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The effect of end-stage renal disease on innate and adaptive immunity

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ABSTRACT: The progressive loss of kidney function is associated with an inflammatory state and functional defects of the innate and adaptive immune system. The combined effects of increased activation and immune dysfunction could explain the susceptibility of patients in End Stage Renal Disease (ESRD) to viral and bacterial infections, their weak responses to vaccination and increased risk of malignant tumors and cardiovascular disease.
It is important to underline that these immune complications mainly affect patients on dialysis. The mechanisms of these immunological disturbances observed in ESRD patients are still unclear.
Early identification of chronic kidney disease allows implementing interventions to slow the progression to ESRD. Therefore, measures aimed at attenuating immune abnormalities in ESRD should be a main research area as this could lead to increased survival and better quality of life in HD patients.

KEYWORDS: renal disease, innate immunity, adaptive immunity.

1 INTRODUCTION

End stage renal disease (ESRD) is simultaneously associated with immune activation, marked by systemic inflammation, and immune deficiency [1-4].

Systemic inflammation contributes to atherosclerosis, anemia, amyloid arthropathy, β2-microglobulin and cardiovascular disease, the major cause of morbidity and mortality in ESRD, accounting for 50% of death in this patient population [1-5].

Immunodeficiency contributes to the high prevalence, increased incidence and severity of infections among hemodialysis patients. In addition, immunodepression explains also among these patients, their anergy in delayed hypersensitivity reactions, their poor response to vaccines against the influenza virus and especially hepatitis B virus (HBV), and finally the abnormal frequency of autoimmune diseases and tumors [5-6].

Several hypotheses have been put forward to elucidate the causes of such an immune system dysregulation in dialysis patients [7]. Understanding the mechanisms behind the immune dysfunction in ESRD generates a perspective to improve lifestyle and reduce mortality in this group of patients.

2 COMPONENTS OF THE INNATE IMMUNITY

2.1 COMPLEMENT

The complement system is a primary contributor to the innate immune system of the host, clearing the body of foreign cells and organisms through direct lysis or by recruiting leukocytes that promote phagocytosis [8]. In addition to uraemia, membrane bioincompatibility and endotoxin leaks through backfiltration lead to complement and leukocyte activation in hemodialysis (HD) [5].

The dialysis membranes composed of cuprophane are well known to activate complement [9, 10]. Biocompatible and synthetic membranes induce less complement activation in vivo [11-13]. Complement activation by these synthetic

membranes involve their properties of plasma protein adsorption [14-16], and follows the alternative and classical pathway [17-18]. The major contribution of biomaterial-induced complement activation could be attributed to the alternative pathway [19]. Also, it has been suggested that lectin pathway may contribute in haemodialysis to complement activation [15].

Complement activation commence immediately after the onset of treatment. This activation is greatest 15 to 20 minutes after the initiation of dialysis and could inhibit its function [10, 20-21]. The alternative pathway was markedly suppressed, and suppression lasted for 4 hours or longer [24]. Complement activation returns to pre dialysis values by the end of the hemodialysis [20]. Accurate measurement of the suppression of complement activation is very difficult and the mechanisms by which membranes suppress different pathways are not clear [21].

Complement-targeted intervention is needed during the dialysis procedure [19-20]. The development of complement therapeutic targeting specific proteins and pathways as means to control the unwelcomed inflammatory responses and consequent pathologies in hemodialysis patients shows high promise, compared to other types of drugs, or to the selection and manufacture of dialysis filters with improved biocompatibility, and may result in urgently desired novel treatment options for patients suffering from ESRD [19-20].

Restoring complement activity to full capacity between sessions of dialysis reduces concerns of long-term immunosuppression [20].

2.2 POLYMORPHONUCLEAR LEUKOCYTES (PMNS)

PMNs are the first line of defense against invading microbes and important players in inflammation. They have many intracellular granules that contain bactericidal proteins. PMNs are short-lived in blood [22-24]. The neutrophil is a critical effector cell in both innate and humoral immunity. However, the capacity for bacterial killing carries with it an implicit capacity for host tissue destruction, as observed in inflammatory and autoimmune disease; accordingly, neutrophil function must be tightly regulated [22, 25].

Patients with ESRD exhibit basal upregulation of Toll-like receptor (TLR-4, TLR-2) and integrin expressions, increased reactive oxygen species (ROS) production and marked degranulation reflecting their spontaneous activation [25-27]. These abnormalities contribute to the prevailing systemic oxidative stress, inflammation and tissue damage in this population [1].

Defects in phagocytosis and bactericidal activity are reported from the pre-end-stage chronic renal failure stage; these abnormalities are intensified by hemodialysis. The first weeks of dialysis are characterized by a fall in PMNs functional capacity, as well as by an acute and a chronic decrease in circulating PMNs number [24, 26-28]. Most likely as a result of exposure to dialyzer membrane, cytoskeletal stresses from the roller pump, and influx of impurities from the dialysate compartment [28-31].

In fact, phagocytic capacity of PMNs of patients on dialysis cellulose acetate or polysulfone is significantly lower than that of patients without dialysis treatment or on peritoneal dialysis [24, 32]. Decreased phagocytic function affect phagocytosis complement dependent as well as dependent immunoglobulin receptor (FcγR) [33-34]. Certain uremic toxins are apoptogenic and can accelerate neutrophil apoptosis [35-37]. Chronic hemodialysis also plays a role. Neutrophils from hemodialysis patients have a greater cytoplasmic expression of pro-apoptotic protein (p53) [38]. In contrast, the low-level detection of Bcl2 was found in PMNs from HD patients [39].

Migration is an essential anti-infection property of PMNs. It is necessary for a rapid mobilization of these cells to the inflammatory site. Several uremic toxins have the ability to inhibit neutrophil migration in response to classical chemoattractants, thereby reducing the number of effector cells to the inflammatory site and therefore bacterial clearance [40-43].

Bearing in mind that the antimicrobial efficiency of human neutrophils depends not only on the generation of oxygen, free radicals and other reactive oxygen species (ROS), but also on the release of enzymatic or antimicrobial protein content in the granules [44-45]. Indeed, improper stimulation of degranulation by uremic proteins or adjuvant therapies during hemodialysis sessions leads to a relative lack of bactericidal enzyme of PMNs [26-27, 46-48].

Studies investigating the production of reactive oxygen (ROS) in HD patients have produced conflicting results [25, 44]. Decreased [40-41, 49-50], unchanged [44], or increased levels of ROS production, reported by numerous published studies [26-27, 36-37, 51-52]. Some studies report a partial correction of PMNs function following hemodialysis. This result argues for the existence of one or more factors uremic modulators of PMNs activity [53-55].

Despite the progression of new technologies of renal replacement therapy, it is almost impossible to completely remove the uremic toxins retained by impaired renal function, which cause disturbances of several functions of PMNs [3]. Deranged functions of PMNs contribute to the increased risk of bacterial infections and represent a main cause for the enhanced risk of morbidity and mortality among chronic kidney disease (CKD) patients [25].

2.3 NATURAL KILLER (NK)

Natural killer (NK) cells provide a first line of immune defense towards infections and tumors, NK cells are also thought to play a role in autoimmune diseases and transplant rejection [56-57]. Additionally, NK cells are not a homogeneous population. Two distinct populations of human NK cells can be identified based upon their cell surface density of CD56 [58]. In contrast to adaptive response, NK activation provides an immediate immune response to pathogen-induced changes tumors [56-57]. Through their activating and inhibitory receptors, NK cells sense cellular target ligands that modulate their potential to kill target cells [57].

There is comparatively little information regarding the role of NK cells in CKD, and the studies in the current literature report conflicting results [56]. Of the previous studies examining NK cell function and renal failure, some report increases in NK cell numbers [59-61], or decreases in numbers and cytotoxic activity [56-57, 62-66] or no change [67-68]. Whereas, the recent studies are for that NK cells counts were statistically significate lower in HD compared to healthy individuals [57, 66]. It is possible that this change may be related to improvements in modern dialysis technique and efficiency, water purity, and membranes. Analysis revealed that the type of hemodialysis membrane was the variable with the greatest effect on the cytotoxic activity of NK cells, followed by age [60].

Indeed, a decrease in the cytotoxic activity of the NK cells compared with controls has been found in patients on haemodialysis, in particular those dialysed with cuprophan membranes [60]. The cuprophan membranes were also found to induce a higher degree of NK cell activation, measured as the number of CD16+/HLA-DR+ cells [60, 66]. Patients on chronic haemodialysis have a decreased NK cell activity as indicated by decreased expression of the δ-chain on NK cells, an early marker of NK cell activation [69], and decreased expression of the pivotal activating receptor NKG2D [70]. This decrease might be caused directly by ROS or indirectly by upregulation of the NKG2D ligand [71]. Recently, it has been demonstrated that expression of the activation markers CD69 and NKp44 was increased on NK cells from patients with ESRD [70].

There was a correlation between NK cytotoxicity and phosphate [72]. This is an interesting finding in light of the increasing evidence supporting a role for phosphate in cardiovascular disease and increased mortality [73], not only in the ESRD population [74-75], but also in populations without CKD [76], and the emerging evidence for the role of NK cells in atherosclerosis. Furthermore, the treatment with calcitriol increases the circulating level and the cytotoxic activity of NK cells in dialysis patients [77].

In spite of this knowledge, information on NK cells in hemodialysis patients is still scanty and the results obtained are inconclusive [60]. The high incidence of cardiovascular disease in this patient population with more evidence of the contributing role of the immune system, in particular NK cells, to atherosclerosis stresses, show the need for further studies to evaluate the role they have to play in CKD patients and their link with vascular calcification.

2.4 MONOCYTES

Monocytes play a key role in host defense against microbial infections. They engulf microbes, infected cells, and tissue debris directly or via intermediary proteins such as antibodies or complement components. Monocytes/Macrophages participate in healing of the damaged tissues, development of local and systemic inflammation and oxidative stress via production of cytokines and ROS, release of growth factors, metalloproteinases, and tissue factor [1].

Patients with ESRD typically have an increased number of circulating proinflammatory monocytes compared with healthy controls [70]. These preactivated monocytes with increased expression of integrin and TLRs (TLR2 and TLR4) express high levels of TNFα, IL-6 and IFNγ upon stimulation [26-27, 69-70, 78]. The over produce of proinflammatory cytokines such IL-12 is associated with reduced efficacy of the vaccination response in these patients [79]. Il-12 shifts the globally reduced activation of T helper cells towards the Th1 function. This causes further deterioration of the antibody response to vaccination antigens [78].

The reason for monocytes preactivation is not absolutely known, but frequent infections, degree of uraemia, systemic inflammation, endotoxins in dialysis solution and contact with the dialysis membrane could all be involved in this situation [1-2, 69-70, 78]. The possibility exists that activation of monocytes by the dialyzer might result in upregulation of TLR4 [70].

However, decreased phagocytic activity has been documented [24, 80-82], after the hemodialysis session by cellulose acetate membrane [3].

Interestingly, downregulation of proinflammatory response might be influenced by the production of the anti-inflammatory cytokine, IL-10 [78, 82]. Reduced production of IL-10 in a subset of patients with ESRD might prevent adequate downregulation of harmful excessive proinflammatory cytokine responses in these patients, resulting in increased inflammation [83-84].

MCP-1 (monocyte chemoattractant proteinand), a potent monocyte attractant, exerts its effects through binding to G-protein-coupled receptors on the surface of leukocytes targeted for activation and migration. The role of MCP-1 and its receptor CC chemokine receptor 2 (CCR2) in monocyte recruitment during infection or under other inflammatory conditions is well known [85].

Numerous studies suggest that 1,25-$(OH)_2D_3$ has an anti-inflammatory effect. Vitamin D_3 may play an important role in the prevention or treatment for induced inflammation in monocytes or macrophages by down-regulation of LPS-induced MCP-1 [85].

It should be noted that in uremic patients, monocytes undergo accelerated apoptosis in vitro compared to control subjects [86-88]. This apoptosis through activation of caspase 3 [87], seems to be closely related to the severity of uraemia and type of dialysis therapy [88]. Several studies have shown that cultured monocyte cells from patients with CKD are less able to stimulate T cells than those from healthy controls, independent of the maturation stimulus used [80]. Monocytes and monocyte-derived dendritic cells have been shown to display decreased endocytosis and impaired maturation when cultured in uremic serum [27] or when obtained from ESRD patients [26, 70]. Thus, Ruiz et al. [34] showed that the internalization of opsonized particles by monocytes, via their receptors for the Fc fragment of IgG, is reduced in hemodialysis patients, suggesting that their ability to present antigen is also altered [2].

Finally, this finding might be related to the decreased expression of the pivotal costimulatory molecule, CD86 (B7-2), in response to a uraemic environment [70, 78, 89-90]. Indeed, previous studies indicated that a lack of CD86 expression on antigen presenting cells was an important factor in uraemia-associated T-cell dysfunction [70, 78, 90].

3 COMPONENTS OF THE ADAPTIVE IMMUNITY

In addition to profoundly affecting the structure and function of the innate immune system, ESRD adversely impacts the agents of adaptive immunity [1].

3.1 LYMPHOCYTES T CELLS (LT)

T cells represent a major component of adaptive immune system and play a central part in cell mediated immunity [1]. In the initial stages of adaptive immune response, exposure to antigen leads to clonal expansion and differentiation of antigen-specific naive T cells, resulting in generation of the memory T cells and effector T cells [91]. At the conclusion of an immune response, effector T-cell populations contract and only a small number of the given memory T cells are maintained [91-92]. Effector T cells perform their effector function via secretion of cytokines and destruction of target cells [93].

The increased rate of infections, together with an impaired response to vaccination and a common failure of tuberculin skin test to diagnose latent tuberculosis indicate that the adaptive immunity is weakened in the ESRD population [93-94]. Indeed, ESRD induce a state of immunodeficiency that involves T cell–mediated responses [89, 95-97]. CD4+/CD8+ ratio and the numbers of the naive and CM $CD4^+$ and $CD8^+$ T cells were significantly reduced, whereas the numbers of EM $CD4^+$ and $CD8^+$ T cells were unchanged [93-94, 98-99].

The mechanism responsible for the selective reductions of the naive and CM T cells in the peripheral blood of ESRD patients is not known. The reduction of the given T-cell subpopulations in peripheral blood, combined with a reduced lifespan, may be due either to increased apoptosis or accelerated activation and differentiation of T cells into EM T cell subsets [95-97, 100]. The latter is plausible as dialysis-dependent patients are commonly subject to repetitive exposure to microbial products and other antigenic stimulations that may lead to accelerated turn over and exhaustion of the naive and CM T cells [92-93].

Increased T cell activation associated with immunodeficiency suggests that activated T cells may be driven to apoptosis [95]. Several observations suggest that the reduction in the numbers of naive and CM T cells in ESRD patients may be due to heightened susceptibility of the activated T cells ($CD69^+$ T cells) to apoptosis [95-97] via death receptor Fas (CD95) and its

ligand FAS L (CD95L) is found [96]. It should be noted that $CD45RO^+$ memory cells, which include CM cells, are especially susceptible to apoptotic cell death [97].

The magnitude of the naive and central memory $CD4^+$ and $CD8^+$ T cell depletion is directly related to severity of azotemia, oxidative stress, secondary hyperparathyroidism and iron overload [93]. A significant part of immune alterations in the course of ESRD could probably be attributed to the presence of protein energy wasting (PEW) [101].

Th1 lymphocytes are more prone to apoptosis than Th2 cells in HD patients [97, 102], these patients still present with significantly elevated Th1 levels [94] leading to an increased Th1/Th2 ratio [5]. A possible explanation for the increase in the Th1/Th2 ratio in HD patients could lie in increased production of IL-12, a monokine that acts on T lymphocytes by increasing INFγ production and decreasing IL-4 production, therefore promoting their differentiation into Th1 type [103-104].

It is now acknowledged that altered T lymphocyte function, found in ESRD, can be attributed to impaired function of APCs [78, 94], because T-cell activation by APCs is dependent to a great extent on TLRs. Indeed, decreased TLR4 expression in ESRD patients has been associated with decreases antigen presentation capabilities of dendritic cells and macrophages by alterations in costimulatory molecules (CD80, CD86) [104-105].

Increased apoptosis and marked reduction of the Treg cells ($CD4^+$ $CD25^+$ $FoxP3^+$ T cells) in ESRD dialysis patients was demonstrated, leading to impaired regulation by Treg [106]. Given the critical role of Treg cells in mitigating inflammation, nTreg cell deficiency and dysfunction in ESRD population must contribute to the prevailing systemic inflammation and its cardiovascular and numerous other complications.

3.2 LYMPHOCYTES B CELLS (LB)

B cells contribute to the immune system by producing antigen-specific antibodies [1]. Similar to T cells, progressive loss of renal function is associated with a gradual decline in circulating numbers of B cells, eventually leading to marked B-cell lymphopenia in patients with ESRD [100, 107-109]. Although all of the known B-cell subsets are affected, this decline is most evident in the naive and memory B cell compartments [70, 110].

Indeed, depletion of several B cell subtypes in adult patients with ESRD was demonstrated. The observed B cell lymphopenia was accompanied by elevated levels of IL-7 or BAFF (also known as tumor necrosis factor ligand superfamily member 13B), which are the key B cell differentiation and survival factors. Thus, down regulation of BAAF receptor in uremic environment may interfere with the maturation and differentiation of B cells [109]. An alternative mechanism can account for B cell lymphopenia; the uremic milieu may increase susceptibility of B cells to apoptosis in ESRD patients [94]. Effectively, it is reported an increased apoptosis of B cells associated with decreased expression of the anti-apoptotic molecule Bcl-2 in ESRD patients [111].

Analysis of T lymphocyte intracellular cytokines revealed that differentiation to Th1 lymphocytes dominates in HD patients [103]. Suppression of the Th2 lymphocyte differentiation pathway impairs B lymphocyte function and decreases antibody production against protein antigens [109, 112]. Serum concentrations of immunoglobulins are generally low in patients with ESRD but within the normal range [113]. However, it has been documented that Ig levels, serum IgG isotypes, and both IgM and IgA production are normal in dialysis patients [94]. Even more a change of IgG subclasses was reported, with elevated levels of IgG_3 prior to immunisation [114].

The reasons for these conflicting results in studies of immunoglobulins in uraemia are unclear, but may result from defective production of antibodies of individual subclasses in response to certain types of antigen but not others [114]. Indeed, the serological response to strong antigenic stimuli such as CMV is not affected in ESRD patients [115]. However, the response to pneumococcal vaccines (T-cell-independent vaccines) is reduced in these patients compared with that of healthy controls [70, 114]. In addition, IgG anti-pneumococcal responses were predominantly of the IgG_2 and to lesser extent IgG_1 subclasses, while the IgG response against tetanus toxin was largely IgG_1 with smaller amounts of IgG_4 and IgG_3. More, the post-immunization serum levels of IgG_1 and IgM antibody against both antigens were significantly reduced in the uremic patients compared with controls [114].

This would be in keeping with decreasing antibody responses to hepatitis B vaccines in HD patients compared with healthy subjects. Only 50-75% of adult ESRD patients develop protective antibodies against the hepatitis B virus surface antigen after vaccination [110]. Note that, the injection of GM-CSF improves the immunization response in IRC subjects [116, 117]. This is not the case of injections of interleukin-2 or interferon γ [118, 119]. However, GM-CSF activates the APCs. Dysfunction of antigen presentation could be causing the deficiency of humoral immunity in hemodialysis patients.

4 CONCLUSION

Disturbances of immunity system in ESRD patients are many and diverse. They involve both the innate and the adaptive systems, generating a complex and still not fully understood immune dysfunction.

The main causes of death in patients with chronic kidney disease are cardiovascular and infectious diseases, both being pathologic processes closely linked to immune function. Therefore, measures aimed at attenuating immune abnormalities in ESRD should be a main research area as this could lead to increased survival and better quality of life in HD patients.

We recommend launching a national mass screening program for CKD. This targeted screening is recommended in populations at risk, namely diabetes and / or hypertension, which account for nearly 50% of incidents dialysis.

In perspective, we plan to conduct a study on the immune system perturbations in CKD Moroccans patients during hemodialysis, with introducing of immune function markers.

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