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2. INFLAMMATION, CYTOKINES AND CHEMOKINES IN CHRONIC KIDNEY DISEASE

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2.1 The burden of CKD: improving global outcomes

2.1.1 CKD is common

The World Kidney Day was proposed by the International Society of Nephrology (ISN) and International Federation of Kidney Foundations (IFKF) for reminding the public, government, and medical and healthcare professionals that kidney disease is common, harmful, and treatable besides being very costly and preventable (1). It has been celebrated on every second Thursday of March from 2006 by an increasing number of countries, including Hong Kong that was among the 66 and 88 participants in the last two years.

This continuous alert is well justified because chronic non-communicable degenerative diseases are now the leading cause of death at least in industrialized countries, accounting for 35 of the 58 million deaths worldwide in 2005 from a WHO survey (2). Besides the four top killers of cardiovascular disease (CVD), cancer, chronic respiratory disease and type 2 diabetes, chronic kidney disease (CKD) is increasingly a global health problem. Currently in the US, 13% (26 million) of non-institutionalized adults are estimated to have CKD (3). About 1.0 million patients are being treated for end-stage renal disease (ESRD) with 0.5 million surviving on renal replacement therapy (RRT), while a worrying higher proportion (15 million) are at earlier stages of CKD that may escape timely diagnosis and intervention. Prevalence rates are similar in Europe, Australia and Asia including Hong Kong, where RRT prevalence and incidence in 2007 were respectively 1026 and 164 per million population (pmp) according to the Hong Kong Renal Registry.

2.1.2 KDOGI and KDIGO definition and classification of CKD

CKD is a heterogeneous condition, whose clinical manifestations, progression and management depend on its cause, pathology and other comorbid conditions. Prevailing causes of CKD in Hong Kong were diabetes (23%), glomerulonephritis (GN, 34%) and hypertension (7%) for existing RRT patients surveyed in 2007, with (i) IgA nephropathy being the most common biopsy-proven GN (45%) and (ii) diabetic nephropathy rising to 40% among newly admitted RRT patients in 2006-2007 (Hong Kong Renal Registry), reflecting escalation of diabetes in our community. In 2002,

the Kidney Disease Outcomes Quality Initiative (KDOQI) of the US National Kidney Foundation proposed a simple definition and classification of CKD based on severity that was modified by the Kidney Disease: Improving Global Outcomes (KDIGO) organization in 2004 (4). With such paradigm shift from cause to severity, glomerular filtration rate (GFR) became a central parameter for diagnosis and staging that is comprehensible to nephrology and non-nephrology communities for international development and implementation of clinical practice guidelines. CKD is defined as GFR lower than 60 ml/min/1.73 m^2 or kidney damage for at least 3 months, and staging according to GFR reduction is supplemented by additional classification based on treatment by dialysis (D) or transplantation (T), for examples, stages 3T and 5D (Table 2.1.).

Table 2.1. *Definition and classification of CKD proposed by KDOGI (2002) and modified by KDIGO (2004) (4)*

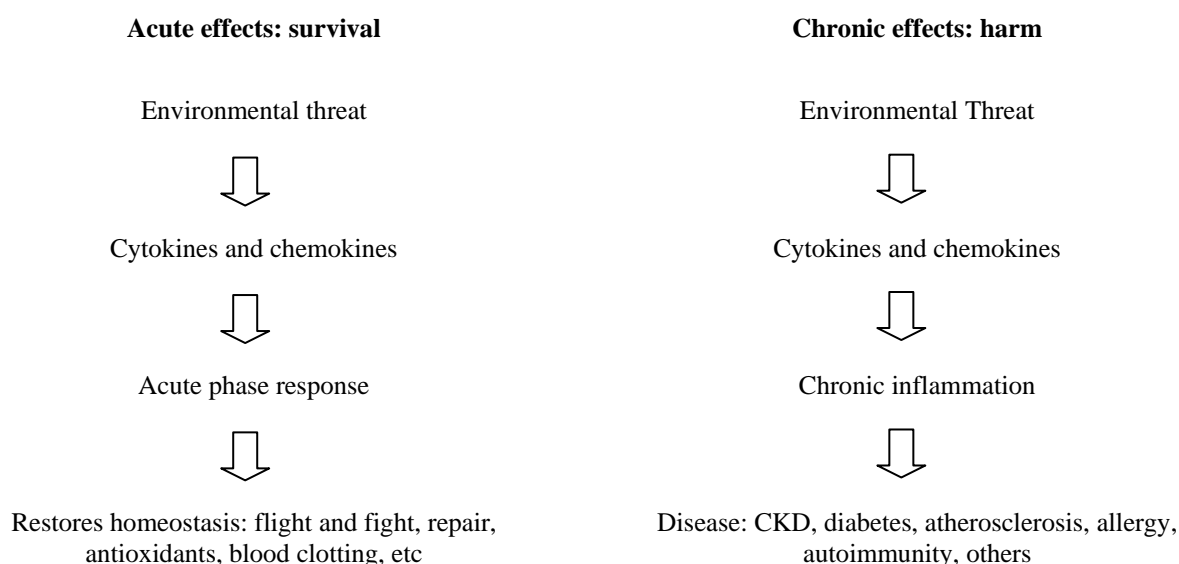| Stage	Description	GFR	Remark
1.	Kidney damage with normal or ↑ GFR	≥ 90	
2.	Kidney damage with mild ↓ GFR	≥ 60 – 89	T if kidney transplant recipient, e.g. 3T
3.	Moderate ↓ GFR	≥ 30 – 59	D if dialysis (HD or PD), e.g. 5D
4.	Severe ↓ GFR	≥ 15 – 29	
5.	Kidney failure	< 15 (or dialysis)	

2.2 Inflammation in CKD: causes and possible outcomes

2.2.1 Renal progression and other causes of inflammation

The most serious adverse outcomes of CKD include not only debilitating metabolic complications of decreased GFR progressing to ESRD (hypertension, anemia, malnutrition, bone and mineral disorders, etc), but also increased risk for CVD, which is 100 times higher than that in the general population, accounting for about half of all deaths in North American patients receiving RRT, although the proportion has been slightly lower in Hong Kong (30-40%) paralleling death from infection (5).

Among risk factors for atherosclerotic vascular disease and cardiac valvular calcification in CKD, inflammation has been identified as epidemiologically most important. Increased circulating inflammatory proteins, such as plasma C-reactive protein (CRP) and amyloid A (SAA), are powerful predictors of all-cause mortality and cardiovascular death in ESRD patients (6, 7). Inflammation involves complex interactions among immune cells and soluble proteins (cytokines, chemokines, adhesion and co-stimulatory molecules) occurring in affected tissues in response to infection, trauma, ischemia or autoimmune injury. Like most immune reactions, inflammation is a two-edged sword. It is an evolutionary advantage that usually leads to recovery from infection or healing (8). However, if the targeted defense or assisted repairs are not properly orchestrated, inflammation can cause progressive tissue damage by leukocytes and collagen resulting in CKD, diabetes, atherosclerosis,

allergy and autoimmunity depending on whether the nephron, pancreatic islet, artery, airway or multiple organs are affected (Figure 2.1.). Although various renal injuries may progress at different rates, there are six sequential mechanisms of CKD that may constitute a common pathway building on each other: (i) glomerular hypefiltration, (ii) worsening prorteinuria, (iii) downstream cytokine and chemokine bath, (iv) interstitial nephritogenic inflammation, (v) tublular epithelial-mesenchymal transition (EMT), and (vi) nephron fibrosis and scarring (9). Other contributing causes of inflammation in CKD include loss of residual renal function (10) resulting in impaired clearance and accumulation of pro-inflammatory metabolites and post-synthetically advanced glycation end products (AGE, 11); increased oxidative stress due partly to depletion of antioxidants (Zn, Se, vitamins C and E) consequent to renal failure or dialysis; exposure of blood to bio-incompatible dialysis membranes and endotoxins in dialysate; and infection from vascular access materials in hemodialysis (HD), peritonitis during long-term peritoneal dialysis (PD), or actively infected graft of transplant recipients (12).

Acute effects: survival	**Chronic effects: harm**
Environmental threat	Environmental Threat
⇩	⇩
Cytokines and chemokines	Cytokines and chemokines
⇩	⇩
Acute phase response	Chronic inflammation
⇩	⇩
Restores homeostasis: flight and fight, repair, antioxidants, blood clotting, etc	Disease: CKD, diabetes, atherosclerosis, allergy, autoimmunity, others

Figure 2.1. *Acute and chronic effects of the inflammatory response. (8)*

As summarized in two continuous reviews over 10 years, the above pro-inflammatory and other cytokines are soluble signaling proteins for intercellular communication amongst immune cells as well as cells of other systems (13, 14). They have been named generically either by their origin such as the interleukins, or according to their biological actions, such as colony stimulating or growth factors, and chemokines, which are a large family of leukocyte chemoattractive cytokines with over > 50 members divisible into 4 groups, the CXC, CC, C and CX3C chemokines depending on the configuration of cysteine residues near the N-terminal end of these chemokine proteins with different specific target cells receptors. For example, the two major chemokine families either have an amino acid between the two N-terminal cysteines, or the two cysteines are next to each other, constituting the CXC and CC chemokines. Similar to all other cytokines and most regulatory molecules, chemokines act on leukocytes via seven transmembrane domain G protein-coupled cell surface receptors that are specific for each of the 4 chemokine families (15). This

has led to a logical receptor nomenclature (in 1996) in which each receptor is designated by the name of the chemokine family (like CC) followed by the letter R for receptor, and then a number based on the chronological sequence of discovery. Until recently, chemokines have been named randomly by trivial names such as monocyte chemoattractive protein (MCP) and monokine induced by interferon-γ (MIG). A similar nomenclature was recommended in Year 2000 by the International Union of Immunological Societies and the WHO using the family name (like CXC) followed by an L for ligand preceding the chronological number of discovery (16). Modern laboratory analysis of cytokines and chemokines include the use of immunoassays, molecular biology and proteomic methods such as RT-PCR of mRNA, real-time quantitative PCR of DNA, gene expression and protein expression arrays, and multi-fluorescence flow cytometry for (i) simultaneous assay of a panel of inflammatory cytokines and chemokines and (ii) intracellular staining of T-helper lymphocyte types 1, 2 and 17 signature cytokines (14).

2.2.2 MIAC syndrome

Returning from causes of inflammation in CKD to possible consequences, malnutrition is prevalent in up to 76% ESRD patients, manifesting reduced body weight, depleted energy store (adipose tissue), and loss of somatic protein (muscle mass), with decreased plasma albumin, transferrin, retinol-binding protein, pre-albumin and apolipoprotein (apo) A-I concentrations (17). These anthropometric and serologic derangements generally cannot be reversed by oral nutritional supplementation, and are associated with poor outcomes. The pathophysiolgy of such type 2 malnutrition in renal failure comprises chronic inflammation driven by pro-inflammatory cytokines (IL-1, IL-6, TNF-α, IFN-γ and others) that accelerate muscle protein catabolism, up-regulate hepatic synthesis of positive acute phase proteins (CRP, SAA, and fibrinogen), and suppress production of negative acute phase proteins including albumin, which is also lost additionally from proteinuria or dialysis to reach very low plasma concentrations (< 30 g/L). Such severe hypoalbuminemia cannot be attributed entirely to anorexia in uremia resulting in decreased protein-calorie intake; it is not even attainable by long-term semi-starvation (e.g. 24 weeks of 1500 kcal / 24 h) in normal subjects causing very marked reduction (e.g. 25%) in body weight.

Inflammation plays an even more life-threatening pivotal role in the initiation and progression of atherosclerosis, and is considered a major non-traditional risk factor for accelerated carotid intima-thickening and plague formation in dialysis patients (18). An elevated plasma CRP concentration (> 5 mg/L) is not only associated with greater prevalence of atherosclerotic vascular disease but also more severe cardiac hypertrophy and dilatation (6). Cellular adhesion molecules which are expressed increasingly in inflammation for enhancing leukocyte-endothelial activation have also been associated with carotid atherosclerosis (19). Other inflammatory proteins that are elevated in CKD and become causative of vascular disease include fibrinogen and lipoprotein (a) that are thrombogenic besides atherogenic. During inflammation, hepatic synthesis of apo A-I, the principal structural protein of high-density lipoproteins (HDL), is suppressed. Consequently, apo A-I on HDL is replaced by the positive acute phase protein SSA altering both the structure and function of circulating HDL resulting in these particles being (i) more adherent to the vascular

endothelial surface causing arterial damage and (ii) less protective of LDL oxidation facilitating atherogeneis.

Inflammation is also involved in the calcification process as evidenced by the strong link between inflammatory cytokines / proteins (e.g. IL-6 and CRP) and coronary artery, aortic and valvular calcification in ESRD (7). Decreased plasma concentration of fetuin-A, another negative acute phase protein and inhibitor of calcification, has been associated with valvular calcification and cardiovascular events in PD patients (20). The vicious cycle of malnutrition, inflammation and atherosclerosis instigated by pro-inflammatory cytokines and chemokines was originally given the acronym of MIA syndrome. Our research group has expanded the designation from MIA to MIAC syndrome paying due concern to the clinical and pathological significance of the concurrent calcification (20).

2.2.3   Renal anemia and erythropoietin resistance

Anemia is a major complication of stages 2-5 CKD affecting > 50% ESRD patients before treatment, consequent again to the chronic inflammatory state resulting in accelerated erythrocyte destruction, low hematocrit and blood hemoglobin (Hb) level, decreased serum iron, transferrin and transferrin receptor concentrations, and hyperferrintinemia that cannot be normalized by the now reduced erythropoietin (EPO) production from nonfunctional peritubular kidney cells (21). Anemia affects cognitive function, exercise capacity, cardiac function and other qualities of life, and is associated with increased CVD and all cause mortality in CKD patients as well as the general population (22). Recombinant human erythropoietin (rHuEPO) has been widely used for treatment of renal anemia. However, up to 25% of dialysis patients are relatively resistant to replacement requiring higher doses to reach target Hb concentration (11 g/dL), and 5-10% fail to respond even on high doses of EPO (23). The immunopathology of EPO resistance is that patients with uremia or other chronic inflammatory conditions have enhanced activation of T-helper type 1 (Th1) lymphocytes and monocytes secreting pro-inflammatory cytokines IL-1, IL-6, IL-12, IFN-γ and TNF-α, and chemokines IFN-inducible protein (IP)-10 / CXCL10 and monocyte chemotactic protein (MCP / CCL2) that exert pro-apoptotic activity to suppress erythrocyte stem cell proliferation (24). This antagonizes the anti-apoptotic effect of EPO on erythroid progenitor cells resulting in rHuEPO resistance. Accordingly, early identification of EPO hypo-responsiveness might alert clinicians to some treatable causes of renal anemia. A potential strategy might involve the use of short-term anti-cytokine or anti-lymphocyte therapy.

2.3   Cytokine and chemokine aberrations in CKD

I shall now very quickly illustrate cytokine and chemokine aberrations in CKD with observations in (i) diabetic nephropathy, (2) lupus nephritis, and (iii) renal dialysis.

2.3.1   Diabetic nephropathy

As mentioned in the beginning of this presentation, type 2 diabetes is an increasingly prevalent, morbid and life-threatening chronic degenerative disease with an epidemiological estimation of 60 million patients in China in Year 2000, 194 million worldwide in 2003, and a projected doubling increase in both prevalence and mortality by 2025. Over the past decade there has been a frightening 88% increase

in younger age of onset in Asia. Within our community, prevalence rate was 10% in Year 2002 and increasing. Twenty five % of our population will eventually be affected. Many will die of heart disease or stroke preceding or following renal damage eventually requiring dialysis, making diabetic nephropathy a particularly important diabetic complication in Asia. Compared to sex- and age-matched control subjects, the 88 type 2 diabetic patients with nephropathy in our study manifested increased plasma concentrations of pro-inflammatory cytokines TNF-α, IL-6 and IL-18, anti-inflammatory cytokines IL-10 and adiponectin, as well as neutrophil chemokine IL-8 / CXCL8, monocyte chemokine MCP / CCL2, and Th1 chemokines MIG / CXCL9 and IP-10 / CXCL10, all of them correlating positively with urine albumin:creatinine ratio, which is a marker of renal involvement, as expected from a Th1 mediated inflammation (25, 26).Adiponectin is a relatively new adipocyte-derived cytokine with anti-atherogenic and anti-inflammatory activities. Hypoadiponectinemia occurs in obesity, type 2 diabetes and other conditions associated with insulin resistance and hyperinsulinemia (27). Elevation of plasma adiponectin concentration in diabetic nephropathy is postulated to be due to impaired renal clearance despite decreased production.

2.3.2 Lupus nephritis

System lupus erythematosus (SLE) is a severe systemic autoimmune disease characterized by derangements of both T and B lymphocytes causing multiple organ damage including and involving the kidneys. Published studies to-date have documented significant increases in an array of Th1, Th2 and B lymphocyte-related cytokines and chemokines, all correlating positively with SLE disease severity index, alerting that derangements are more complex involving both Th1 and Th2 inflammatory pathways for tissue inflammation and production of autoantibodies (28, 29). This reminds us that Nature should unlikely be a purist and we must not over-emphasize or over-classify any disease into a rigid or restricted Th1 or Th2 stereotype. In physics, the co-existing particle and wave properties of radiation were recognized in the beginning of the last century.

It is also reasonable to expect that Nature might employ more than two pathways of T-helper lymphocyte activity. Over the last three years, we have contributed to the concept that newly discovered cytokine IL-23 produced by dendritic cells and macrophages can drive a third T-helper lymphocyte subpopulation, Th17, capable of producing IL-17A and IL-17F that are both cytokine-inducing cytokines in initiating and perpetuating autoimmunity (30). In research, we simply must continuously re-examine old concepts based on new findings.

2.3.3 Renal dialysis

Conventionally, CRP, IL-6, TNF-α and INF-γ have been used as markers of systemic inflammation in ESRD that can be caused by the intrinsic CKD, dialysis membrane or technique, or quality of dialysate. However, previous studies have also shown that T lymphocytes from HD patients are dysregulated and characterized by an increase in circulating Th1 cells with normal number of Th2 lymphocytes. This Th1/Th2 imbalance can be induced by IL-18 produced by monocytes and macrophages. Further, most previous studies used healthy non-CKD subjects as controls instead of pre-dialysis ESRD patients. We have recently reported our study of 146 ESRD

patients treated or not treated by PD or HD, and found that plasma IL-18, IL-6, TNF-α, CRP and cardiac troponin T concentrations were significantly higher in dialysis patients than low creatinine clearance pre-dialysis controls (31). These elevations should confer increased cardiovascular risk of ESRD patients on dialysis.

2.4 Summary remarks

CKD is increasingly a global public health problem. It can cause great suffering and impose a serious financial burden to patients and / or their society. CKD can be diagnosed and monitored using simple laboratory tests. Early treatments can decelerate the progression of renal dysfunction, prevent or delay metabolic complications, and reduce the risk of CVD. The pathogenesis and pathophysiolgy of CKD involve cytokine and chemokine driven inflammation potentially causing the MIAC syndrome, renal anemia, and other adverse outcomes. Therefore, like acute infections (e.g. SARS) and other chronic illnesses (allergy, diabetes and autoimmunity), CKD can also be regarded as a communication disease initiated by derangements of cytokine and chemokine homeostasis activating leukocytes and disrupting their normal trafficking and apoptosis to result in nephron injury. Laboratory and clinical studies of such messenger and message pathology are firstly a noble academic pursuit elucidating the immunological mechanisms of CKD. They also constitute an applied science for (i) monitoring disease severity, (ii) assessing risk, and (iii) developing therapy. In recent years, pharmacological modulation of biological communication has targeted on the development of cytokine and chemokine antibodies, receptor antagonists, soluble receptors, and low molecular-weight inhibitors of intracellular signaling (32). Examples include anti-TNF-α monoclonal antibody (Infliximab) and EGFR tryrosine kinase inhibitors (Tarceva and Iressa) that are being used increasingly for treating rheumatoid arthritis and metastatic non-small cell lung carcinoma, respectively. The newest promising leukocyte migration inhibitors that were featured last month (September 2008) comprise α_4-integrin monoclonal antibodies Natalizumab (Tysabri) and Efaluzimab (Rativa) for anti-inflammatory therapy (33).

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