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# Pathophysiological Events Linked to Oxidative Stress and Chronic Kidney Disease: Knowledge for a Kidney Transplant

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## Introduction

Globally, it is estimated that around 800 million people could have Chronic Kidney Disease (CKD), whose global prevalence ranges between 11 to 13% [1]. CKD is characterized as an irreversible disease with no cure at present. Quite often, the severity of this condition worsens over time and is also associated with clinically significant pathologies and comorbidities. Those patients with a more severe stage of the disease, stage 5 or End-Stage (ESRD), have been shown to have lower long-term survival than those who receive adequate treatment for this stage, such as renal replacement therapy such as dialysis or Kidney Transplant (KT) [2]. An alternative treatment for chronic renal failure patients is Kidney Transplantation (KT), especially for those cases where dialysis fails. Along with KT, during ischemia and reperfusion periods over the course of transplantation procedures, comes the induction of OS, which can lead to complications such as primary miss-function of transplanted graft during the post-transplantation period or the development and progression of chronic allograft nephropathy/shortening of the graft life [3].

When long-term results have been compared between chronic dialysis versus kidney transplantation, the latter is considered the most effective in patients with ERSD, because it substantially improves quality of life, long-term survival of patients and offers an excellent cost-benefit ratio [4]. Despite the potential benefits that exist with kidney transplantation, there are obstacles that make proper treatment difficult. Some well documented in the literature are the cumulative lesions that the transplanted kidney may have, as well as both immune and non-immune mechanisms involved in the recipient [5]. All these mechanisms can eventually lead to chronic interstitial fibrosis together with tubular atrophy. Rejection of the kidney graft in the recipient has been associated as a histopathological consequence, which produces functional repercussion damage to the kidney, finally causing the patient to restart on dialysis or with a new kidney transplant [6]. The aim of this article is to present long-term results of kidney transplant patients in different important pathophysiological situations, such as inflammation as part of the immune response; and oxidative stress and its relationship with negative cardiovascular and malignant effects.

### Role of inflammation and oxidative stress in CKD

Inflammation and oxidative stress interplay in a self-perpetuating vicious circle and drive CKD progression, CVD, and other numerous complications such as malnutrition, atherosclerosis, coronary artery calcification, heart failure, anaemia, and mineral and bone disorders [7].

- **Oxidative stress:** Can be defined as an imbalance between the generation of Reactive Oxygen Species (ROS) and nitrogen (RNS) and the antioxidant capacity of the endogenous antioxidant system [8]. ROS and RNS can damage important biomolecules of cell physiology, such as proteins, lipids, and DNA [9]. ROS are a family of highly reactive species that are formed either from enzymatic and non-enzymatic sources. Enzymatic sources include the xanthine oxidase system, NADPH oxidase system, mitochondrial electron transport chain and uncoupled Nitric Oxide Synthase (NOS) system [10]. In turn, RNS include the free radical nitric oxide ($NO^{\cdot}$) and the nonradical peroxynitrite anion ($ONOO^{-}$), which both are synthesized via the Endothelial Nitric Oxide Synthase (eNOS) [11]. The vast majority of cells produce physiological amounts of ROS. ROS have been shown to act as intracellular mediators in complex signaling mechanisms and defense systems. Some examples are the production of prostaglandins, mitochondrial respiration and the defense of the organism by acting as an immune agent by macrophages [12]. However, and as previously mentioned, the dysregulation of this system can cause important cellular and pathophysiological changes. The importance of knowing about OS is that there exists

evidence of an increase in the levels of ROS and RNS during the development of CKD, which eventually leads to ESRD. Furthermore, a relationship between inflammation and OS has been demonstrated, because ROS are capable of enhancing the inflammatory response and activating inflammatory mediators independently of the action of immune cells [13]. All this leads to the kidney being potentially affected by OS, because this organ is very sensitive to the hypoxic environment. It is explained because the tubular cells of the thick ascending branch of the renal medulla have a great capacity to extract oxygen, which causes them to be extremely sensitive to sudden changes in the levels of oxygen in the body [14]. In the kidneys, the major source of ROS generation is due to the increased function of the mitochondrial respiratory chain, which are produced mainly by the mitochondrial respiratory chain. The different isoforms of the enzyme NADPH oxidase also play an important role. OS is attributed as responsible for the chronic progression of kidney disease after transplantation, which is accentuated by renal ischemia, cell death, glomerular injury, interstitial fibrosis in more advanced stages, and apoptosis of renal cells. All this leads to an increase in severe inflammatory processes in the kidney, worsening the condition [15].

- **Inflammation:** In the presence of harmful tissue or cellular damage, a complex biological response is formed to act at the site of the damage. Inflammation is mainly responsible for specific immune cells such as macrophages and neutrophils, which secrete inflammatory mediators called cytokines (IL-6, TNF-α, IL-1β). On the other hand, non-immune cells, such as endothelial cells, can secrete prostaglandins that favor the dilation and subsequent arrival of immune cells at the noxa site [16]. There are laboratory markers used clinically in CKD, such as C-reactive protein (CRP), cytokines such as interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α), adipokines, the CD40 ligand, among other. The latter has been associated as a sensitive biomarker to the progression of CKD [17]. long-term graft success for kidney transplant recipients can be determined by a variety of factors such as weight gain and obesity, which are significant issues and might compromise and contribute to the development of cardiovascular disease [18]. In conclusion, our study demonstrated that reduced nephron mass because of kidney donation is associated with progressive deterioration of endothelial function along with decreased GFR, increased serum uric acid levels, and markers of inflammation. Our findings suggest that kidney donation might increase the risk of cardiovascular diseases in kidney donors [19].

## Long-term outcomes in KTR

Kidney Transplant Recipients (KTRs), on the other hand, have a particularly high risk of premature mortality, showing an overall mortality rate significantly higher than the age-related control group in the general population [20]. Moreover, a long-standing pattern that has remained uniform over the last years shows approximately half of all kidney allograft losses are due to premature death with a functioning graft [21]. About 10% of Kidney Transplant Recipients (KTRs) have life-threatening illnesses that require hospitalization in an Intensive Care Unit (ICU) [22,23]. Most admissions occur more than 6 months after the renal transplantation [5,24].

In addition, non-immune complications following kidney transplantation, such as recurrence of primary renal disease, and other complications such as cardiovascular disease, infections, and malignancies also play a critical role in transplantation in both poor long-term allograft and patient's survival [25,26]. Cardiovascular disease in kidney transplant recipients is associated with many traditional risk factors such as age, gender, smoking, hyperlipidemia, hypertension, obesity, and diabetes [27]. Among KTR, patients with diabetes-related ESRD had a higher mortality rate than patients with ESRD due to other causes [28]. The burden of cardiovascular disease in ESKD improves after kidney transplantation. However, it continues to be a major cause of reduced morbimortality and early kidney-transplants dysfunction, as it is associated with significant morbidity and healthcare costs [29]. Furthermore, as kidney transplantation aims to restore kidney function, it does not completely mitigate collateral mechanisms of disease such as mild chronic inflammation with persistent redox and mineral imbalances, further studies examining specific clinical and laboratory findings that have been suggested to be involved in such pathological pathways may indicate non-traditional risk factors and reveal new targets for clinical intervention [30,31]. Reperfusion and oxidative injury also occur during kidney preservation and may correlate with the immediate and long-term kidney function [32].

## OS in CV and malignancy

A variety of cardiovascular diseases have been shown to be associated, at least partially, with an excess production of Reactive Oxygen Species (ROS) [33]. The NOX (NADPH Oxidase) family of NADPH oxidases are transmembrane proteins that transfer a single electron from NADPH to molecular oxygen, resulting in the formation of superoxide. Physiological production of ROS usually occurs as a by-product. However, this is not the case with NOX enzymes. This is because the production of ROS represents their main biological function. In fact, NOX-induced ROS release, also known as oxidative burst, promotes the destruction of bacteria-infiltrating macrophages and neutrophils [34]. The endothelium secretes a diversity of molecules: NO and prostacyclin (PGI2) exhibit vasodilator, antithrombotic and antiproliferative effects; ET-1 and AngII, vasoconstrictor effects; plasminogen activator inhibitor-1 (PAI-1) and von Willebrand factor (vWF), prothrombotic functions; and anticoagulants, such as tissue plasminogen activator (tPA). Of all the molecules mentioned, NO is considered to be one of the most crucial in endothelial dysfunction, since low

concentrations may induce this imbalance [35]. High levels of ROS directly attack endothelial cells and interfere with the action of the oxidative systems, reducing the ability of iNOS to produce NO, leading to a pro-inflammatory environment. Similarly, another molecule involved in this NO deregulation is the overexpression of NOX4 in the endothelium. This is because it has been shown to improve vasodilation and lower blood pressure by producing more $H_2O_2$ and reducing NO inactivation [36].

Multiple studies have confirmed a strong relationship between oxidative stress and the formation or progression of several human pathologies including cancer [37]. There is substantial experimental evidence to support the role of ROS in tumor initiation, promotion and progression [38,39]. During normal cellular metabolism, ROSs are produced. As its formation plays a crucial role in normal cell signaling pathways, excessive ROS levels may lead to genomic and mitochondrial DNA damage, resulting in DNA alteration, mutation of molecules, and modified signaling pathways. DNA molecules are sensitive to hydroxyl radicals' attacks resulting in damage and modification of purine and pyrimidine bases [40]. Oxidative stress has been shown to induce genetic mutations through the formation of oxidative adducts and/or the inhibition of particular oxidative enzymes which play a physiological role in DNA restoration. Concerning cancer, ROS have been shown to influence the expression of important genes in cancer through modification of second messengers and transcription factors [41]. Cancer is one of the three leading causes of death after a kidney transplant. The appearance of malignant tumors after transplantation is widely recognized. The effects of viral infection, induction maintenance therapy and immunosuppression have been suggested as important risk factors for post-transplant malignancies. The increased risk of cancer may be due to immunosuppressive-induced viral reactivation or reduced immune surveillance leading to faster tumor growth [42,43]. Wang et al. [44] found that renal transplant recipients had a higher risk of all cancers, including colon cancer, hepatocellular carcinoma, gastric cancer, pancreatic cancer, lung cancer, urinary bladder cancer, thyroid cancer, renal cell cancer, melanoma and non-melanoma skin cancer, Hodgkin's lymphoma and non-Hodgkin lymphoma, lip cancer, breast cancer and ovarian cancer.

**Inflammation and OS in long-term outcomes of KTR**

Summarizing what has been stated so far, successful KT leads to improved graft function and decrease in OS. Even if KTR have a stable graft, they still suffer from OS, which OS levels, in comparison to hemodialysis patients, are usually lower, yet still higher than those present in the general population [45].

**Antioxidant Therapy**

- **Vitamin C:** Also known as ascorbic acid, vitamin C is an essential antioxidant capable of donating electrons to both enzymatic and non-enzymatic processes. Working as a cofactor, it gets involved in processes such as collagen synthesis, the prevention of fatal genetic mutations, leukocytes' protection, and supports the production of carnitine, which is associated with metabolic energy [46]. At the lipidaqueous interphase, ascorbic acid can react with oxidized tocopherol radicals bound to the membrane and reduce it to regenerate active tocopherols and perform their antioxidant function [47]. Ascorbic acid reduces oxidative damage, inflammation and nephrotoxicity in several animal models, as well as acute kidney injury due to nephrotoxicity, ischemia and rhabdomyolysis-induced renal damage [48]. This particular assortment of biochemical properties renders vitamin C as a compelling research candidate to broaden the understanding of the interaction between inflammation and oxidative stress in the mechanisms leading to a higher risk of premature death post-kidney transplantation. It should be taken in consideration that pre-transplant ESKD patients often have an imbalance of several critical trace elements and vitamins [49]. Through an inverse mediating effect on inflammatory signaling biomarkers, It has been hypothesized that sub-physiological levels of vitamin C (depletion) might suggest being involved in mechanisms that are associated with an increased risk of adverse long-term outcomes [50,51].
- **Vitamin E:** Vitamin E is a fat-soluble vitamin whose main active compound is α-tocopherol. The alpha-tocopherol is capable of counteracting the lipid peroxidation of cell membranes and stopping the radical chain by forming a low-reactivity derivative unable to attack lipid substrates [52]. Thus, vitamin E accomplishes its role in membrane preservation against free radical damage promoted by low-density lipoproteins. It can actively modify oxidative stress biomarkers, improve erythropoiesis, or reduce the required dose of erythropoietin [53]. In ESRD, vitamin E levels have been found to be low, normal or increased [54]. In addition to oral administration, vitamin E-coated membranes have been used to reduce oxidative stress during hemodialysis and have been reported to have a variety of beneficial effects [55].
- **Vitamin D:** Vitamin D is important not only for calcium/phosphorus homeostasis and bone health, but also for many extraskeletal functions. In particular, vitamin D deficiency is commonly observed in CKD and ESRD [56]. Serum concentrations appear to be inversely related to renal function and a particular prevalence in hemodialysis patients [57]. Growing evidence indicates that vitamin D deficiency may contribute to deteriorating renal function, as well as increased morbidity and mortality in patients with CKD [58,59]. In other preclinical studies, vitamin D has shown, through the inhibition of multiple key pathways in kidney injury, such as the Renin-Angiotensin-Aldosterone System (RAAS), NF-κB, TGF-β/Smad and Wnt/β-catenin signaling pathways, to be useful at mitigating kidney injury by suppressing inflammation, apoptosis and fibrosis [60].

## Conclusions

In conclusion, CKD is a disease characterized by an irreversible progression to end stages, with no cure nowadays. Impacting a large number of patients worldwide, it has been associated with a lower life span, which could be expanded, improving quality of life, by receiving adequate treatment, such as dialysis or KT. Although the transplantation therapy presents obstacles and complications inherent to the treatment, evidence has shown that successful KT manage to improve the graft function on par with a drop on OS biomarkers levels, which, even though are not equivalent to a non-transplanted normal functioning kidney controls, are lower than those present in hemodialysis patients, decreasing the risk of developing a series of diseases that have been associated to high OS levels, for example cardiovascular pathologies and cancer.

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