

# Immune Disorders in Hemodialysis Patients

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**Keywords.** end-stage renal  
disease, hemodialysis, immune  
system diseases

Immunologically, end-stage renal disease is associated with some disorders in both innate and adaptive immune system in such a form that there is a coexistence of both immune activation and immune suppression. Although these disorders are complex yet thoroughly unknown, there is a close relationship between the progressively defective immune system and side effects as well as mortality causes, including cardiovascular problems, infections, and malignancies. From the other viewpoint, chronic inflammation as a major determinant of “dialysis syndrome” is considered as the main factor of morbidity and mortality in dialysis patients. Such inflammation is generally arisen from immune system response to uremia and individual’s repetitive contact with dialysis instruments, and in the long-term, it leads to premature aging via intensifying tissue degeneration. Therefore, the immune system is known as one of the most important therapeutic targets to reduce morbidity and mortality in uremic and dialysis patients. This review addresses different aspects as well as mechanisms of immune system dysfunction and possible therapeutics in dialysis patients.

IJKD 2015;9:84-96  
www.ijkd.org

## INTRODUCTION

Immunologically, end-stage renal disease (ESRD) is associated with some disorders in both innate and adaptive immune system in such a form that there is a coexistence of both immune activation and immune suppression. Although these disorders are complex yet thoroughly unknown, there is a close relationship between the progressively defective immune system and some medical complications, as well as mortality causes, including cardiovascular problems, infections, and malignancies.

From the other viewpoint, chronic inflammation as a major determinant of “dialysis syndrome” (including malnutrition, cachexia, and vasculopathy) is considered as the main factor of disability and mortality in dialysis patients. Such inflammation is generally arisen from immune system response to uremia and individual’s frequent contact with dialysis instruments, and in the long-term, it leads to premature aging via intensifying tissue degeneration.

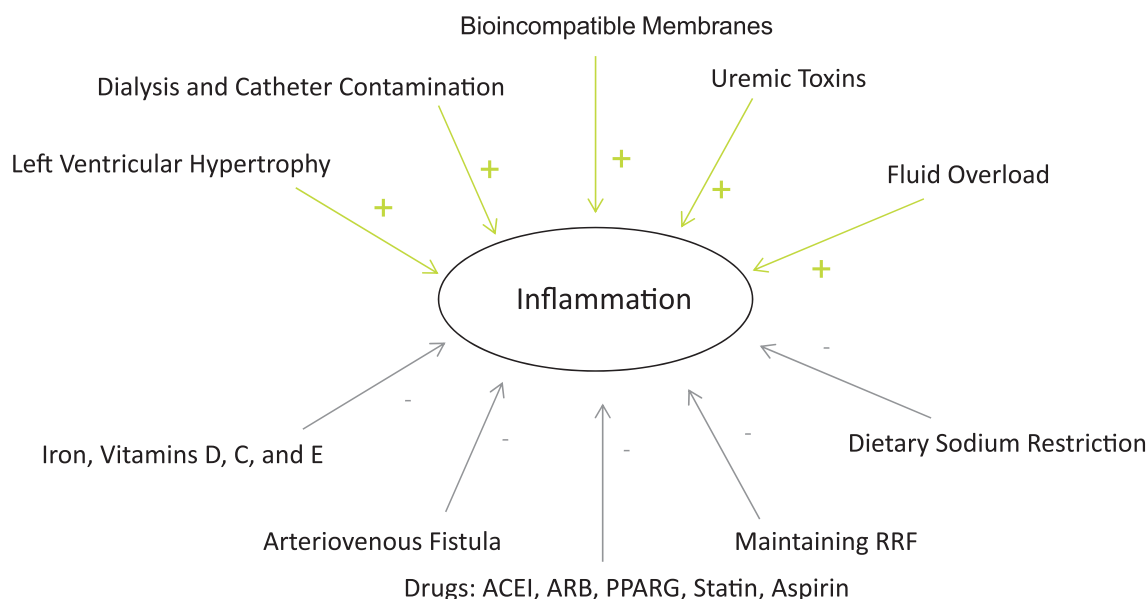
Therefore, the immune system is known as one of the most important therapeutic targets to reduce morbidity and mortality in uremic and dialysis patients. This review addresses different aspects as well as mechanisms of immune system dysfunction and possible therapeutics in dialysis patients.

## IMMUNE SYSTEM STIMULATORS

Immune system stimulators in uremic and hemodialysis patients leading to immune disorders are numerous and generally include uremic toxins and dialysis-related factors (Figure 1).<sup>1</sup>

### Uremic Toxins

The reduction of kidney function and subsequent uremic toxicity causes the increase of plasma concentrations of inflammatory biomarkers,<sup>2</sup> which may be decreased using more frequent dialysis,<sup>3</sup> yet would not be possible to be removed thoroughly even using advanced dialysis treatments.<sup>4</sup> Uremic



**Figure 1.** Immune system stimulators and inhibitors in hemodialysis patients. RRF indicates residual renal function; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and PPARG, peroxisome proliferator-activated receptor  $\gamma$ .

toxins contain about 90 heterogeneous components comprising organic materials such as urea, lipids, and peptides including immunoglobulin free light chains of kappa and lambda with pro-inflammatory effects.<sup>5,6</sup> Some metabolic reactions of uremic patients in the forms of nonenzymatic glycation, oxidation, and enzymatic carbonilation of aldehyde or ketonic carbohydrates and lipids along with different amino acids of proteins result in production of other uremic toxins, including advanced glycation end products, such as pentosidin and carboxy methyl lysin, and advanced lipo-oxidation end products, such as malondialdehyde-lysine. Due to the reduction of kidney’s clearance, these toxins are accumulated and directly or indirectly stimulate immune cells (by receptors), including advanced-glycation-end-products-receptor-family-containing ones such as scavenger liver sinusoidal and kupffer cells. Such stimulation leads to different aspects of inflammation and endothelial dysfunction, including overproduction of reactive oxygen and nitrogen species as well as inflammatory cytokines by phagocytes and endothelial cells, monocyte chemotactic stimulation, smooth muscle cell proliferation, and collagen secretion in synovial cells.<sup>7-9</sup>

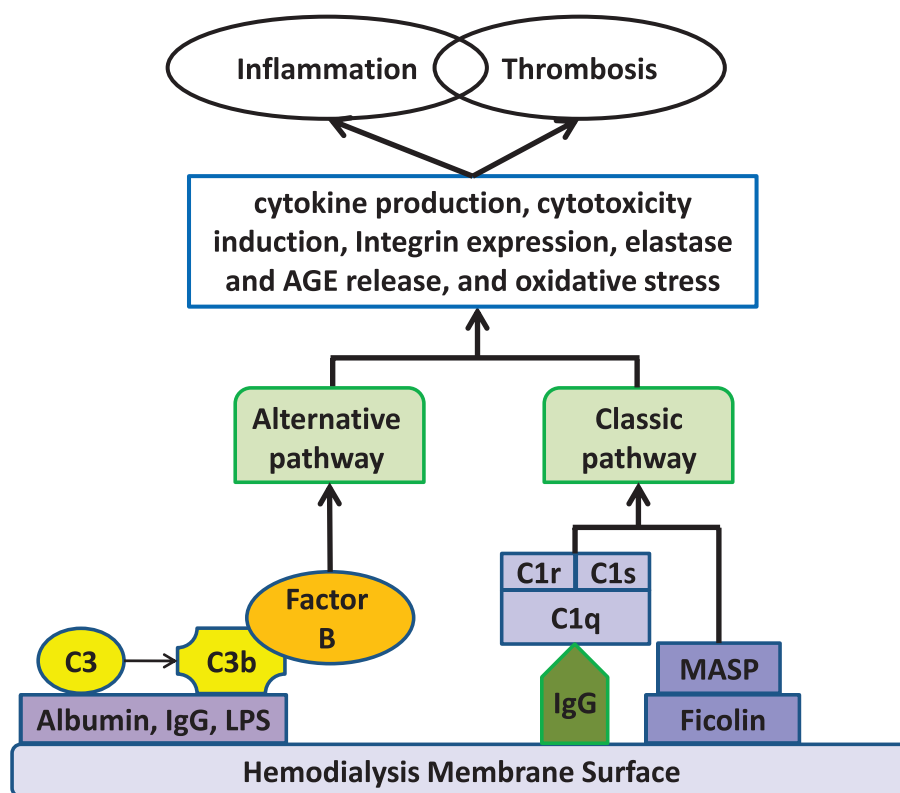
**Dialysis-related Factors**

Another group of immunostimulants in dialysis patients is the dialysis-related factors among which

the interaction of blood with bio-incompatible membranes and the contamination of dialysis solutions and catheters are the most important ones.<sup>10</sup> Bio-incompatible synthetic or cellulosic polymeric membranes lead to acute-phase responses, oxidative and carbonyl stress, endothelial production of both nitric oxide, and inducible nitric oxide Synthase, all of which result in tissue injury and its side effects, including cardiovascular disease and reactive amyloidosis.<sup>8,11</sup> Using ultrapure dialysis solutions as well as tunneled catheters effectively reverses such effects and limits the risk of infections in hemodialysis patients.<sup>12,13</sup>

**COMPLEMENT DISORDERS**  
**Complement Activation**

The main step of complement activation in hemodialysis patients is the addition of factor B to covalently-bound C3b and its breakdown by factor D to make alternative pathway C3 convertase inside the vessels or on dialysis membranes outside the patient’s body.<sup>12</sup> Oxidized lipids of blood vessels and dialysis synthetic or cellulosic polymeric membranes coated with albumin, immunoglobulin G (IgG), lipopolysaccharide, and other bacterial products present in infected water or dialysis solutions, all make nucleophilic surfaces which provide covalent binding of C3b and continuation of complement alternative pathway in uremic and dialysis patients (Figure 2).<sup>11</sup> The classical and



**Figure 2.** Complement activation in hemodialysis patients. AGE indicates advanced glycation end products; C1, complement C1; C3, complement C3; IgG, immunoglobulin G; MASP, mannose-binding lectin-associated serine protease; and LSP, lipopolysaccharide.

lectin pathways are also activated in hemodialysis patients through adhesion of C1q to membrane-adsorbed IgG and polysulfone membrane-deposited ficolin-2, respectively (Figure 2).<sup>14,15</sup> Apart from the reduction of mannose-binding lectin in infected hemodialysis patients,<sup>16</sup> increase of functional mannose-binding lectin,<sup>17</sup> activity of C3 as well as terminal components of the complement,<sup>18</sup> and the production of factor D by adipocytes are evident.<sup>8</sup> All of these demonstrate an overactivity of the complement system despite improvements in the biocompatibility of modern hemodialysis membranes and other biomaterials.<sup>19</sup>

### Complement and Inflammation

Complement products, including C3a and C5a anaphylatoxins, Ba and C3b factors, and membrane attack complex, enhance the inflammation through cytokine production, cytotoxicity induction, elastase and advanced glycation end products release, and oxidative stress.<sup>19</sup> One result of complement activation in hemodialysis patients is the induced expression of adhesion molecules on leukocytes especially CD11b/CD18. On the other hand,

after dialysis, the endothelium of the patients is activated via overexpression of plasmin-antiplasmin complex, soluble factor 8 (von willebrand factor), and E-selectin, which interact with leukocyte integrins, allowing cell extravasation and induction of inflammatory effects.<sup>8</sup>

### Complement and Thrombosis

The presence of C3, C4, and membrane attack complex has been shown in the intima of the atherosclerotic vessels of patients undergoing dialysis. Notably, in addition to thrombosis initiated through C5a-induced tissue factor production by neutrophils,<sup>20</sup> such complement products recruit inflammatory cells to induce vascular lesions.<sup>19</sup> The vicinity of membrane attack complex with smooth muscle cells (which do not express the regulatory factor CD59) in vascular intima repetitively stimulates them to produce chemokines such as monocyte chemoattractant protein-1,<sup>8</sup> which accumulates integrins and increases their affinity to the endothelium, facilitating the extravasation of leukocytes. In dialysis periods, due to incompatibility with dialysis membranes,

repetitive inflammatory reactions lead to acute-phase responses, including the secretion of acute-phase proteins such as C-reactive protein (CRP), which is a complement activator whose presence with activated complement in inflammatory tissues, including atherosclerotic blood vessels and infarcted myocardium, emphasizes its pathogenic role.<sup>21</sup>

### Complement Regulation

In uremic and dialysis patients, secondary to oxidative and carbonyl stress, nonenzymatic glycation of CD59 occurs. Such occurrence blocks CD59 as a regulatory factor, which naturally hampers the addition of C9 molecules to C5b6-8 complex.<sup>22</sup> There are also some reports demonstrating the decrease of complement receptor 1 (C3b receptor) and its association to poor prognosis in hemodialysis patients.<sup>23</sup>

## INNATE IMMUNITY DISORDERS

### Cellular Compartment

Different cells of innate immunity are stimulated in response to chronic exposure to uremic toxins and dialysis-related factors. Neutrophils and monocyte-macrophages are the main elements of such chronic inflammation whose main

disadvantage is their more apoptosis to an extent that could not to be normalized by hemodialysis (Table).<sup>24,25</sup> Likely, such apoptosis happens to young and functional neutrophils and finally ends in leukopenia as well as the impaired cellular innate immune responses.<sup>26</sup> Actually, senescent neutrophils accumulate in hemodialysis patients because they express low amount of CXCR4 which interacts with CXCL12 and coordinates the returning of senescent neutrophils to bone marrow to undergo apoptosis.<sup>27</sup> The leukopenia can also be due to adhesion of activated granulocytes to hemodialysis membranes after being exposed to bio-incompatible ones and endotoxins which leak through back filtration.<sup>28,29</sup> Such leukopenic events along with compromising the microbicidal ability and nitric oxide synthesis inhibition of innate immune cells attenuates their responsiveness to infections from one side and enhances the inflammatory reactions because of predisposing the patients to recurrent infections from the other side.<sup>10</sup> The main reason for infection in uremic patients is bacteria<sup>30</sup>; therefore, reinforcing mechanisms of adaptive immunity is always needed to eradicate them. Nevertheless, lymphocyte disorders as well as dendritic cell depletion and dysfunction in such patients attenuate the efficiency of innate immunity

The effect of Hemodialysis on Cells of the Innate and Adaptive Immune System

Immune Cells	Hemodialysis-associated Changes	
	Number of Circulatory Cells	Altered Functions
Innate immune cells		
Phagocytes	Decreased	Increased apoptosis Increased production of main proinflammatory cytokines Decreased microbial ability Increased degranulation Decreased nitric oxide synthesis Increased adhesion to hemodialysis membranes
Antigen presenting cells	Decreased	Decreased endocytosis capabilities Decreased maturation Decreased interleukin-12 production Decreased B71
Natural killer cells	Decreased	Increased activity in long hemodialysis Decreased expression of activatory receptors
Adaptive immune cells		
B lymphocytes	Decreased	Increased apoptosis BAFF downregulation Reduced Ab production (in some studies) Increased production of proinflammatory cytokines
T lymphocytes	Increased (T helper 2, T helper17, Regulatory T cells) Decreased (T helper 1)	Increased apoptosis Increased angiogenin Decreased production of interleukin-2 Increased production of 2,3-dioxygenase Increased production of arginase type-1

and weaken the responses to bacterial infections as well as vaccination.<sup>31-33</sup> In an in vitro study, endocytosis capability as well as the maturation of monocytes and monocyte-driven dendritic cells of uremic patients was defective, but the defects of interleukin (IL)-12 production and allogenic proliferation of T cells were amended when T cells were cultured in the serum of normal (nonuremic) donors.<sup>34</sup> This means that the communicative interface between innate and adaptive immunity is lost. This phenomenon explains in part the immunodeficiency of these patients.<sup>7</sup> Surprisingly, such defective responses may be accompanied by over activation of innate immune cells.<sup>35</sup>

Some recent reports have focused on the immune status of natural killer (NK) cells (Table). Although a decreased expression of the pivotal activating receptor, *NKG2D*, on NK cells from dialysis patients has been reported,<sup>36</sup> an increased NK cell activity has been revealed in long-term hemodialysis.<sup>37</sup>

### Humoral Compartment

Inflammatory reactions during the dialysis sessions are associated with the activation of innate immune cells. The most important of such reactions is the secretion of inflammatory cytokines and other inflammatory intermediates such as arachidonic acid metabolites, platelet-activating factor, and oxidative stress.<sup>38</sup> Actually, the serum level of cytokines in hemodialysis patients is very controversial and the underlying reasons are not yet well elucidated (reviewed by Jacobs and colleagues<sup>39</sup>). However, it is clear that part of clinical manifestations of the patients including their morbidity and mortality is due to cytokine secretion from peripheral blood mononuclear cells; and IL-6,<sup>40</sup> tumor necrosis factor (TNF)- $\alpha$ , and inflammatory marker of CRP are the most investigated ones.<sup>40-42</sup> Such morbidity and mortality may also be associated with other markers, some of the newly investigated of which are as follows: increased levels of vascular endothelial growth factor,<sup>43</sup> indoleamine 2,3-dioxygenase,<sup>44</sup> hepatic hormone hepcidin (as the master regulator of circulating iron levels and a possible role player of atherosclerosis),<sup>45</sup> fibroblast growth factor 23,<sup>46</sup> insulin-like growth factor-1,<sup>40</sup> and basal nitric oxide;<sup>47</sup> and reduced serum levels of soluble  $\alpha$ -Kletho,<sup>48</sup> IgM antibodies against oxidized cardiolipin,<sup>49</sup> plasma zinc,<sup>50</sup> fetuin A,<sup>51</sup> and hypo- hyperphosphatemia.<sup>52</sup> Apart from the abovementioned markers, there

are growing reports that demonstrate the increase of other serum markers in hemodialysis patients, including hepatocyte growth factor, soluble urokinase plasminogen activator receptor,<sup>46</sup> nicotinamide phosphoribosyltransferase or visfatin (a potent adipokine enzyme marker of endothelial inflammation and dysfunction that promotes B and vascular smooth muscle cell maturation and inhibits neutrophil apoptosis),<sup>53</sup> YKL-40,<sup>54</sup> cytochrome C (as a damage-associated molecular pattern),<sup>55</sup> total homocysteine, transferrin, ferritin and fibrinogen,<sup>56</sup> procalcitonin (as a marker of infection),<sup>57</sup> and endothelin-1.<sup>58</sup> Despite the normality of the production of some cytokines by monocytes and macrophages especially in interdialysis periods,<sup>59</sup> the repetitive dialysis periods increase some cytokines, especially TNF- $\alpha$ , IL-6,<sup>60,61</sup> and anti-inflammatory cytokine IL-10,<sup>60,62-64</sup> resulting in a periodic chronic inflammation. Additionally, TNF- $\alpha$ , IL-8,<sup>63</sup> pentraxin-3, and IL-6<sup>65</sup> appear to be valid biomarkers of the intradialytic inflammatory response. Although in dialysis periods, active macrophages may try to limit the inflammatory response through the secretion of IL-10,<sup>66</sup> which is capable of inhibiting many tasks of the macrophages themselves, defective feedback inhibition of pro-inflammatory cytokines such as TNF- $\alpha$  may contribute to a chronic inflammatory state.<sup>67</sup> Such factors along with chronic activity of the platelets and endothelial cells also take part in the pathogenesis of the atherosclerotic and hemorrhagic lesions and thrombotic manifestations of the dialysis patients.<sup>27,68</sup> Tumor necrosis factor- $\alpha$  in particular, seems to be associated with left ventricular hypertrophy in hemodialysis patients.<sup>61</sup> A few hours after the dialysis, active monocytes leave the circulation and enter the blood vessel wall. One probable result of such infiltration is the progress of atherosclerosis. That is due to their conversion to foam cells, a phenomenon that intensifies the atherosclerosis.<sup>11</sup>

During hemodialysis, the production of cytokines happens due to the following: (1) inductive effects of oxidative stress intermediates and other active inflammatory components (including C3a, C5a, and C5 to C9) after direct contact of complement/immune cells to exogenous factors such as dialyzate pyrogens, short bacterial DNA fragments, bioincompatible dialysis membranes, artificial shunt materials during extracorporeal circulation,



and bacterial derivatives (lipopolysaccharid) transported from dialysis solutions to circulation; and (2) endogenous factors such as rennin-angiotensin-aldosterone system and nuclear factor kappa B (NF- $\kappa$ B) system activation, loss of renal excretion of cytokines, and an imbalance of tissue T helper type 1 and tissue T helper type 2 cells owing to uremic toxins.<sup>62</sup>

Hemodialysis results in further activation and degranulation of neutrophils and macrophages in ESRD patients.<sup>69</sup> Such activation causes extra production of reactive oxygen and nitrogen species and peroxidant factors such as myeloperoxidase and lactoferrin, all as the main reasons of tissue damage during inflammatory reactions of dialysis patients.<sup>8,10,24</sup> The indispensable role of oxidative stress, known as a risk factor for cardiovascular diseases and a possible reason for premature aging as well as general complications associated with kidney failure, can be manifested by the aggregation of biomolecular damage indicators such as products of lipid oxidation and of DNA and protein oxidation and glycation.<sup>70</sup>

### Toll-like Receptors

Toll-like receptors (TLR) and their signaling mediators like NF- $\kappa$ B have an important role in chronic inflammation of hemodialysis patients.<sup>26</sup> Different molecular patterns including uremic toxins and other factors produced during dialysis treatment activate TLRs.<sup>7</sup> The increased expression of TLR2 and TLR4 at monocytes, TLR4 at neutrophils, as well as TLR4 activity in hemodialysis patients represents another dimension of inflammation in such patients.<sup>71</sup> Toll-like receptor-4, which is widely expressed on macrophages and other organs including the kidneys, heart, blood vessels, and lipid tissues, is able to recognize uremic toxins and infections,<sup>7</sup> dietary saturated fatty acids,<sup>72</sup> and endogenous ischemic ligands.<sup>73</sup> Such recognition, especially in the presence of dialysis membrane, cytoskeletal stresses from the roller pump, and influx of impurities from the dialysate compartment, might eventually lead to a decrease in TLR4 expression.<sup>74</sup> Reduced TLR-4 expression may be associated with the compromised immune function in hemodialysis patients. Toll-like receptor-4 on renal cells, when stimulated by lipopolysaccharid, can trigger these cells to secrete monocyte chemoattractant protein-1 and the chemokine

regulated on activation, normal T cell expressed and secreted, which both recruit leukocytes.<sup>75</sup>

### C-reactive Protein

Although some recent reports indicate no changes in the production of CRP,<sup>37,65</sup> some others reveal that hemodialysis patients with low CRP levels,<sup>63</sup> including Asian ones<sup>76</sup> have better survival and are probably well protected against micro-inflammation than hemodialysis patients with high CRP levels,<sup>63</sup> including Caucasian ones. What proves this is that the balance between pro- and anti-inflammatory cytokines and receptors is more favorable in patients with low CRP levels than those with high CRP levels.<sup>63</sup> Moreover, Glasgow Prognostic Score, based on serum albumin and highly sensitive CRP, has a powerful prognostic value for mortality prediction in hemodialysis patients.<sup>77</sup>

It should be noted that the impaired immune defense in dialysis patients is not due to a deficiency in  $\alpha$ -defensins; as neither basal levels nor expression during infections were reduced compared with subjects with normal kidney function.<sup>78</sup>

### Transcriptomic Profile

Recently, 2 studies have revealed the transcriptomic profile of the peripheral blood mononuclear cells of hemodialysis patients with an emphasis on pivotal role of up- or downregulation of some factors. The upregulated ones are heparanase<sup>79</sup> and 2 other factors primarily involved in chronic inflammation including pentraxin-3, as an acute-phase protein, and IL-15 involved in the proliferation and cytotoxicity of NK cells. The downregulated one is human leukocyte antigen-G as an inhibitory ligand of NK cell receptors as well as an inhibitory factor of cytolytic function of T lymphocytes and dendritic cells maturation.<sup>37</sup> Additionally, protein as well as transcript levels of CX3CR1, a highly selective chemokine receptor and surface marker of cytotoxic effector NK cells/T lymphocytes, was expressed highly in hemodialysis patients.<sup>37,63</sup> Such genes and proteins could be useful as potential diagnostic biomarkers as well as new therapeutic targets.

### LYMPHOCYTE DISORDERS

Uremic toxins and dialysis therapeutics influence lymphocytes, as the main effector cells of adaptive immunity (Table).

### B Lymphocytes

Although there may be both an elevation in B-cell growth as well as differentiation in the amount of its survival factors such as IL-7 and BAFF, hemodialysis could be associated with a diffuse reduction of B-cell subpopulations.<sup>80</sup> Such reduction could be due to either their increased susceptibility to apoptosis<sup>81</sup> or downregulation of BAFF receptor that can constitute resistance to the biological actions of BAFF, as a potent B-cell differentiation and survival factor.<sup>80</sup> However, antibody production may be normal or reduced in hemodialysis patients.<sup>74,82</sup> A report demonstrated a significant increase in immature regulatory B cells in hemodialysis patients compared to predialysis patients, potentially due to resolution of uremic toxicity by hemodialysis.<sup>64</sup> Despite their reduced numbers, the uremic B cells of hemodialysis patients have a heightened capacity to produce inflammatory cytokines of TNF- $\alpha$  and IL-6, suggesting their possible participation in the prevailing inflammatory milieu in uremia.<sup>80</sup> B lymphocytes can directly recognize polysaccharide antigens and respond to them through antibody production, but in the case of protein antigens, they need the specific help of T lymphocytes. Even in the normal functioning of B cells,<sup>83</sup> T-cell help may be impaired in hemodialysis patients.<sup>31,83</sup> The evidence of this claim is that despite CD40L induction,<sup>84</sup> there is a reduced renal clearance of the soluble form of CD40 in hemodialysis patients which antagonizes CD40/CD40L interaction in the process of T- and B-cell activation.<sup>85</sup> The impaired T-helping effect could be the reason for normal response of some uremic patients to nonprotein antigens such as pneumococcal polysaccharide vaccine.<sup>11</sup>

### T Lymphocytes

T cell immune profile in ESRD patients shows significantly higher percentages of T helper 2, T helper 17, CCR4<sup>+</sup>CCR6<sup>+</sup>CD4<sup>+</sup> T cells, IL-17 producing memory T cells, and CD45RA(+) T effector memory subsets of CD8<sup>+</sup> T cells that could not be corrected with hemodialysis.<sup>86,87</sup> However, the increased number of the T lymphocytes may be normalized through apoptosis<sup>84</sup> during hemodialysis treatment. There is also an impaired T-cell function during hemodialysis that could be at least partly due to increased angiogenin level as an

acute phase reactant which is contributed to T-cell zeta-chain downregulation.<sup>88</sup> The ratio of CD4<sup>+</sup> to CD8<sup>+</sup> cells may be normal in hemodialysis patients<sup>11</sup> that may explain the long-term immunogenicity of an influenza vaccine in such patients.<sup>89</sup> A low frequency of T helper 1 cells in hemodialysis patients has been reported likely due to little production of IL-2 and higher production of indoleamine 2,3-dioxygenase and arginase type I which exert proapoptotic and antiproliferative effects on T cells.<sup>11,90</sup> Such defective count as well as function may also be rooted in co-stimulatory mechanisms of antigen-presenting cells.<sup>91</sup> Actually, T cells of dialysis patients act in a normal way when they encounter an antigen presented by antigen-presenting cells driven from normal people.<sup>11</sup> In dialysis patients, antigen-presenting cells express too little amount of co-stimulatory molecule B7-2 (CD86) and enough amounts of B7-1 (CD80) and HLA class II molecules. B7-2 induces T cells to produce IL-2 whose production and secretion has been critically decreased in dialysis patients.<sup>31</sup> In vitro addition of IL-2 to T cells of uremic patients reverses their proliferative capacity.<sup>8</sup> Due to a defect in IL-2 production, T helper 2 may also be decreased in uremia, but there are some controversies regarding the relative preference of T helper 1 cells compared to T helper 2 cells in hemodialysis patients. Some reports demonstrate a relative preference of T helper 1 cells whose probable reason is an increased production of IL-12 (which induces the conversion of T helper 0 to T helper 1) by monocytes<sup>11</sup> and decreased expression of IL-4 receptor (which suppresses IL-2 activation pathway at the level of signal transduction).<sup>63</sup> Moreover, some others demonstrate a T helper 2 preference consistent with the increased levels of IL-4.<sup>86</sup> That T helper 1 cytokines inhibit the differentiation of T helper 0 to T helper 2 diminishes the humoral response to T-dependent antigens.<sup>11</sup> That is why these patients are unable to respond properly to some vaccines including tetanus, diphtheria, and hepatitis. As we discussed earlier, defective T lymphocytes are not able to help properly to B cells and this is the second reason for such an improper response to the above-mentioned vaccines.<sup>11</sup>

Increased apoptosis as well as reduced function of the naturally occurring regulatory T cells (CD4<sup>+</sup>CD25<sup>+</sup>) and NK T cells (which are conserved, immunoregulatory T lymphocyte subsets) has

been demonstrated in dialysis patients.<sup>74,92</sup> Likely, such observation in addition to aforementioned T helper 1 preference in dialysis patients may explain some clinical manifestations of kidney-involved autoimmune diseases. For instance, in T helper 1-dependent Wegener granulomatosis, the patient should continue immunosuppressant even on dialysis.<sup>11</sup>

It should be noted that accumulated cell-free DNA released from different leukocytes by ongoing apoptosis, as mentioned earlier in the plasma of hemodialysis patients, is selectively able to induce the production of the pro-inflammatory cytokine IL-6 in human monocytes.<sup>93</sup> This process may contribute to the pro-inflammatory environment of such patients.

### PREVENTION AND TREATMENT

Dialysis could not substantially affect the average of a 20-year difference between the calendar age and the immunological age of ESRD patients, which was analyzed by T cell telomere length and T cell receptor excision circles content, that is genomic DNA remnants produced during T cell receptor rearrangements.<sup>94</sup> Therefore, immune stimulation in hemodialysis patients should be prevented (Figure 1). While using newer modified cellulose or Low- and high-flux polysulphone membranes have similar effects on lipids and inflammatory markers in chronic hemodialyzed patients,<sup>95</sup> microbial decontamination remains the main preventive strategy of immune stimulation especially in the case of occult microbes including chlamydia pneumonia, helicobacter pylori, hepatitis C virus, gingivitis-producing microbes,<sup>80</sup> and different parasites.<sup>96</sup> Such preventive strategy might be critical in hepatitis C virus-infected dialysis patients who are not candidates for kidney transplantation, as the indication for antiviral therapy is limited to significant fibrosis (fibrosis  $\geq 2$  on the METAVIR scale).<sup>97</sup> A newly conducted study showed that the use of iron preparations and  $1\alpha$ -hydroxylated vitamin D is potentially associated with less risk of developing herpes zoster reactivation in maintenance hemodialysis patients.<sup>98</sup> A lot of water is consumed during hemodialysis which can also induce inflammatory responses after penetration to dialysis membranes despite being internationally standard.<sup>12</sup> The risk of blood contamination as well as mortality

increases if hemodialysis catheters even tunneled ones be used and decreases if an arteriovenous fistula provides a permanent access to the blood.<sup>13,99,100</sup>

Complement-targeted interventions during hemodialysis may reduce complement activity as well as concerns of long-term immunosuppression especially when blood is in contact with the filter membrane. Such interventions include 1) systemic administration of C5 antibody (eculizumab), C5aR antagonists such as PMX-53, C3 cleavage inhibitors such as compstatin, soluble complement inhibitors such as C1-INH and C2) targeting direct contact of complement inhibitors such as soluble CR1 and M protein-derived peptides of streptococcus pyogenes (which recruits C4BP as a complement regulator to polystyrene surfaces and reduces complement activation) to biomaterials (reviewed by DeAngelis and coworkers<sup>19</sup>).

Because of a reverse correlation between the serum concentration of different inflammatory cytokines and glomerular filtration rate, it is likely that residual renal function of dialysis patients be important in controlling the abnormal stimulation of immune system. It has been shown that the peritonitis increases when residual renal function decreases.<sup>101</sup> As a conservative treatment, it is necessary to maintain the residual renal function of dialysis patients.

Fluid overload, a common phenomenon in dialysis patients, has some roles in inducing inflammation as well as left ventricular hypertrophy, as there is a direct proportion between the fluid overload volume and the serum level of CRP.<sup>7,102,103</sup> Dietary sodium restriction is associated with the attenuation of the inflammatory state, with or without changes in blood pressure<sup>104,105</sup>; therefore, it is strongly recommended. Additionally, in chronic kidney disease, most likely because of decreased renal excretion power, the level of some inflammatory adipokines such as IL-6 and CRP in fat storage tissue increases.<sup>106</sup> The interaction of adipokines and fat tissues may be critical from the viewpoint of their influence on inflammation, vascular wellbeing, and dialysis results.<sup>76</sup>

Erythropoietin resistance in hemodialysis patients may be due to abnormally raised levels of the pro-inflammatory cytokines such as TNF- $\alpha$ , interferon- $\gamma$ , and IL-6, as well as anti-inflammatory cytokines such as IL-10 and IL-13, all of which are known to



inhibit erythropoiesis.<sup>107,108</sup> Therefore, anticytokine therapies such as pentoxifylline in addition to ascorbic acid supplementation and intravenous iron therapy with care to avoid their overload can restore the response to erythropoietin and improve hemoglobin levels.<sup>109-112</sup> Anti-inflammatory drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, peroxisome proliferator-activated receptor  $\gamma$ , statins, and vitamins have been recommended for the treatment of ESRD.<sup>76</sup> For instance, angiotensin-converting enzyme inhibitors decrease serum level of CRP as well as TNF- $\alpha$ , and simvastatin and atorvastatin decrease serum level of CRP in hemodialysis patients.<sup>113-115</sup> More investigation is needed to elucidate the role of such drugs in decreasing the inflammation-induced cardiovascular disease.

Careful monitoring and correction of 25-hydroxyvitamin D levels have been recommended not only for correction of bone mineralization, but also for controlling inflammatory complications and erythropoietin hyporesponsiveness in hemodialysis patients.<sup>116-118</sup> While some studies recommend using antioxidant of vitamin E and  $\alpha$ -lipoic acid supplementation which may reduce such inflammatory state and improve lipid profile in hemodialysis patients,<sup>120</sup> others have not found such results.<sup>119,121</sup>

One study identifying genomic pattern of dialysis-related systemic microinflammation, revealed an increased expression of migration inhibitory factor, which activates macrophages to produce pro-inflammatory mediators and to migrate to the sites of inflammation. Therefore, it is likely that existing anti-migration-inhibitory-factor therapy (N-acetyl-*p*-benzoquinone imine) may in the future represent a novel therapeutic strategy to reduce chronic inflammation in dialysis patients.<sup>26</sup>

An upregulation of NF- $\kappa$ B and glutathione synthetase in hemodialysis patients has been observed. This emphasizes the necessity to eliminate drugs and chemicals known to enhance NF- $\kappa$ B expression like nicotine, and the benefit to prescribe anti-oxidant drugs like acetyl-L-carnitine and N-acetylcysteine.<sup>26,122</sup>

Finally, low-dose aspirin therapy attenuates inflammation in either pediatric or adult dialysis patients through the decrease of the serum concentration of various proinflammatory cytokines with no adverse effects noted.<sup>123</sup>

## ACKNOWLEDGMENTS

This review was originated from the studies related to a research supported by the Deputy of Research, Kashan University of Medical Sciences, Grant No 92113.

## CONFLICT OF INTEREST

None declared.

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Received April 2014  
 Revised July 2014  
 Accepted August 2014