REVIEW PAPER

Cardiovascular Disease and Chronic Inflammation in End Stage Kidney Disease

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Abstract

Background: Chronic Kidney Disease (CKD) is one of the most severe diseases worldwide. In patients affected by CKD, a progressive destruction of the nephrons is observed not only in structural but also in functional level. Atherosclerosis is a progressive disease of large and medium-sized arteries. It is characterized by the deposition of lipids and fibrous elements and is a common complication of the uremic syndrome because of the coexistence of a wide range of risk factors. High blood pressure, anaemia, insulin resistance, inflammation, high oxidative stress are some of the most common factors that cause cardiovascular disease and atherogenesis in patients suffering from End Stage Kidney Disease **(**ESRD). At the same time, the inflammatory process constitutes a common element in the apparition and development of CKD. A wide range of possible causes can justify the development of inflammation under uremic conditions. Such causes are oxidative stress, oxidation, coexistent pathological conditions as well as factors that are due to renal clearance techniques.
Patients in ESRD and coronary disease usually show increased acute phase products. Pre-inflammatory cytokines, such as IL-6 and TNF-a, and acute phase reactants, such as CRP and fibrinogen, are closely related. The treatment of chronic inflammation in CKD is of high importance for the development of the disease as well as for the treatment of cardiovascular morbidity.
Conclusions: The treatment factors focus on the use of renin-angiotensic system inhibitors, acetylsalicylic acid, statins and anti-oxidant treatment in order to prevent the action of inflammatory cytokines that have the ability to activate the mechanisms of inflammation.

Key words: Chronic Kidney Disease, uremic syndrome, inflammation, cytokines, hemodialysis

Introduction

CKD is one of the most severe public health disorders worldwide with complications such as renal failure, cardiovascular disorders and early death (Harrison 2005; Levey et al. 2005, Theofilou 2011a, 2011b). CKD is a chronic situation including irreversible, structural or functional nephron abnormalities. CKD pathophysiology is related to the progress of the disease. As CDK causes chronic damage, the renal function as a whole diminishes progressively and irreversibly. As a result, at end stage, a limited number of increased-charge nephrons accomplish the processes of renal function. The pathogenicity of CKD results from the combinations of the detrimental effects that include water and electrolytes homeostasis disorders, reduced removal of soluble organic substances and reduced hormone production. The Glomerural Filtration Rate (GFR) is the amount of water filtered by the glomerulus in the capillary tuft in a particular period and is an index that controls kidney function (Vander et al. 2001; Kalantar-Zadeh et al. 2006; Pragna et al. 2008). GFR reduction <60 ml/min/1,73 m^2 of the body surface for ≥3 months determines CKD (National Kidney Foundation 2002; Levey et al. 2005). The rating of CKD (Table A) in an

ascending scale according to its severity depends on GFR values (Levey et al. 2005).
The loss of endogenous renal function leads to a uremic syndrome and in the long run the patient might be in need of renal function substitution (Harrison 2005; Kalantar-Zadeh et al 2006; Pragna et al. 2008). There are two types of disorders depending on the pathophysiologic mechanism of the syndrome: Disorders as a consequence of the accumulation of protein metabolism products and disorders as a consequence of renal failure, such as homeostasis of water and electrolytes as well as hormonic disorders.
The uremic syndrome (TABLE B) can be treated to a certain extent with renal function extracorporeal substitution. However, some of the disorders may not respond to the treatment, they may even deteriorate (Harisson 2005).

Table A. Classification of chronic kidney diseases in order of increasing severity

Stage	Description of chronic kidney disease	GFR(ml/min/1.73 m^2)	Associated terminology
1	*Kidney damage with normal or high glomerular filtration rate*	*≥90*	*Albuminuria, proteinuria, hematuria*
2	*Kidney damage with mildly low glomerular filtration rate*	*60-89*	*Albuminuria, proteinuria, hematuria*
3	*Moderate glomerular filtration rate decrease*	*30-59*	*Chronic/early renal insufficiency*
4	*Severe glomerular filtration rate decrease*	*15-29*	*Chronic/ late renal insufficiency*
5	*Kidney failure*	*<15*	*End-stage renal disease, uremia*

CKD is associated with two risk factors with a bidirectional relation leading to increased morbidity and mortality in patients with end-stage renal disease (ESRD). Those are: cardiovascular disease (CVD) and the inflammation pathogenic mechanisms. Apart from the improved modern renal dialysis techniques, morbidity and mortality indexes for ESRD patients remain quite high. Cardiovascular disease (CVD) is one of the main reasons of this effect with its presence being further enhanced by coexisting situations. The inflammation is another factor that is responsible not only for CKD evolution but also for the appearance of CVD. The inflammation mechanism enhances CVD pathogenicity together with other clinical findings of the uremic syndrome.

Epidemiology

Cardiovascular diseases are main morbidity and death causes in CKD patients, and especially to ESRD ones, with an annual frequency of 9%. Death caused by CVD is by 10-20 times more frequent in patients with CKD than in the rest of the population. In CKD patients, the risk of death after CVD is much higher than the risk of death after a hemodialysis.
This shows that CKD patients differ from other patients when it comes to cardiovascular vulnerability, as C-Reactant Protein (CRP) inflammation index is increased. It is estimated that 30-50% of those patients show activated inflammatory response. The increased (>8-10 mg/L) levels of CRP serum result in atherosclerosis (Locatelli et al. 2003; Nalbandi 2008; Stefanadis 2008).

Atherosclerosis Pathogenicity

Atherosclerosis is a disease of big and middle muscle arteries where atheromatous plaques are formed as a result of the complex accumulation of cells and extracellular substances in the endothelium and the tunica intima of the vessels. Even though the inflammation is a non-traditional risk factor for atherosclerosis, it has proved to play an important role in the appearance and the progress of the atheromatous process. There

are many different theories on atherosclerosis pathophysiology. The dominant one is endothelial function disorder resulting from the existence of risk factors such as dyslipidemia, diabetes, smoking, high blood pressure (HBP) and hyperhomocysteinemia bacterial and viral infections (mainly Chlamydia pneumonia, Helicobacter pylori and cytomegalovirus) (Fertakis 1988; Bocker et al. 2007; Papasteriadi 2008).

The inflammation is the common denominator in a series of cardiovascular risk factors such as hyperlipidemia, HBP etc. In case the inflammatory process is not successfully treated, the atheromatous lesions may evolve silently to obstructive lesion and may lead to rupture of the atheromatous plaque and acute clinical syndromes (Caimi et al. 2005; Bocker et al. 2007; Papasteriadi 2008).

Inflammation And CKD

Inflammation is the initial response of the body to harmful stimuli such as infection, injury or toxic damage. It is a protective physiological response that destroys pathogenic factors that have caused the damage, as well as damaged tissues. It is a mechanism of exceptional importance and constitutes an integral part of our defense system. Under normal conditions the inflammation is acute (Pragna et al. 2008; Roit et al. 2004).

A cascade of biochemical events propagates and matures the inflammatory response. Prolonged inflammation, known as chronic inflammation may bear destructive consequences for the organism. The inflammation index are closely associated with anorexia, increased reduction of the protein rate by skeletal muscles and other tissues, loss of adipose and muscle tissues, hypoalbuminemia and hypercatabolism, endothelial dysfunction and atherosclerosis. As a result, inflammatory process is a common element in CKD. About 30-60% of individuals undergoing extrarenal dialysis in Europe and North America show an increased inflammation index (Kalantar-Zadeh et al. 2006; Axelsson et al. 2007; Pragna et al. 2008).

The inflammation is an important parameter for CKD appearance and evolution. Research has shown that patients undergoing renal dialysis techniques and protein energy malnutrition tend to show increased levels of inflammatory index and pro-inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6) and TNF.

Those indexes are proportional to the anorexia levels in such patients (Vander et al. 2001). Other CKD factors contributing to the inflammation are high levels of acute-phase CRP, advanced enzymic glycation end products (AGEs) and advanced oxidation protein products (AOPPs) (Kalantar-Zadeh et al. 2006; Axelsson et al. 2007; Pragna et al. 2008), (14), (13).

A wide range of possible causes can justify the development of inflammation under uremic conditions such as oxidative stress, oxidation, coexisting pathological situations and factors due to the renal dialysis techniques (**TABLE C**), (Kalantar-Zadeh et al. 2006).

Cytokine Role

Cytokines play an integral part in the inflammation process. During the inflammation, there is an imbalance between pro-inflammatory and anti-inflammatory cytokines. Uremic toxins in CKD activate pro-inflammatory cytokines independently of whether the patient is at a stage before renal dialysis or already undergoing a treatment technique (hemodialysis or peritoneal dialysis). The disturbance of this balance contributes to atherogenesis thus promoting the development of CVD. Diminished renal function increases cytokine concentration in the organism even in cases of membrane bioincompatibility in dialysis techniques. At the same time, oxidative stress, oxidation and coexisting pathological situations promote inflammatory action (Stenvinkel et al. 2002; Jacobs et al. 2004; Kalantar-Zadeh et al. 2006). However, there is no specific way to control the severity rate of the inflammation in CKD patients. During an inflammatory response there is an increase in positive acute-phase proteins, such as CRP and ferritin, and a reduction in negative acute-phase proteins, such as albumin or transferring (Kalantar-Zadeh et al. 2006; Axelsson et al. 2007; Pragna et al. 2008).

CRP is a positive acute-phase protein that increases during systemic inflammation. Its

composition takes place in the liver and its levels show the levels of tissue damage or the extent of the inflammatory response. Normally its value is about <1mg/L. Increased CRP quantities imply that an inflammatory response is taking place. High CRP levels in healthy patients have been identified as an important risk factor for CVD, coronary disease and specific bacterial or viral infections. At ESRD, CRP levels remain >5mg/l for >3 months. In case of chronic inflammation, it remains at high levels for years thus signaling an increased risk for atheromatous cardiovascular disease. In CKD and residual renal functions (RRF) patients, CRP is between 5-50 mg/L. CRP has been isolated from the inflammatory damage of atheromatic vessels and a slight increase constitutes important risk and disease index (14 MIA). CRP levels also show an increased production of pro-inflammatory cytokines IL-1, IL-6 and TNF-a making them a very important index in CKD (Jacobs et al. 2004).

Interleukin-6 (IL-6) is a pleiotropic cytokine with a dominant role.

It regulates the inflammatory responses and the composition of hepatic acute-phase proteins. In healthy patients, IL-6 mRNA is expressed at low levels by various cell types including peripheral lymphocytes, spleen, liver, kidney, and intestine. During an infection, injury or immune challenge, almost every tissue and cell type of the organism composes and expresses IL-6.

Moreover, IL-6 launches an increased production of hepatic acute-phase proteins that regulating the composition of CRP. This differentiates it from IL-1 and TNF-a cytokines that reduce production of such proteins by hepatocytes (Pragna et al. 2004; Kalantar-Zadeh et al. 2008). Moreover, insulin stimulates IL-6 gene expression.

Interleukin 1 is a multifunctional cytokine. There are two types of interleukin: lL-1a and IL-1b with unclear effects in biological activity. Interleukin is involved in the regulation of cell division and cell differentiation and is a highly inflammatory cytokine (Stenvinkel et al. 2000; Pragna et al. 2008).

TNF-a is produced by active monocyte macrophages and is of great importance in inflammation pathogenesis, septic shock and tissue injury. TNF-a comes from the liver. Intrinsic and extrinsic factors such as bacteria, viruses, parasites and tumors are able to cause its production (Vander 2001).

It contributes to the progress of endothelial dysfunction and increases insulin reaction. At the same time, it also reduces apolipoprotein E secretion. (Mavromatidis 2008).

Together with the other pro-inflammatory cytokines, TNF-a promotes protein catabolism and inhibit albumin, pro-albumin and transferrin composition.

Studies have shown that pro-inflammatory cytokines have atherogenic properties. Firstly, IL-6 increased levels are a stimulus for soluble intracellular adhesion molecule 1 (sICAM-1) that acts as a mediator in leukocyte adhesion and leukocyte migration on the endothelial surface.

Moreover, IL-6 promotes atherosclerosis through various metabolic, endothelial and coagulant mechanisms. It is not just an atheromatous index. It has been proved that increased IL-6 expression is involved in the formation of the fibrous plaques in the atheromatous process (Zyga et al. 2011).

Insulin Resistance

Insulin resistance is an ESRD parameter and it has been proved that hypoglycaemia and hyperglycaemia contribute to early atherogenesis in ESRD patients. In ESRD, insulin resistance may result from various factors such as reduced renal catabolism of regulatory proteins, metabolic oxidation, uremic toxins, protein catabolism products, reduced physical activity, anemia, chronic inflammation, hypothrepsia. Insulin resistance syndrome is an independent factor for cardiovascular mortality prevision in ESRD.

Pro-inflammatory and pro-atherogenic cytokines like IL-6 and TNF-a factor, accumulate as residual renal function deteriorates.

TNF-a action reduces glucose storing in cells after insulin action, while inactivity enhances insulin sensitivity. The inflammation is associated with various insulin resistance factors.

In elderly non-diabetic patients, mild chronic inflammation and high sICAM-1 levels have been found, as well as a disproportional

relation between insulin sensitivity and IL-6 levels. Consequently, low level chronic inflammation contributes to the relation between insulin resistance and CVD risk (Mavromatidis 2008; Kalantar-Zadeh et al. 2008).

TABLE B. FINDINGS OF CLINICAL PATHOLOGY OURAIMIAS		
Fluid and electrolyte disorders	**Neuromuscular disorders**	**Skin disorders**
Increase (dilation) and volume contraction	*Fatigue*	*Paleness*
Hypernatremia and hyponatremia	*Sleep disorders*	*Hyperpigmentation*
Hyperkalemia and hypokalemia	*Headache*	*Itching*
Metabolic acidosis	*Mental deficiency*	*Ecchymosis*
Hyperfosfatiaimia	*Lethargy*	*Uremic salt deposition in the skin on the form of ice (uremic frost)*
Hypocalcemia	*Astirixia*	**Gastrointestinal disorders**
Endocrine - Metabolic disorders	*Muscle irritability*	*Anorexia*
Secondary hyperparathyroidism	*Peripheral neuropathy*	*Nausea and vomiting*
Adynamic osteomalacia	*Syndrome of "restless legs"*	*Uremic exhalation*
Osteomalacia due to deficiency of vitamin-D	*Paralysis*	*Gastroenteritis*
Intolerance to carbohydrates	*Myoclonus*	*Peptic ulcer*
Hyperuricemia	*Seizures*	*Gastrointestinal bleeding*
Hypertriglykeridaimia	*Coma*	*Hepatitis*
Elevated levels of lp(a)	*Muscle cramps*	*Idiopathic ascites*
Decreased levels of high density lipoprotein	*Syndrome breaking the balance in dialysis*	*Peritonitis*
Nutritional disorder caused by inadequate intake of protein-energy	*Myopathy*	**Haematological and immunological disorders**
Slowdown in growth and development	**Cardiovascular and pulmonary disorders**	*Anemia* *Leucopenia*
Amenorrhea	*Arterial hypertension*	*Lemfokyttaropenia*
Infertility and sexual dysfunction	*Congestive heart failure and pulmonary edema*	*Bleeding*
Hypothermia	*Worsening atherosclerosis*	*Increased susceptibility in infections*
B2-microglobulin deposition	*Hypotension and arrhythmias*	*Splenomegaly and hypersplenism*
Amyloidosis	*Calcification of vascular*	*Decreased levels of C*

TABLE C. Causes of chronic inflammation in Chronic Kidney Disease
A. Causes of inflammation due to CKD or decreased GFR
1. Decreased clearance of pro- inflammatory cytokines
2. Volume overload with or without endotoxemia
3. Accumulation of uremic toxins
4. Oxidative stress (e.g. oxygen radicals)
5. Carbonyl stress(pentoside and advanced glycation products)
6. Decreased levels of antioxidants (vitamin E, vitamin C, carotenoids, selenium, glutathione)
7. Deteriorating protein- energy nutritional state and food intake
B. Coexistence of cormobid conditions
1. Increased prevalence of cormobid conditions (cardiovascular disease, diabetes, advanced age, obesity, dyslipidemia, etc.)
2. Remnants from previous allograft transplantation of solid organa
3. Inflammatory diseases with kidney involvement (with HIV disease or SLE), chronic obstructive urinary ouropatheia
C. Additional inflammatory factors related to dialysis treatment
I. Hemodialysis
1. Exposure to dialysis tubing
2. Dialysis membranes with decreased biocompability
3. Impurities in dialysis water and/ or dialysate
4. Back-filtration or back- diffusion of contaminants
5. Foreign bodies (such as PTTE) in dialysis access grafts
6. Intravenous catheters
II. Peritoneal dialysis
1. Episodes of overt or latent peritonitis
2. PD-catheters as a foreign body and its related infections
3. Constant exposure to PD solution

Treatment In CKD Statines

Statines show important anti-inflammatory action and reduce CRP levels independently from their impact of inhibiting lipid composition. They are also connected with reduced mortality levels in CKD patients that are due to heart diseases (Vander 2001).

Angiotensin-converting enzyme inhibitors (ACE inhibitors)

They have anti-inflammatory action in the general population and in patients suffering from ESRD and they are connected with a delay in the progress of CKD, thus improving the clinical result in individuals suffering from the disease.

ACE inhibitors have the ability to suppress the production of certain cytokines, such as TNF-a or IL-1b, whereas in ESRD patients they reduce CRP levels (Vander 2001; Francesco et al. 2003; Nalmbandi 2008).

Acetylsalicylic acid

Acetylsalicylic acid reduces CRP and IL-6 levels in patients with coronary disease. Moreover, CRP levels seem to be closely connected to myocardiac infarction risk reduction with the use of aspirin. Consequently, it could be used for the treatment of the chronic inflammation of CKD patients.

Antioxidant treatment

Vitamin E has anti-inflammatory action and its administration is connected with a low risk of cardiovascular mortality in patients at a dialysis. It has been claimed that vitamin E has a protective role against the inflammatory process and atherosclerosis as it inhibits the action of protein kinase C and nuclear factor kappa-b. Other studies have shown that when the dialysis filters contain vitamin E, oxidative stress is reduced, whereas its use through dialysis membranes reduces myeloperoxidase release, suggesting a lower neutrophil activation. However, further research has to be conducted on the exact action and its relativity/connection to the inflammation and its parameters, as well as on atherosclerosis and its contribution to the clinical result (Vander 2001; Mavromatidis 2008).

Moreover, the use of biocompatible membrane and ultrapure hemodialysis can reduce hemodialysis-connected inflammation and the improvement of the dialysis techniques in hemodialysed patients with inflammation is very important. Similarly, new and more biocompatible solvents of peritoneal dialysis should be applied in patients that show elements of inflammation (Kalantar-Zadeh et al. 2006; Mavromatidis 2008).

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