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REVIEW ARTICLE

THE ROLES OF FREE RADICALS IN THE RED BLOOD CELL DAMAGE IN CHRONIC KIDNEY DISEASES: A REVIEW

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Abstract

Chronic kidney disease (CKD) is common in older people. However, while young her CKD patients usually experience a progressive loss of renal function, his 30% of his CKD patients aged 65 years and older have stable disease. Red blood cells are constantly exposed to high concentrations of oxygen that promote the production of reactive oxygen species (ROS). Within 24 hours, 3% of haemoglobin is oxidized to form superoxide radicals. Studies have shown that haemoglobin itself is a catalyst for free radical reactions, and redox balance is maintained by the presence of antioxidant enzymes and low molecular weight reducing agents. Kidney tubular cells are rich in mitochondria. This is because reabsorption of solutes requires energy, making kidney cells particularly susceptible to oxidative stress and damage. In addition, free radicals and preoxidants produced during acute kidney injury (AKI) and CKD can exacerbate the damage. It may also play a role in the development of severe complications in distant organs commonly seen in AKI and CKD. B. Cardiovascular disease and neurological complications. Several studies have shown that plasma markers of oxidative stress are elevated in CKD patients, indicating increased systemic oxidative stress. Biomarkers for this disease are found in blood, serum, urine, and saliva, and the use of these fluids in clinical practice can help monitor disease.

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Introduction:-

Chronic Kidney Disease (CKD) or Chronic Renal Failure (CRF) has historically been defined as any degree of loss of renal function, ranging from injury impairment to mild, moderate, and severe chronic renal failure (Arora *et al.*, 2021). Chronic kidney disease is a global public health problem. The incidence and prevalence of renal failure is increasing in the United States, leading to poor outcomes and high costs (Arora *et al.,* 2021).

Chronic kidney disease is a condition in which the kidneys are damaged and cannot filter blood well. Because of this, excess water and waste products from the blood remain in the body and can lead to other health problems such as heart disease, high blood pressure, diabetes and stroke.

More than 1 in 7

15% of US adults are estimated to have chronic kidney disease that is about 37 million people.

Some other health consequences of CKD include:

- Anaemia or low number of red blood cells
- Increased occurrence of infections
- Low calcium levels, high potassium levels, and high phosphorus levels in the blood
- Loss of appetite or eating less
- Depression or lower quality of life

CKD has varying levels of seriousness. It usually gets worse over time though treatment has been shown to slow progression. If left untreated, CKD can progress to kidney failure and early cardiovascular disease. When the kidneys stop working, dialysis or kidney transplant is needed for survival. Kidney failure treated with dialysis or kidney transplant is called end-stage renal disease (ESRD).

Risk Factors

- Diabetes
- High blood pressure
- Heart disease
- Family history of CKD
- Obesity

Body cells use oxygen to produce energy, and free radicals are produced as a result of ATP (aden-osine triphosphate) production by mitochondria. These byproducts are generally reactive oxygen species (ROS) and reactive nitrogen species (RNS) resulting from cellular redox processes. At low or moderate concentrations, ROS and RNS exert beneficial effects on cellular responses and immune function. At high concentrations, they generate oxidative stress, a deleterious process that can damage all cellular structures

. Formation of ROS and RNA occurs in two ways within cells:enzymatic and non-enzymatic reactions. Enzymatic reactions that generate free radicals include those involved in the respiratory chain, phagocytosis, prostaglandin synthesis, and the cytochrome P450 system. For example, the superoxide anion radical (O2•-) is produced via several cellular oxidase systems such as NADPH oxidase, xanthine oxidase, and peroxidase. Once formed, it participates in multiple reactions that generate various ROS and RNS such as hydrogen peroxide, hydroxyl radical (OH•), peroxynitrite (ONOO–) and hypochlorous acid (HOCl). H2O2 (non-radical) is

produced by the action of several oxidase enzymes such as amino acid oxidase and xanthine oxidase. The latter catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to uric acid. The hydroxyl radical (OH•), the most reactive free radical in living organisms, is formed by the reaction of HeO2 and H2O2 in the presence of Fe2+ or Cu+ (catalyst). This reaction is known as the Fenton reaction. Hypochlorous acid (HOCl) is produced by the neutrophil-derived enzyme myeloperoxidase, which oxidizes chloride ions in the presence of H2O2. Nitric oxide radicals (NO•) are formed in living tissues from the oxidation of L-arginine to citrulline by nitric oxide synthase. Free radicals can be generated by non-enzymatic reactions between oxygen and organic compounds, similar to those initiated by ionizing radiation. Non-enzymatic processes may also occur during mitochondrial oxidative phosphorylation.
ROS and RNA are produced from endogenous or exogenous sources. Endogenous free radicals are generated by immune cell activation, inflammation, psychological stress, excessive exercise, ischemia, infection, cancer, aging, etc. Exogenous ROS/RNS can be found in air and water pollution, cigarette smoke, alcohol, heavy or transition metals (Cd, Hg, Pb, Fe, As), certain drugs (cyclosporine, tacrolimus, gentamicin, bleomycin), industrial occurs from solvents, cooking (smoking), meat, waste oil (grease), radiation. After entering the body through various pathways, these exogenous compounds are degraded or metabolized into free radicals.

The body has several antioxidants that counteract oxidative stress by producing antioxidants that are either naturally produced in the body (endogenous antioxidants) or obtained from the diet (exogenous antioxidants). The role of antioxidants is to neutralize excess free radicals, protect cells from toxic effects, and help prevent disease.

The functional role of red blood cells (RBCs) is to transport oxygen from the lungs to tissues and thereby provide all cells with the oxygen they need. During circulation, red blood cells are continuously exposed to both endogenous and exogenous reactive oxygen species (ROS), which can damage them and impair their function.

Red blood cells (RBCs) are deformed and must pass through small capillaries. Therefore, reduced deformability of RBCs is one of the factors contributing to the elimination of aged or damaged RBCs from circulation. Also, this process can lead to impaired oxygenation, which contributes to the pathology of many diseases. Red blood cells are continuously exposed to both endogenous and exogenous sources of reactive oxygen species (ROS) such as superoxide and hydrogen peroxide (H2O2). Most ROS are neutralized by the RBC antioxidant system, which is composed of both nonenzymatic and enzymatic antioxidants such as catalase, glutathione peroxidase and peroxiredoxin-2

Partially oxygenated Hb molecules formed in the RBCs in microcirculation, when oxygen is being transported by them to the tissues, have an elevated affinity for the RBC membrane and have an increase in autoxidation producing ROS that are not completely neutralized by the RBC antioxidant system. This source of RBC oxidative stress is involved in a number of the factors that contribute to RBC aging and the removal of RBCs from the circulation. This oxidative process, thus, explains the dominant role of oxidative stress in RBC aging (Mohanty *et al*., 2014).

Kidney

In the review by Ivy & Bailey (2014), the role that the kidney plays in the long-term regulation of blood pressure is discussed. Such regulation is multifaceted, involving a complex interplay between the kidney, cardiovascular and autonomic nervous systems. Although controversial, for many years the kidney has been thought to be the main player in the long-term control of blood pressure, and this review presents the evidence for and against this role of the kidney in preventing hypertension. It is clear that mutations in proteins that impact on sodium handling by the kidney, for example in Liddle's syndrome and apparent mineralocorticoid excess, lead to hypertension. In addition, transplantation of a normal kidney into animal models of hypertension reduces blood pressure, indicating that the kidney plays a dominant role in determining blood pressure. However, more recent work challenges this model, showing that there are changes in the immune system in hypertensive animals. Given the worldwide estimates of the occurrence of hypertension (over one billion individuals), a thorough understanding of the mechanisms controlling blood pressure regulation are essential if we are to win the fight against this silent killer.

Another example of the kidney having a wide impact is in cardiorenal syndrome (Lekawanvijit and Krum, 2014). In this syndrome, there is cross-linking between the systems, such that failure in one organ leads to failure in the other. Interestingly, a decrease in renal function following the development of cardiovascular disease is a strong predictor of mortality in patients, while cardiovascular disease is the main factor in the death of many dialysis patients. In this review, the authors have examined the current state of play in terms of renal biomarkers to identify cardiorenal syndrome and the role of uraemic toxins in disease progression. A number of markers are discussed, such as creatinine, cystatin C, neutrophil gelatinase-associated lipocalin and kidney injury molecule-1, but all have issues meaning that they are not as effective as they need to be for use in the clinic, highlighting that more work is needed in this area. The review also identifies uraemic toxins as possible players in the development of cardiorenal syndrome, discussing the impact of these toxins on the fibrosis, inflammation and endothelial dysfunction that is typically observed. Interestingly, this review raises the possibility that uraemic toxins impact on the levels of serum fibroblast growth factor 23 and klotho, factors that are known to regulate Ca^{2+} and phosphate handling by the kidney.

This links with our third review, which focuses on the regulation of serum phosphate by parathyroid hormone, vitamin D and fibroblast growth factor 23 and the cofactor klotho (Lederer, 2014). Abnormal serum phosphate levels are a known risk factor in both renal and cardiovascular diseases. The regulation of phosphate handling by the kidney, intestine and bone is therefore critical for normal physiology. What is clear from the work presented is that all three of these systems work in an integrated manner and are important for normal phosphate homeostasis. Changes in the levels of any one of these hormones, for example due to inherited disorders such as familial humoral calcinosis or as a consequence of autoimmune disease, have a significant impact on the physiology of the individual. Of interest, there are also changes in the levels of these hormones in chronic renal disease, leading to changes in serum phosphate levels that contribute to vascular calcification. Once again, this highlights the close links that exist between the renal and cardiovascular systems.

In the fourth review, Mora-Fernández *et al*. (2014) focus on the impact of diabetes mellitus (one of the most common chronic diseases) on renal physiology. Many patients with this disease have significant renal dysfunction Diabetic Kidney Disease (DKD) and often develop end-stage renal disease. Diabetes is, in fact, the most common cause of end-stage renal disease, and given the worldwide rise in individuals diagnosed with this disease (366 million in 2011) it is critical that we have an in-depth understanding of the reasons underlying DKD. In their review, Mora-Fernández *et al*. (2014) consider the role of genetic factors (not everyone with diabetes will develop DKD), metabolic processes (exactly how is glucose handled by cells in patients?), haemodynamic changes (here again is a strong link between the renal and cardiovascular systems), inflammatory mediators (changes in signalling molecules have been observed) and novel, emerging factors. The multitude of factors presented shows the complexity of the progression of DKD.

The final review (Savige, 2014) also considers chronic renal failure, this time in the context of the inherited disease, Alport syndrome. As with DKD, patients show progressive loss of renal function, with proteinuria and a fall in glomerular filtration. Patients also have hearing loss and ocular defects, indicating an impact across more than one organ system. The mutations carried by these patients impact on collagen IV, which is a key component of the basement membranes in the glomerulus, cochlea and retina. The mutations lead to changes in the composition of the basement membrane, meaning that membranes are more prone to damage due to mechanical stresses. In patients, the kidney demonstrates intraglomerular hypertension, and this increased pressure contributes even further to the fall in glomerular function over time. To link back to the recurring theme in these topical reviews (the kidney and the cardiovascular system), one treatment that slows progression of the renal symptoms in Alport syndrome is block of the renin–angiotensin system. This reduces the hypertension observed in patients, reducing the damage to the glomerular basement membrane and therefore slowing (although not stopping) the progression of renal failure.

These five reviews, which highlight examples where defects in renal function impact widely, underscore the critical role of the kidney in whole-body function. These impacts include altered renal sodium handling and the development of hypertension, the increased risk of cardiovascular disease when renal function is compromised and vice versa, changes in bone and the development of ectopic calcifications in response to alterations in renal phosphate handling, the renal impact of diabetes mellitus, and the impact that apparent small changes in basement membrane structure can have in Alport syndrome. The inter organ connections made by the kidney highlight for me one of the key features of physiology, that it is an integrated science. In this molecular age, it is all too easy to end up focusing not simply on one organ, but on one protein, in one cell type in an organ. The reviews presented in this special edition remind us that as physiologists we must consider the whole picture and not forget the importance of looking more globally across the organ systems.

The Level of Haeme Degradation, a Measure of Red Blood Cell Oxidative Stress

The presence of antioxidant enzymes as well as the relative instability of ROS makes it very difficult to quantitate the pool of un-neutralized ROS that reflect RBC oxidative stress. This affects both the RBC and other cells the RBC comes in contact with. As a solution for this

problem we have found that a small fraction of the non-neutralized hydrogen peroxide degrades the protoporphyrin producing fluorescent haeme degradation products (HDPs) that can be detected even at very low concentrations (Nagababu and Rifkind, 1998). These HDPs are also not neutralized by the RBC antioxidant systems and are, therefore, much more stable.
These HDPs were originally detected (Nagababu and Rifkind, 1998) when a 10 fold excess of hydrogen peroxide was added to oxyhemoglobin (oxyHb). At this concentration, in addition to the formation of methaemoglobin (metHb), 5% of the haemes were degraded producing two fluorescent products. One of those has an excitation wavelength of 321 nm and emission wavelength in the region of 465 nm and the second product has an excitation wavelength of 460 nm and emission wavelength in the region of 525 nm. Confirmation that these fluorescent bands are attributed to HDPs is based on the observation that the same fluorescent bands were obtained when hydrogen peroxide reacted with haeme or haemin, although these reactions required much higher levels of hydrogen peroxide. In addition, the excitation and emission wavelengths for these bands were distinct from those of globin fluorescent amino acids like tryptophan, tyrosine or di-tyrosine (Giulivi and Davies, 1993) as well as free protoporphyrin IX. Thus, these fluorescent bands originating from haeme degradation are considered as markers of RBC oxidative stress.

The mechanism for the formation of these degradation products was shown to require (Nagababu and Rifkind, 2000) an initial reaction with hydrogen peroxide producing Fe (IV) ferrylhaemoglobin (ferrylHb). The formation of ferrylHb was confirmed by showing that sodium sulfide, which reacts with ferrylHb, inhibits the formation of the HDPs. FerrylHb then reacted with a second molecule of hydrogen peroxide. The requirement for this hydrogen peroxide was demonstrated by the finding that catalase added after the ferrylHb had formed, inhibited the formation of HDPs. This second molecule of hydrogen peroxide produced metHb and a superoxide radical, which was retained in the haeme pocket and was detected by electron paramagnetic resonance. The retention of this superoxide in the heme pocket much longer than the superoxide formed during Hb autoxidation (see above) facilitates a reaction of the superoxide with the porphyrin initiating the haeme degradation process.

The significance of this reaction is indicated by the demonstration that the same HDPs are generated from the low levels of hydrogen peroxide constantly being produced by the dismutation of superoxide released (Nagababu and Rifkind, 2000) during the autoxidation of purified Hb.

In studies with intact RBCs. It was found that we can detect the same fluorescent band (Ex: 321 nm) as in HDPs described above in any fresh RBC sample (Nagababu et al., 2010). We further demonstrated that the amount of haeme degradation increased for RBCs in circulation for a longer period of time (older RBCs) (Nagababu and Rifkind, 2004). These results indicate that HDPs are produced in the RBCs even though they have an extensive antioxidant system that should react with any amount of hydrogen peroxide formed.

This paradox is explained by the finding that in RBCs, almost all of the HDPs are located on the membrane (Nagababu et al., 2010). To rule out the uptake of cytoplasmic HDPs by the more hydrophobic membrane, we incubated Hb reacted with hydrogen peroxide with RBC membranes and found no increase in the level of membrane fluorescent products over a period of 12 hours.

These results thus indicate that the HDPs generated in the RBC are formed on the RBC membrane and not in the cytoplasm.

Haemoglobin is known to bind to the cytoplasmic end of band present in the membrane. It has been documented that deoxyhaemoglobin (deoxyHb) has an appreciably higher affinity for band 3 than oxyhaemoglobin. This difference has been attributed to changes in the subunit interactions, which facilitate interactions between the cytoplasmic end of band 3 and Hb. While these earlier studies have compared fully oxygenated and fully deoxygenated Hb with known differences in quaternary structure, we have been involved in the studies with partially oxygenated Hb present in RBCs in the microcirculation. Evidence for a distinct conformation for partially oxygenated Hb was initially demonstrated by the dramatic increase in the rates of autoxidation when Hb is partially oxygenated (Abugo and Rifkind, 1994; Balagopalakrishna et al., 1996). Recent studies (Cao et al., 2009) imply that this same conformational change, which alters the interactions between Hb subunits, also has a dramatic effect on their affinity for the RBC membrane. We, thus, found that low levels of nitrite/NO reacted Hb present in fully deoxygenated RBCs have an affinity >100-fold greater for the RBC membrane than deoxyHb. We have attributed this to the nitrite/NO bound fraction of the Hb that is partially liganded, with properties similar to that of partially oxygenated Hb.

Thus, the partially oxygenated Hb is responsible for the bulk of the ROS formed by Hb autoxidation. However, with the elevated affinity of this fraction of Hb for the RBC membrane, the superoxide and hydrogen peroxide formed during the autoxidation of this Hb, is relatively inaccessible to the cytosolic catalase and superoxide dismutase. So, an appreciable fraction of these ROS can react with the Hb before being neutralized by the RBC antioxidant system. Unlike the potential for such reactions with endogenously generated ROS, the addition of exogenous hydrogen peroxide is immediately transported into the RBC before it can react with membrane bound Hb and is neutralized predominantly by cytosolic catalase (Nagababu et al., 2010). While catalase does not seem to be able to compete with Hb in reacting with the pool of hydrogen peroxide generated on the membrane, glutathione peroxidase (Nagababu et al., 2003) and PRDX-2 (Nagababu et al., 2013) may play a role in neutralizing ROS generated on the RBC membrane. Glutathione peroxidase is known to react with membrane ROS (Horton and Fairhurst, 1987) and its inhibition was found to dramatically increase the formation of HDPs. Although PRDX-2 is primarily a cytosolic enzyme, ~5% of it is membrane associated (Moore et al., 1991; Low et al., 2004). The neutralization of membrane generated ROS by PRDX-2 was postulated to explain an increase in heme degradation in PRDX-2 knockout mice (Nagababu et al., 2013).

Contribution of RBC Oxidative Stress to Red Blood Cells Aging

The RBC, continuously undergoing normoxic and hypoxic cycling, is constantly exposed to oxidative insults during its 120 day life-span that results in continuous biochemical, physical, and structural changes. These changes impair the ability of the RBC to transport oxygen and eventually trigger its removal from the circulation by the reticulo-endothelial system. The reticulo-endothelial system involves the mononuclear phagocytic cells primarily in the spleen, but also in the liver and lymph nodes.

The processes responsible for the actual triggering of the removal have been extensively studied (Ajmani and Rifkind, 1998; Barvitenko et al., 2005; Rogers et al., 2009; Antonelou et al., 2010). Many of the processes involve oxidative stress.

The RBC membrane band 3 is the dominant integral trans-membrane protein. It has several crucial functions including: (1) the maintenance of anion homeostasis, (2) providing a link between the membrane and the cytoskeleton responsible for maintaining the cell shape and (3) providing for the interaction of a number of cytosolic proteins with the membrane via the amino terminal region that protrudes into the cytosol. This region of band 3 binds competitively both Hb, and a number of glycolytic enzymes (Mohandas and Gallagher, 2008). The changes in Hb binding to band 3 as a function of the Hb oxygenation, therefore, couple Hb oxygenation, Hb autoxidation, glycolysis and ATP production (De Rosa et al., 2008).

Oxidative damage to band 3 has been linked to RBC aging including the exposure of senescent specific neo-antigens that bind autologous IgG triggering RBC removal (Kay, 1993). IgG binding has also been linked to band 3 clusters, which is triggered by the binding of denatured oxidized Hb (haemichromes) to band 3 (Ferru et al., 2011).

Caspase-3 activation, which involves oxidative stress, also cleaves the cytoplasmic end of band 3 (Mandal et al., 2003) affecting the interactions of band 3 with cytosolic proteins as well as the linkage to ankyrin and the cytoskeleton, which also induces PS exposure (Grey et al., 2012).

Membrane micro-vesiculation is a process that accelerates in the formation of older cells (Willekens et al., 2008). These changes limit the ability of the RBC to maintain the highly deformable biconcave shape necessary to pass through narrow pores, thus contributing to their removal from circulation. While cell shrinkage and vesiculation can be induced by various factors, some of which may not involve oxidative stress, the shrinkage associated with potassium leakage through the Gardos channel is triggered by oxidative stress. This process is initiated by damage to Ca-ATPase, which maintains a low intracellular concentration of free calcium ions (Larsen et al., 1981). Damage to Ca-ATPase is responsible for the age induced increase in intracellular calcium and is generated by oxidative damage to the ATPase (Samaja et al., 1990; Kiefer and Snyder, 2000). The increase in intra-cellular calcium activates the Gardos channel causing the leakage of potassium from the cell resulting in cell shrinkage and impaired deformability (Brugnara, 1993; Foller et al., 2008b).

An increase in intracellular calcium also activates calpain, transglutaminase-2 and some caspases that can degrade/crosslink cytoskeleton proteins (Redding et al., 1991). It also inhibits phosphotyrosine phosphatase increasing band 3 phosphorylation (Zipser et al., 2002).

The RBC lipid bilayer contains an asymmetric distribution of phospholipids with PS being maintained on the inner surface of the membrane by the competition between Scramblase, which randomizes the distribution and Flippase, which internalizes the PS. Coupled with an increase in Sphingomyelinase that increases ceramide, increased intracellular calcium has been linked to the exposure of PS and to a reduction in Flippase activity (Burger et al., 2013), that triggers the interaction of RBCs with macrophages and eryptosis (Daleke, 2008; Foller et al., 2008a; Weiss et al., 2011). Despite the important role of macrophages in the removal of RBCs, it is not clear

that the interaction of RBCs with macrophages is responsible for the removal of aged RBCs from circulation (Dasgupta et al., 2008; Saxena et al., 2012).

Oxidative Stress in the Pathophysiology of Chronic Kidney Disease

Dysregulated metabolic waste disposal in later stages of CKD is also an important contributor to oxidative stress induction. In ESRD, renal replacement therapy with maintenance haemodialysis can aggravate oxidative stress in each session, due to ROS excretion by phagocytes on the surface of dialysis membranes. In addition, haemodialysis further exhausts the antioxidant capacity of the body. Oxidative stress may contribute to endothelial dysfunction and can also aggravate atherosclerosis and lead to the development of cardiovascular disease or various malignancies in ESRD patients. Increased ROS production also induces structural changes in β2-microglobulin, which are associated with the incidence of amyloidosis due to inflammatory processes in CKD. Other features associated with oxidative stress in CKD include anaemia, hypertension, kidney fibrosis, neurologic disorders, and accelerated aging (Gyurászová et al., 2020).

According to (Gwozdzinski *et al.*, 2021) Reactive oxygen species (ROS) released in cells are signaling molecules but can also modify signalling proteins. Red blood cells perform a major role in maintaining the balance of the redox in the blood. The main cytosolic protein of RBC is haemoglobin (Hb), which accounts for 95-97%. Most other proteins are involved in protecting the blood cell from oxidative stress. Haemoglobin is a major factor in initiating oxidative stress within the erythrocyte. RBCs can also be damaged by exogenous oxidants. Hb autoxidation leads to the generation of a superoxide radical, of which the catalysed or spontaneous dismutation produces hydrogen peroxide. Both oxidants induce hemi chrome formation, heme degradation, and release of free iron which is a catalyst for free radical reactions. To maintain the redox balance, appropriate antioxidants are present in the cytosol, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and peroxiredoxin 2 (PRDX2), as well as low molecular weight antioxidants: glutathione, ascorbic acid, lipoic acid, α-tocopherol, β-carotene, and others. Redox imbalance leads to oxidative stress and may be associated with overproduction of ROS and/or insufficient capacity of the antioxidant system. Oxidative stress performs a key role in CKD as evidenced by the high level of markers associated with oxidative damage to proteins, lipids, and DNA in vivo. In addition to the overproduction of ROS, a reduced antioxidant capacity is observed, associated with a decrease in the activity of SOD, GPx, PRDX2, and low molecular weight antioxidants. In addition, haemodialysis is accompanied by oxidative stress in which low-biocompatibility dialysis membranes activate phagocytic cells, especially neutrophils and monocytes, leading to a respiratory burst (Obeagu, 2018; Eze *et al.*, 2016)

.CONCLUSION

Oxidative stress is believed to play an important role in the pathophysiology of CKD. The disease results from accumulation of toxic end products of nitrogen metabolism and creatinine in the blood, decreased urine output, or both. CKD comes in varying degrees of severity. It usually gets worse over time, but treatment has been shown to slow progression. Left untreated, CKD

can lead to renal failure and early cardiovascular disease. If your kidneys fail, you will need dialysis or a kidney transplant to survive. Kidney failure treated with dialysis or a kidney transplant is called end-stage renal disease (ESRD).

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