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Role of Oxidative Stress on Chronic Kidney Disease Progression

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30

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8

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ABSTRAK

49

Penyakit Ginjal Kronik (PGK) merupakan masalah tidak hanya di Indonesia namun juga di dunia dengan angka insidensi yang cenderung meningkat. Sebagian besar pasien PGK meninggal akibat komplikasi kardiovaskular, dibandingkan akibat PGK nya sendiri. Faktor risiko tradisional saja tidak mampu menerangkan tingginya komplikasi kardiovaskular, namun faktor non-tradisional seperti stres oksidatif turut berperan dan menjadi target terapi.

Stres oksidatif terjadi akibat ketidakseimbangan antara faktor pro oksidan yang dominan dibandingkan faktor antioksidan yang menurun pada penderita PGK yang menjalani hemodialisis (HD). Tindakan HD pun menggunakan membran selulosa dan semi selulosa turut berperan terhadap peningkatan oksidan serta mengaktifkan sistem komplemen, merangsang proses inflamasi yang berakhir dengan perburukan stress oksidatif.

Kata kunci: penyakit ginjal kronik, oksidan, stres oksidatif.

ABSTRACT

37

Chronic kidney disease (CKD) is a worldwide health problem with a high incidence not only in western countries but also in Indonesia as well. The majority of patients with CKD died due to cardiovascular disease than CKD progression itself. In addition to traditional risk factors, cardiovascular disease in CKD might also due to non-traditional risk factors. Oxidative stress, as non-traditional risk factors, is not only able to explain the high incidence of cardiovascular disease in CKD, but also become a new target in therapeutic intervention.

Oxidative stress in patients with CKD appears due to increased oxidant activity and decreased antioxidant system. Hemodialysis (HD) with the use of a cellulose and semi-cellulose membrane also contribute to increase oxidant that can activate the complement pathway. It stimulates inflammation that will further expand the production of oxidants and will ultimately increase oxidative stress.

Key words: chronic kidney disease, oxidant, oxidative stress.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide health problem with a high incidence rate.¹ This disease affects 10% of the adult population in the United States² with a mortality rate of 20-50%.³ In Indonesia, the incidence of CKD per million populations in 2002 was 14.5% and increased to 30.7% in 2006. Similarly, the prevalence per million populations increased from 10.2% in 2002 to 23.4% in 2006.⁴ Chronic kidney disease will progressively develop into terminal renal failure. Kidney function decreases and leads to the emergence of a wide variety of complications including cardiovascular disease.^{2,5}

Cardiovascular disease is the leading cause of death in the world, both in the general population and in patients with CKD. The majority of patients with CKD die due to cardiovascular disease than CKD progression itself.^{6,7} In addition to traditional risk factors, cardiovascular disease in CKD can also due to non-traditional risk factors. Oxidative stress, which is a non-traditional risk factors, is not only able to explain the high incidence of cardiovascular disease in CKD, but also has become a new target in therapeutic intervention.⁸

Oxidative stress in patients with CKD appears due to increase oxidant activity and decrease antioxidant system. Increased oxidant activity, inflammation, and endothelial dysfunction are the triad foundation of atherosclerosis in patients with CKD.⁸ Hypertension, uncontrolled high blood sugar and severe proteinuria in patients with CKD are also associated with oxidative stress and with the disease progression.⁹ Hemodialysis (HD) with the use of a cellulose and semi-cellulose membrane also contribute to increase oxidant that can activate the complement pathway and stimulates inflammation that will further expand the production of oxidants and will ultimately increase oxidative stress.^{3,10,11} This literature review will discuss the role of oxidative stress on the progression of CKD and antioxidants as therapeutic effects of oxidative stress.

CKD AND PROGRESSIVITY

Chronic kidney disease is a pathophysiological processes associated with renal function

abnormalities and progressive reduction of glomerular filtration rate (GFR).³ Chronic kidney disease is defined as kidney damage or decreased kidney function (decreased GFR) for 3 months or more with or without regard to the presence or absence of the causes of kidney damage.¹² However, it should still be attempted to establish the diagnosis of CKD causes, degree of renal impairment, degree of decline in kidney function and the risk of further loss of kidney function, as well as the risk of cardiovascular disease.¹³

Table 1. Stages of chronic kidney disease⁵

Stages	Description	GFR (mL/min/1.73 m ²)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with normal or mild GFR ↓	60-89
3	Mild GFR ↓	30-59
4	Severe GRF ↓	15-29
5	Renal failure	<15 or dialysis

Chronic kidney disease is defined as the presence of kidney damage and/or GFR <60mL/minutes/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or damage markers, including abnormalities in blood or urine tests or radiological examinations.

The pathophysiology of CKD involves two mechanisms. First, the initial mechanism of the specific underlying etiology (e.g., immune complex glomerulonephritis and inflammatory mediators to a specific type, or exposure to toxins in some renal tubules and interstitial disease). Second, a series of progressive mechanisms, involving hyperfiltration and hypertrophy of remaining viable nephrons due to a long-term decrease in renal mass. However, hyperfiltration and hypertrophy induced by vasoactive hormones, cytokines, growth factors, and increased activity of the intrarenal renin-angiotensin system are short-term adaptation mechanisms that cause an increase intrarenal pressure and lead to the nephrosclerosis.³

Identification of the risk factors is necessary because the incidence of this disease is still high. CKD risk factors that cannot be modified include older age, family history of renal disease, reduced renal mass from childhood (in babies with low birth-weight), African ancestry, and low socio-

economic status. Other risk factors that can be modified and facilitate the occurrence of CKD are also important to consider, such as diabetes, hypertension, autoimmune diseases, systemic infections, urinary tract infections, urinary tract stones, lower urinary tract obstruction, and drug toxicity.¹²

The major outcome of CKD is loss of kidney function leading to the emergence of complications of renal failure and cardiovascular disease. Progression of CKD is defined as a decline in kidney function, estimated by measuring GFR, creatinine clearance, or serum creatinine level.⁵ There are two factors that can explain the progression of CKD, hemodynamic and non-hemodynamic factors.¹ Six mechanisms that occur through hemodynamic factors are: 1). Persistent glomerular injury produce local hypertension in capillary vessel, increasing GFR in every-single nephron and engenders protein leak into the tubular fluid. 2). Proteinuria increases angiotensin II production. 3). Cytokine is accumulated (cytokines bath) and able to induce the accumulation of mononuclear cells in the interstitial. 4). Interstitial neutrophils will be quickly replaced by macrophages and T-lymphocytes and induces nephrogenic immune response producing interstitial nephritis. 5). Inflammation causes renal tubular cells move away from basal membrane and form new interstitial fibroblasts (epithelial-mesenchymal transitions). 6). Fibroblast lay down a collagenous matrix that disrupt adjacent capillaries and tubular nephrons, resulting a scar and ends up as fibrosis.³

Glomerular hypertension and hyperfiltration may cause damage in podocyte cells and endothelial cells, as well as mesangial cell proliferation.¹ Remaining viable nephrons lose the ability to perform autoregulation, resulting in systemic hypertension, which will ultimately be more damaging to the glomerulus and worsen the CKD progression.³

¹⁰ There are many non-hemodynamic factors play a role in the progression of CKD. Some of these include angiotensin II, aldosterone, endothelin, acidosis, and oxidative stress. Angiotensin II will result in a reduction in glomerular size and selectivity, proteinuria,

increased hydraulic pressure of the glomerulus and podocyte cell damage. Angiotensin II also increases the synthesis of extracellular matrix, activating cytokines, adhesion molecules, transcription factors and monocytes, causing inflammation. Aldosterone causes the proliferation of mesangial cells, apoptosis, hypertrophy, and podocyte cell damage which will exacerbate glomerular damage.¹ Moreover aldosterone also acts as a mediator of angiotensin II which causes structural and functional damage to the blood vessels.¹⁴ Endothelin is a potent vasoconstrictor. In CKD the formation of endothelin will increase, and cause higher pressure on efferent blood vessels than afferent blood vessels, thus resulting in increased glomerular hydraulic pressure. Acidosis is often present in patients with CKD with a GFR below 20%. Acidosis activates the alternative complement pathway by increasing the formation of ammonia and induces the formation of endothelin and aldosterone production. Oxidative stress has contributed to worsening the progression of CKD through cardiovascular complications, including hypertension, inflammation, fibrosis and apoptosis, as well as damage to the glomerular filtration barrier.¹

The assessment of CKD progression is often done by measuring GFR currently. This is because the rate of decline in GFR is relatively constant so that it can be used to estimate the time of renal failure occurrence. There are two approaches to estimate GFR decline. The first is the direct calculation of GFR by using formula. When GFR in the past and present is known, then the decline in GFR in the future could be predicted. The second approach is to look for the ascertain factors associated with a "fast" or "slow" GFR decline. These factors include the type of kidney disease and the modifiable and non-modifiable factors. Diabetic kidney disease, glomerular disease, polycystic kidney disease, and renal disease after transplantation are types of kidney disease that accelerate GFR decline. Non-modifiable factors include older age, male gender, African-American race, lower baseline level of kidney function will accelerate the decline in GFR. Modifiable factors include higher level of proteinuria, lower serum albumin

levels, higher blood pressure, poor blood sugar control and smoking are associated with a faster GFR decline, thus worsening CKD progression.⁵

OXIDATIVE STRESS

Oxidative stress is a state of imbalance between excessive oxidant formation and lack of antioxidants as a defense mechanism.^{8,15} Oxidant formation is physiologically important step in the process of tissue repair as a result of inflammation. This situation illustrates the self-defense mechanism against microorganisms and other foreign antigens. However, when this process occurs in chronic pathological conditions, it will have a detrimental effect and contribute to cell and tissue damage.^{7,8}

Reactive oxygen species (ROS) is an oxidant produced by oxygen metabolite. ROS is radical because it has a single electron and an unpaired electron in the outer orbit. Radical oxygen metabolites include superoxide ($\bullet\text{O}_2^-$) and hydroxyl ($\bullet\text{OH}$) while the non-radicals are hydrogen peroxide (H_2O_2), and singlet oxygen (IO_2). They are all unstable substrates and highly reactive.¹⁷ Sources of ROS include the mitochondrial electron transport system (univalent reduction of molecular oxygen, NADH complex oxygenase), endothelial cells (xanthine oxidase reaction), inflammatory cells (myeloperoxidase, NADPH oxidase), catecholamine oxidation, and metabolism of arachidonic acid.^{16,17} One electron reduction of oxygen molecule may produce peroxide radicals ($\bullet\text{O}_2^-$). By interfere of superoxide dismutase (SOD) enzyme, superoxide radical ($\bullet\text{O}_2^-$), which is very unstable, will be converted into hydrogen peroxide (H_2O_2) immediately. Both superoxide radical ($\bullet\text{O}_2^-$) and hydrogen peroxide (H_2O_2) are precursors of the formation other more powerful oxidants. Hydrogen peroxide (H_2O_2) is a strong oxidant that can interact with many organic substrates. Hydrogen peroxide (H_2O_2) generates hydroxyl radical ($\bullet\text{OH}$) via the Fenton and Haber-Weiss reactions. Hydroxyl radical ($\bullet\text{OH}$) has a very high reactivity, so they can immediately react with the target molecule formed around the place. Hydrogen peroxide (H_2O_2) and chlorine (Cl^-) will be metabolized to hypochlorous acid (HOCl) by myeloperoxidase/

MPO.^{15,16} Superoxide radical ($\bullet\text{O}_2^-$) will react with nitric oxide (NO) to form peroxynitrite (ONOO^-). Peroxynitrite (ONOO^-) will cause the endothelial nitric oxide synthetase (eNOS) become unpaired (uncoupled eNOS) that will form more superoxide radical ($\bullet\text{O}_2^-$) and a cascade of ROS formation.¹⁷

The physiological formation of oxygen radicals will be detoxified by endogenous antioxidants. There are two types of antioxidants, enzymatic and non-enzymatic. Endogenous antioxidant generally present as enzymatic antioxidants, including SOD, catalase, and glutathione peroxidase containing selenium (GSH-Px). SOD will increase the speed of dismutase from superoxide ($\bullet\text{O}_2^-$) to hydrogen peroxide (H_2O_2). Thus, this enzyme is regarded as the first line of antioxidant defense. Exogenous antioxidants obtained from daily food intake is a type of non-enzymatic antioxidants, classified into hydrophilic (ascorbic acid/vitamin C, bilirubin, albumin, and flavonoids) and lipophilic (α -tocopherol/vitamin E, ubiquinol, and carotenoids). Vitamin C cleans the superoxide radical ($\bullet\text{O}_2^-$) and hydroxyl radical ($\bullet\text{OH}$), while vitamin E protects cell membranes from lipid oxidation.^{15,16} Many antioxidants have synergistic relationship and mutually reinforcing. For example, vitamin C has the ability to recycle α -tocopherol. There are other types of exogenous antioxidants known as therapeutic agents previously, such as N-acetylsisteine (NAC), bardoxolone methyl¹¹, and ACE-I/ARB.¹⁸

ROLE OF OXIDATIVE STRESS IN CKD PROGRESSIVENESS

Oxidative stress as part of non-hemodynamic factors plays a role in the progression of CKD, both directly through glomerular damage and renal ischemia or indirectly associated with inflammation, hypertension, and endothelial dysfunction.⁹ Factors that cause an increase in oxidative stress in CKD include malnutrition, inflammation, increased phagocytic activity, increased oxidase activity, and a decrease in oxidative defense mechanisms.¹⁵

Oxidants produced by oxidative stress are a highly reactive component and has a very short half-life. Thus, the measurement is very

difficult. Oxidant is capable to oxidize wide variety components such as lipids, proteins, carbohydrates, and nucleic acids. Therefore, the oxidation product has a longer half-life, ranging from hours to weeks, so the product can be used as a marker of oxidative stress.⁸

There are many biological markers in patients with CKD, but the oxidation product of LDL (ox-LDL), advanced glycosylation end products (AGEs), and oxidized thiol components have contributed to the pathogenesis of cardiovascular disease and inflammation in CKD patients with uremic state. A study found that the levels of thiobarbituric acid-reactive substance (TBARS), which is a result of lipid oxidation, will increase in patients with CKD and is associated with the occurrence of endothelial dysfunction.²⁰ Whereas, the advanced oxidation protein products (AOPPs), which is a result of oxidation of the protein, will also increase in the uremic state, and the levels progressively rise in accordance with the decline in renal function.^{1,5} Oxidants also interact with nucleic acids of a cell, leading to the inactivation of mitochondrial enzymes, and it will directly cause DNA damage, DNA repair enzymes and transcription factors, subsequently resulting in the death of these cells.¹⁹ Nucleic acid oxidation

product, known 8-hydroxy-2'-deoxyguanosine (8-OHdG) was found increase in patients with CKD. Therefore, AOPPs and 8-OHdG are also often used as markers of oxidative stress in patients with CKD.⁸

CKD patients are in a state of chronic inflammation and will activate inflammatory cells such as polymorphonuclear (PMNs) and monocytes.²¹ These inflammatory cells will increase the secretion of NADPH oxidase and MPO that will also enhance the formation of ROS oxidants.^{7,8} Leukocytes of CKD patients with uremia are known to be superoxide radical ($\bullet\text{O}_2^-$) production source.¹⁵ Indoxyl sulphate (IS) is a form of the urea toxin that normally excreted through the kidneys. In patients with CKD, these organic anions will accumulate in the blood, aggravate inflammatory conditions and impair vascular endothelial function, thus worsening the progression of CKD.¹⁸

Superoxide radical ($\bullet\text{O}_2^-$) inactivates NO, a paracrine which has an important role in the regulation of vascular tone. Physiologically, NO inhibits adhesion between leukocytes and vascular endothelial cells, proliferation of vascular smooth muscle cells (vascular smooth muscle cell/VSMC), and platelet aggregation. Thus, ensuring the surface of the blood vessels healthy and intact. If there is a decrease in NO level by any cause, there will be a decrease in the ability of blood vessels dilatation that contribute to hypertension.^{17,19}

Nitric oxide is formed from semi-essential amino acid L-arginine with the aid of nitric oxide synthase (NOS) and tetrahydrobiopterin (BH4) as a cofactor. L-arginine is formed from citrulline, a result of amino acid metabolism in the digestive tract wall. Conversion of L-citrulline to L-arginine occurs in the kidney, so the amount of arginine in patients with CKD will reduce. Because of the lack of raw materials, the production of NO also reduced. In addition to inactivate NO, superoxide ($\bullet\text{O}_2^-$) is also capable to react with NO itself. Their reaction produces a very strong oxidant, peroxynitrite (ONOO-). Peroxynitrite (ONOO-) is a nitrosating agent that has an ability to oxidize NOS and make it unstable. This unstable NOS will further augment superoxide ($\bullet\text{O}_2^-$) production. Superoxide ($\bullet\text{O}_2^-$)

Table 2. Markers of oxidative stress and antioxidant⁸

Markers of oxidative stress	Antioxidants
Lipid peroxidation	Enzymatic
- Acrolein	Superoxide dismutase
- Malonyldialdehyde	Catalase
- 4-Hydroxynonenal	Glutathione peroxidase
- Thiobarbituric acid-reactive substance	Non enzymatic
- F2 isoprostanes	Glutathione
- Advance lipid oxidation products	Vitamin E
- Oxidized LDL antibodies	Vitamin C
Protein oxidation	Ferritin
- Advanced oxidation protein products	Transferrin
Carbohydrate oxidation	Albumin
- Advanced glycosylation end-products	etc.
Nucleic acid oxidation	
- 8-Hydroxy-2'-deoxyguanosine	

is also able to oxidize tetrahydrobiopterine (BH4), causing NOS uncoupling, resulting in excess production of ROS.^{17,19}

NOS activity inhibited by a NOS inhibitor. One of the examples is the asymmetric dimethylarginine (ADMA).²² ADMA works as a competitive inhibitor of endogenous NOS and inhibits NO formation that contributes to hypertension through vasoconstriction and inhibition of sodium excretion in the kidney. ADMA metabolic enzyme due to the increase in oxidative stress associated with angiotensin II. ADMA accumulation in CKD patients occurs via four mechanisms, increasing in methylation of proteins, increased protein turnover, decreased metabolic function of dimethylargininedimethylaminohydrolase (DDAH) as the impairment of renal excretory function.⁹ Patients with CKD will also have homocysteine accumulation (hyperhomocysteinemia/hHcy) due to interference of protein metabolism. This situation will increase ROS, increase ADMA,³⁵ and lowering NO. Thus, hHcy also becomes a risk factor for cardiovascular events in CKD that will worsen its progressiveness.²³

An increase oxidative stress that plays a role in endothelial dysfunction also occurs through the accumulation of ADMA and reduction in NO bioavailability. Changes in vascular permeability will lead to the entry of LDL cholesterol into intimal layer. In patients with CKD whom in a state of uremia, oxidized LDL is easier happened than in normal person. Oxidized LDL (Ox-LDL) is a highly atherogenic molecule that initiates an inflammatory process in blood vessels. This process leads to the expression of leukocyte adhesion molecules and bound to inflammatory cells in the circulation. Then, these cells will migrate to the sub-endothelial cavity. Ox-LDL is going to be digested by monocytes which then turned into foam cells and form the fatty streak, the earliest structural changes that occur in atherosclerosis process. Along with its development, smooth muscle cells also migrate from the media to the intima layer, proliferate and produce extracellular matrix such as collagen, and form a fibrous cap. The ongoing inflammatory process cause

the cap's walls become thin and rupture easily. When the plaque ruptures, there will be thrombus formation, resulting acute myocardial infarction and stroke.^{7,15} A study by Alegeff et al., describes the process of atherosclerosis that occurs in patients with CKD proved by the presence of carotid artery thickening associated with increased ADMA levels in plasma.²⁴ This explains that oxidative stress worsen CKD progression through atherosclerosis process.^{7,15}

Renin-angiotensin system plays an important role in regulating blood pressure. This system also has a role in the pathogenesis of inflammation and progression of CKD. T cells, natural killer cells, and monocytes are formed when many inflammatory processes have ability to express angiotensin II and AT1 receptor. Angiotensin II, through AT1 receptor, can stimulate oxidative stress through oxidative burst, has the ability to stimulate the activity of phagocytes and chemotaxis. So, in addition to the influence of inflammation on its formation, angiotensin II also causes inflammation and aggravates the process itself.²¹ In addition to work against NO, oxidants will also activate angiotensin II and aggravate vasoconstriction. Hypertension initially occurs in renal vasculature but then it will occur systemically. Angiotensin II can cause apoptosis of mesangial cells, damaging podocyte cells and tubulointerstitial cells, macrophage accumulation in the interstitial myofibroblast, and collagen deposition. It will eventually damage the whole kidney with the evidence of proteinuria.¹⁴

Proteinuria is a sign of glomerular damage and is associated with cardiovascular events and CKD progression.¹ While proteinuria occurs, pro-inflammatory cytokines will be secreted. This will increase the production of ROS, aggravate fibrosis, and in the end worsening renal damage. Oxidative stress has a role in the occurrence of proteinuria by ADMA activity, leading to endothelial dysfunction, to the occurrence of cardiovascular disease, and ultimately contributes to the progression of CKD. Although the mechanism is not clearly known but one study explained that the decrease in ADMA levels in the blood is associated with a decrease in the degree of proteinuria.^{6,9}

Diabetes mellitus, in addition to be one of the traditional risk factors of cardiovascular disease emergence, apparently has correlation with oxidative stress in patients with CKD. The state of hyperglycemia would increase oxidative stress. Mitochondrial dysfunction, angiotensin II and the formation of AGEs as a product of oxidation of carbohydrates will increase the hyperglycemic state. AGEs increased the activity of NADPH oxidase and also increase oxidants formation. This causes deterioration of renal function through the glomerulosclerosis due to decreased podocyte cells, mesangial cells and transcription pathway activation. AGEs also cause endothelial dysfunction, stimulate monocyte influx and proliferation of cells that play a role in the atherosclerotic process. This can explain why hyperglycemic state may exacerbate CKD progression, either directly or indirectly, through vascular complications.^{2,8}

In a state of oxidative stress the oxidation of blood cell lipid membranes may occur. This is proved by the increase in malondialdehyde (MDA) as a marker of lipid oxidation on erythrocyte surface of patients with CKD. Changes in the structure and function of erythrocytes will cause a decrease in erythrocyte membrane elasticity so it will shorten the lifespan of erythrocytes and increase the hemolysis probability. This might explain the cause of anemia in patients with CKD in addition to the reduction of its formation.^{5,25}

CKD patients with regular HD also have increasing oxidative stress. Patients with HD may have cardiovascular events 3-50 times higher than those without undergoing HD.¹⁰ Oxidative stress that occurs in HD is caused by the interaction between blood and dialysate membrane (bioincompatibility), bacterial products (endotoxins) in the dialysate which is able to cross the dialysis membrane and directly or indirectly stimulates the release of reactive species by neutrophils, loss of antioxidants during HD, and malnutrition related to poor intake of vitamins due to restrictions on fruits and vegetables to avoid hyperkalemia.^{8,11,15}

ANTIOXIDANT SUPPLEMENT AND OXIDATIVE STRESS MANAGEMENT IN CKD

Antioxidants are now widely used as a therapy to reduce oxidative stress. There are two types of antioxidants, the endogenous and exogenous antioxidants.¹⁷ Exogenous antioxidants that obtained from outside the body are including vitamin C and vitamin E, N-acetylcystein (NAC), bardoxolone methyl, and ACEI/ARB.^{11,18}

Vitamin E is a lipid-soluble antioxidant to regulate superoxide ($\bullet\text{O}_2^-$) and hydrogen peroxide (H_2O_2) formation.¹⁷ Although vitamin E is reported to decrease oxidative stress, there are some contrasting result studies. The Secondary Prevention with Antioxidants of Cardiovascular Disease in End Stage Renal Disease (SPACE) reported an association between a high intake of vitamin E with lower incidence of cardiovascular disease in CKD patients undergoing HD. However, Heart Outcomes Prevention Evaluation (HOPE), shows that vitamin E does not have the benefits of prevention and even increases the risk of cardiovascular disease.^{26,27} Vitamin C also has controversial results in its use as an antioxidant as vitamin C is metabolized into oxalate. Oxalate is insoluble. If it is in high amounts in the plasma, it will cause precipitation in soft tissues including kidney, so it will aggravate kidney damage, especially in patients with renal failure who have not been undergoing HD. Vitamin C supplementation is allowed no more than 60 mg/day, while the studied dose considered successful in reducing oxidative stress is 250-1000 mg/day.^{11,26}

N-acetylcystein is an antioxidant often used as a mucolytic, acetaminophen poisoning antidote, and to avoid contrast induced nephropathy (CIN). N-acetylcystein will increase glutathione, an endogenous antioxidant with a help from cysteine.¹¹ Several studies in experimental animals showed that NAC improve NO availability, reduce ADMA through increased DDAH activity, improves endothelial function, lowering albuminuria, so it can be used to prevent the risk of cardiovascular

disease. Research by Thaha et al., revealed that per-oral administration of NAC at a dose of 2x600 mg in 3 months showed oxidative stress restoration through ADMA levels reduction and albuminuria in patients with non diabetic CKD stage I-IV.²⁸ Another research by Thaha et al., explained intravenous administration of 5 g NAC decrease MDA level in CKD patients undergoing HD²⁵ and with the same dose will reduce Hcy levels in patients with CKD associated with improvements in pulse pressure, which is expected to reduce the risk of cardiovascular events in CKD.²³ Bardoxolone methyl has anti-inflammatory effects that inhibit the production of oxidants and maintain kidney function and structure. Bardoxolone methyl at a dose of 25, 75, or 150 mg once a day is said to be able to increase GFR in patients with CKD.¹⁸

ACE-I/ARB has an antioxidant effect by inhibiting angiotensin II action. Angiotensin II has the effect to increase NADPH oxidase and damage cell DNA that causes increased oxidative stress.¹⁸ In addition to lowering blood pressure, this drug will also lead to the formation of NADPH oxidase barriers, inhibiting lipid oxidation, inhibits DNA damage and reduces the occurrence of proteinuria, so it will reduce oxidative stress in patients with CKD.^{14,18}

Oxidative stress in HD can be reduced by using interventions, reducing the activity of inflammatory cells and removing inflammatory mediators. Reduction of inflammatory cell activity achieved by using biocompatible synthetic dialysis membranes (e.g., polysulfone) and using ultrapure dialysate. Inflammatory mediators can be removed by haemolipodialysis, using vitamin E coated dialysis membrane and the use of electrolyzed reduced water.²⁹ Some studies investigate the use of HD-vitamin E coated dialysis membranes. Vitamin E coating on cellulose membranes can reduce oxidative stress and prevent damage of endothelial function due to HD. However, the use of vitamin E-coated membranes showed similar results to the level of a marker of oxidant when compared with synthetic membrane types. Therefore, it is not fully clear whether vitamin E coated membranes

are more superior in reducing oxidative stress than synthetic membranes.¹⁵ In the end, it is still debatable when the right time to start a regular HD and whether HD implementation is able to repair or even aggravate oxidative stress that occurs in patients with terminal renal failure.⁸

CONCLUSION

The incidence of CKD is still high. This disease will progressively lead to end-stage renal disease. Many factors affect the speed of progression of CKD. One of them is oxidative stress. Oxidative stress occurs when there is an imbalance between oxidant formation and insufficient amount of antioxidants as a defense mechanism of the body. Oxidative stress causes cardiovascular disease easily occurs in patients with CKD through the mechanism of inflammation and endothelial dysfunction. In addition to directly damage the kidney, oxidative stress will be also associated with the excessive production of angiotensin II, hyperglycemia and proteinuria that may cause a worsening of CKD progression. Oxidants are capable to oxidize a wide variety of cell components such as carbohydrates, proteins, lipids, and nucleic acids, which in turn will further damage the kidneys. In patients with CKD, excess oxidant is not offset by sufficient antioxidants. At first, HD is proven to reduce oxidative stress as marked by a decrease in markers of oxidative stress. However, in the end HD itself will only lead to repeated oxidative stress through the bioincompatibility between dialysate membrane and blood, endotoxin in the dialysate, and the loss of antioxidant components during HD. Although still debated, the current administration of antioxidants is considered as one of the new therapeutic interventions in reducing oxidative stress. Antioxidants work through several mechanisms, such as damaging oxidants and inhibiting its formation either directly or indirectly, increase the activity of DDAH, thereby reducing ADMA and increase NO bioavailability NO, and inhibit the activity of the enzyme oxidase. All of these are expected to reduce oxidative stress and slower the progression of CKD.

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