production stimulates the recruitment of numerous inflammatory cells and production of inflammatory cytokines such as IL-1, growth factors such as PDGF and transcription factors implicated in the pathological processes of diabetic nephropathy. Excessive infiltration of macrophages and T cells play a pivotal role in initiating renal damage in diabetic nephropathy (Chow et al., 2004).

According to our results and the previous studies we can confirm that oxidative stress status in chronic kidney disease patients is aggravated even though the GSH levels in blood plasma were not changed. This aggravation is the consequence of the reduced functions.

CONCLUSION

It is clear that oxidative stress has a link with CKD and end-stage renal disease in several pathological cases. The enhanced oxidative stress status that characterizes HD patients is mainly due to poor dietary intake of exogenous antioxidants, accumulation of oxidative products, and loss of antioxidant molecules during HD and is highly linked with development of atherosclerosis and chronic inflammation (Liakopoulos et al., 2017).

Although the administration of antioxidants seems to play a beneficial role against oxidative stress development in maintenance HD patients, it has not yet been adopted in the usual clinical practice. Large prospective studies are urgently needed to elucidate the possible protective role of antioxidant administration against cellular stress that hold the promise to improve the cardiovascular risk profile in CKD and end-stage renal disease. It seems that oxidative stress is an undisputed component of the uremic environment.

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