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Immune dysfunction in patients with end-stage chronic renal disease

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This literature review presents an immune system disorder in end-stage renal disease (ESRD), emphasizing the specific role of uremia and related changes. Finally, on the basis of new relationships between the changes in the immune system of ESRD patients, it emphasizes the potential role of the immune dysfunction as the main cause of the high mortality in this patient population and the need for further research in this area.

Keywords: immune dysfunction, uremic toxicity, chronic kidney disease, inflammation.

Rationale. The changes in the immune system in ESRD represent a complex problem. On the one hand, hypercytokinemia is a typical feature in uremia, and is probably associated with the accumulation of proinflammatory cytokines due to a reduced renal function, and their impaired elimination from the blood [1, 2], on the other hand, it is associated with the immunosuppression because of the impact on immunocompetent cells. Patients with ESRD have chronic stimulation of macrophages induced by inflammation and oxidative stress [3]. A number of authors [4] have found that monocytes in the patients receiving peritoneal dialysis are hyporesponsive to lipopolysaccharides of bacterial cell walls (compared to

hemodialysis patients), as they produce less IL (interleukin)-1β and TNF (tumor necrosis factor)-α. The monocytes and dendritic cells cultured on uremic serum obtained from ESRD patients demonstrated a decreased endocytosis function and an impaired maturation [5, 6]. K.Anding et al. noted decreased bactericidal capacity of the hemodialysis patients neutrophils compared to the control group [7]. The authors suggest that dialyzable substances might impair neutrophil functions. These impairments can be caused by the impact of uremic solutes on the balance between the processes of neutrophil apoptosis and necrosis [8]. The examples of uremic solutes that affect neutrophil apoptosis include the light chains of immunoglobulins (Ig), glycated end products, oxidized low-density lipoproteins, and TNF-α [9, 10]. ESRD causes the imbalance of the cytokines that are characterized by hypercytokinemia, and the accumulation of anti-inflammatory factors, such as IL-10, as well as pro-inflammatory cytokines such as TNF-α, and IL-6 [11, 12]. In addition to uremia, the membrane bio-incompatibility and the endotoxins that can enter the blood at back filtration during a hemodialysis session cause a leukocyte activation [13], which, in turn, increases the granulocyte adhesion into the membrane at hemodialysis, leading, in turn, to leukopenia [14].

In vitro studies have demonstrated a T-cell proliferation decrease in uremic environment. T-helper lymphocytes (Th cells) play a key role in the regulation of immune response. Thus, several Th1 cells produce proinflammatory cytokines, in particular, such as TNF-α, IL-12 and IFN (interferon)-γ. Th2 cells, in turn, produce mainly IL-4 and IL-5 [15, 16].

Cytokines pose diverse effects on the immune response. So, Th1 cells activate macrophages and neutrophils, while Th2 cells are involved in

promoting humoral immunity. An imbalance between Th1 and Th2 cells predisposes to the progression of vascular atherosclerotic lesions.

After a hemodialysis treatment session in a patient with ESRD, the levels of Th1 cells remain elevated which leads to the distortion of Th1/Th2 cell ratio [17]. The Th1/Th2 debalance at hemodialysis treatment can possibly be explained by the increased production of IL-12, the monokine that acts on T-cells **by** raising INF-γ and lowering the production of IL-4, thereby improving Th1 cell differentiation e[17]. It has been proved that the altered functions of T-cells in ESRD are associated with the impaired function of antigen-presenting cells (APCs) [18]. This response is antigen-specific and requires the presence of the antigen. It is based on the activation of two main types of lymphocytes, namely T- and B-cells. Naive T-cells in the thymus are activated by the signals such as the processed bacterial cell wall components associated with the major histocompatibility complex (MHC). This turns them into functional T-cells that must perform a killer function (T-killer cells) or run the immune response (T-helper cells). B-cells that bind specific foreign antigens are converted into plasmatic ones and initiate the production of specific antibodies. After a successful elimination of foreign pathogens, some lymphocytes form the memory for a further stronger response to the pathogen invasion. T-cells require two signals for their activation. One of them is a complex of a peptide with MHC molecule, and the other is the signal mediated through CD80- and CD86-molecule production on APCs. The CD80- and CD86-molecule production is controlled through recognition receptors, the so called Toll-like receptors (TLRs) [19]. One of the main causes of B-cellular lymphopenia in hemodialysis is an increased apoptosis of B-cells [20]. Nevertheless, it has been documented that Ig levels in patients on dialysis remain normal. A

compromised immunity in ESRD can be explained by protein-energy insufficiency [21]. This condition in ESRD correlates with increased morbidity and mortality [22] and is associated with lymphocytopenia, and impaired T-cell function [23, 24].

Functional disorders of monocytes, neutrophils, and dendritic cells are directly related to the risk of infection in this patient population [25]. An impaired Th cell maturation in patients on dialysis results in the immune system dysfunction and the susceptibility to infection. The lack of immune response to a vaccine against hepatitis B, influenza virus, *tetanus* or *diphtheria* is also believed to be caused by the T-cell functional alterations.

TLR functional impairments in uremia may lead to an insufficient prevention of urinary tract infections. The most widely studied among TLRs are the TLR4, the receptor that recognizes the lipopolysaccharides in the cell wall of *E. coli* that is the cause of urinary tract infections in up to 80% of cases. In humans, TLR4 polymorphism was observed to be associated with an increased susceptibility to infectious diseases, including a septic shock [26]. The patients with the disorders at TLR4 level are more susceptible to infections caused by Gram-negative bacteria. TLRs recognize different general pathogen constituents such as lipopolysaccharides, peptidoglycans, RNA viruses, and bacterial oligodeoxynucleotides [27, 28]. TLRs stimulate the phagocytosis functions and complement activation pathways by means of numerous cytokines such as IL-1β, IL-6, and TNF-α. TLRs are also involved in the maturation of dendritic cells that have the function of presenting the antigen to lymphocytes, thereby activating them. In patients with ESRD, urinary tract infections are a common problem, and the decreased urine output may predispose to the damage of the physical barrier (low urine flow) which facilitates the invasion of the urinary tract with

pathogenic microorganisms; and the impairment of TLR function may result in inflammation, possibly contributing to a further loss of the residual renal function. A significant increase in the level of mannose-binding lectin [29] have been reported in ESRD. Its high blood level in the pre-transplant period is associated with worse patient survival after simultaneous kidney and pancreas transplantation [30]. For example, a high level of mannose-binding lectin in infected patients on hemodialysis has been associated with an increased mortality.

Conclusion

Thus, uremia is associated with the immune system dysfunction and is characterized by the immunosuppression that probably contributes to a high prevalence of infections due to an impaired white blood cell proliferation, and also by a pronounced immune activation as a result of inflammation, and by severe complications. The immune dysfunction in uremia creates a significant risk of premature mortality and infectious complications. Measures aimed at identifying immune disorders in ESRD should be a major area of research because this can help to improve the treatment outcomes.

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