Review

Dialysis-Induced Immune Dysregulations and Their Possible Impacts on COVID-19

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Hemodialysis (HD) patients display metabolic and immunologic alterations that renders their immune responses to be dysregulated. These patients generally have problems in mounting effective immune responses against pathogens such as viruses. On the other hand they typically have higher levels of inflammatory cytokines in their peripheral blood. Both of these features may work in favor of COVID-19. Since robust immune responses are needed to prevent infection in the initial stages of COVID-19, the impaired immune system may not be able to cope effectively with the highly replicating SARS-CoV2. In advanced stages of the disease wherein the inflammation as well as the cytokine storm are the core players, a high baseline inflammatory cytokines could intensify and substantially exacerbate the immunopathological situation. Presence of COVID-19 in HD patients may also be a complex immunological condition. Immunological alterations in HD patients and their potential effects on the fate of the SARS-CoV-2 infection are discussed here. Case reports describing the occurrence of COVID-19 in HD patients have also been reviewed in this study.

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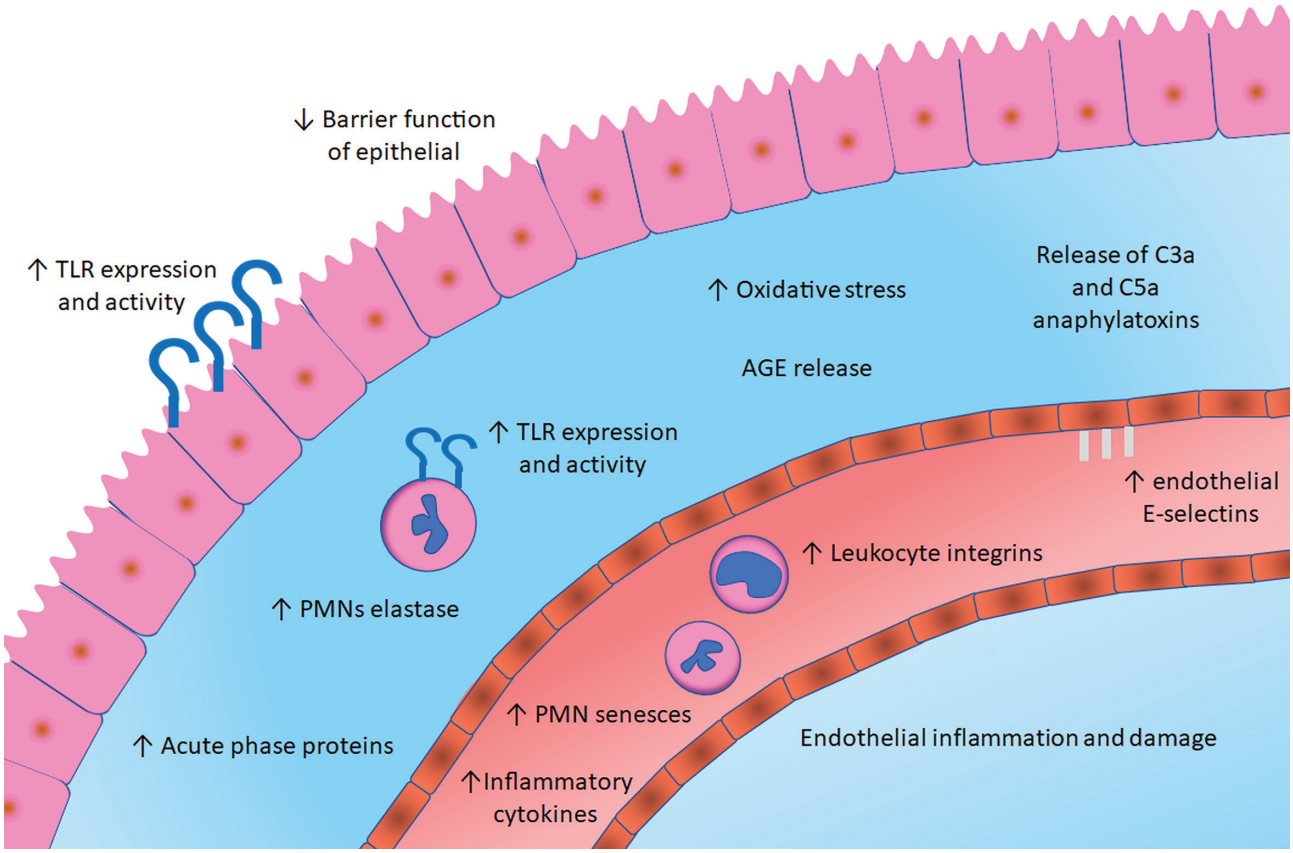
INTRODUCTION

Hemodialysis (HD) is a life-saving treatment for numerous end-stage renal disease (ESRD) patients. Sustained uremia and consistent contact with dialysis membranes lead to alterations in either innate or adaptive immunity. Urea results in the formation of several new molecules in combination with other substances, some of which exhibit pro-inflammatory properties. Urea can even induce various post-transcriptional changes in proteins that makes them pro-inflammatory and in some cases, immunogenic.[1,2] On the other side, dialysis membranes can activate serum complement components resulting in the release of anaphylatoxins and inflammatory mediators.[3,4] A summary of uremic toxins and their possible effects on immune cells are presented in Table 1. HD is usually followed by lymphopenia and neutrophilia.[5] Monocytes of HD patients exhibit phenotypic differences with monocytes of healthy individuals and show weaker effector properties.[6] Innate immunity plays a crucial role in the establishment of systemic inflammation in HD patients.[7] Figure schematically illustrates various dysregulation in the immune system of HD cases. Sustained inflammation existing in HD, causes naïve T cells to experience senescence prior to maturation and activation.[8] Examples of the alterations in the immune cells of maintained HD patients are summarized in Table 2. For example, uremic toxins have been reported to adversely affect the outcome of influenza vaccination.[9] Also, HD has been associated with perturbations in serum levels of some hormones and growth factors.[10–14]

Despite a sustained inflammation, the immune system of HD patients fails to establish functional responses against a myriad of pathogens. These patients usually exhibit higher morbidity and

Table 1. Examples of Uremic Toxins and Their Impact on Monocyte/Macrophages and Lymphocytes

Uremic Toxin	Effect on Monocytes and Lymphocytes	Reference
Phenylacetic Acid	Decrease in iNOS expression in monocyte/macrophages	42
Guanidino Compounds	Pro-inflammatory and anti-inflammatory effects on monocytes	43
Indoxyl Sulfate	Macrophage shift to anti-inflammatory and pro-fibrotic phenotype	44
Methylglyoxal	Monocyte apoptosis as a result of oxidative stress	45
P-cresyl Sulfate	Decrease in peripheral blood B cell and NK cells Decrease in IFN-γ producing Th1 cells and IFN-γ production In high concentration, disturbs oxidative burst, phagocytosis, antigen presentation, and T cell activation of monocyte/macrophages	46–48



Alterations in the Immune System of Maintained Hemodialysis Patients. Uremic toxins and complement activation are two main causes of the sustained inflammation in hemodialysis patients. Uremic toxins increase the expression and activity of TLR2 and TLR4 in neutrophils and epithelial cells that lead to an increase the in pro-inflammatory cytokine levels. On the other hand, complement-derived anaphylatoxins trigger the release of pro-inflammatory cytokines and cause the activation of endothelium. Sustained inflammation seems to decrease the potential of the adaptive immune system in establishing strong immune responses (Abbreviations: PMNs, polymorphonuclears; AGE, advanced glycation end products).

Table 2. Alterations in Immune Cells in Maintained HD

Immune Cell	Change in Counts	Change in Function	Reference
PMNs	↓	Apoptosis, Senesce, Impaired Migration	49,50
Monocyte Macrophages DCs	↓	Impaired Maturation, Decreased Endocytosis and Antigen Process, Disturbed Cytokine Response	51
NK Cells	↓	Decrease in NKG2D Activating Receptor Expression	52
T Cells	Th1 ↓, Th2, Th17, Treg ↑	Apoptosis, Decreased IL-2 Production, Increased IDO Expression, Downregulation of Zeta-chain	14,53,54
B Cells	↓ Breg ↑	Apoptosis, BAFF Survival Receptor Downregulation, Impaired CD40/CD40L Interaction	55–59

mortality rates facing infections with the bacterial and viral pathogens.[15–17]

IMMUNE RESPONSE AGAINST COVID-19

COVID-19 is a serious pandemic health problem threatening the lives of millions of people, worldwide. This infection could be immunologically divided into two stages; the incubation stage and the severe stage. During the incubation period, effective immune responses are required for limiting the virus propagation and its spread through the contaminated cells. Efficient and specific T and B cell responses can prevent the progression of the infection. The susceptibility of host such as HLA background could be a determining factor in the fate of the infection. So that, a proportion of HLA molecules are capable of presenting specific antigens more potent than the others. The better the antigen presentation, the better the effector immune response. This is one of the explanations for the different susceptibilities to specific infections in different individuals.[18] When an HLA haplotype is unable to present the key pathogen-associated antigens efficiently, the effector immune responses will fail to establish and this will allow the highly replicating virus to get spread out, resulting in the progression of the infection to severe stage. During the incubation period, strategies for reinforcing the immune system such as convalescent plasma therapy and pegylated IFN-α could be beneficial.[19–22] These boosters might increase the potential of the host to establish endogenous protective responses against SARS-nCoV-2. As the virus propagates, ACE2 expressing tissues such as intestine and kidney could be involved that culminate in the shift of infection to the severe stage. Interestingly, use of ACE inhibitors, have been accompanied with poor prognosis in some COVID-19 cases.[23] Tissue damage is accompanied by a massive release of danger-associated molecular patterns (DAMPs). These mediators lead to a sustained systemic inflammation that causes severe alveolar damage. In the severe COVID-19 stage, the majority of attempts should be taken to manage the detrimental inflammation.[18,24]

IMPACT OF COVID-19 ON THE IMMUNE SYSTEM

COVID-19 is represented by severe lymphopenia, atrophy of spleen and lymph nodes, decrease in immune cell population in lymphoid organs, and heavy monocyte/macrophage but not lymphocyte infiltrations into the involved tissues.[25] Although a robust immune response is required for the elimination of virus-contaminated cells and limitation of the infection spread in initial steps of COVID-19, a sustained highly active immune response results in a systemic cytokine storm (CS). Activated monocytes and T cells are the main sources of cytokine release in response to the highly replicating virus. A high magnitude of pro-inflammatory cytokines can cause complicated consequences in multiple organs. Several conditions such as rheumatologic diseases, infections, and cancer immunotherapies can cause a similar CS.[26] In the case of infection, a localized cytokine response can eventuate into a systemic CS. During severe COVID-19, heavy pro-inflammatory cell infiltrations and CS are the main explanations for the progressive alveolar tissue damage and acute respiratory distress syndrome (ARDS) that is the main cause of mortality in COVID-19.[18,24] Unlike other CS situations in which the hepatosplenomegaly is evident,[26] spleen and lymph nodes undergo an atrophy in COVID-19. Regarding that lymphocytes are not abundant neither in peripheral blood nor in infiltrations, it has been declared that these cells are destroyed as a result of a sustained CS.[25]

Pro-inflammatory cytokines not only exert detrimental effects on organs such as kidney and liver[26] but also contribute to alveoli endothelial and epithelial cell activation. Upon activation, these cells acquire a proinflammatory phenotype by upregulation of cell adhesion molecules, pattern recognition receptors (PRRs) such as TLRs, and other inflammatory mediators.[18] One of the important events triggered by CS is the upregulation of hyaluronic acid synthase-2 (HAS-2) enzyme. During COVID-19, a high activity of HAS-2 causes an extensive accumulation of hyaluronic acid in alveolar spaces. Regarding that hyaluronic acid is capable of water absorption in magnitudes even 1000 times higher than its molecular weight,[24] this phenomenon results in the formation of a jelly-like substance in alveoli that its accumulation disturbs the normal alveolar function.[27] Therefore, one of the important mortality mechanisms of COVID-19 is somewhat an immunopathogenesis event. This explains the effectiveness of immunosuppressive agents and pro-inflammatory cytokine antagonists in the control of severe and progressed cases of COVID-19.[25]

COVID-19 IN HEMODIALYSIS PATIENTS

Renal complications have been introduced as the important risk-factors for COVID-19. So that, in patients suffering from chronic kidney disease, renal dysfunction is linked with COVID-19-associated mortality. Serum creatinine and BUN levels in these patients have been shown to be positively correlated with poor prognosis of COVID-19.[41] Ossareh and colleagues through a screening on hemodialysis patients in a referral hemodialysis unit in Iran, showed that 28.7% of patients exhibited COVID-19 complication in chest CT while only 15.2 of them were PCR verified. This study demonstrated a high incidence of asymptomatic COVID-19 among hemodialysis patients.[28] Alberici *et al.*[29] reported 21 HD patients with confirmed COVID-19 in Brescia, Italy. Since the majority of these patients were elderly and with various co-morbidities, they were not qualified to be admitted to the intensive care unit. Five of these patients died and four discharged after 7-17 days.

A summary of the demographic characteristics of these cases is presented in Table 3. In a comprehensive study carried out in an HD center in the Renmin Hospital of Wuhan University, 37 HD patients from a total of 230 HD patients were

Table 3. Demographic Characteristics of Some COVID-19 Cases Among Hemodialysis Patients

Case #	Age	Sex	Diabetes	Fever	Abdominal Pain	Dry Cough	Dyspnea	WBC Count $\times 10^9$ /L	Ref
1	61	Male	No	Yes	No	No	No	WBC = 6.84 Neu = 5.69 Lymph = 0.63	60
2	62	Male	No	No	No	Yes	No	WBC = 7.50 Neu = 5.65 Lymph = 0.84	60
3	47	Female	No	Yes	Yes	No	Yes	WBC = 7.73 Neu = 6.28 Lymph = 0.80	60
4	67	Female	Yes	Yes	Yes	No	Yes	WBC = 10.76 Neu = 9.24 Lymph = 0.92	60
5	51	Male	No	No	No	No	No	WBC = 5.03 Neu = 4.29 Lymph = 0.49	60
6	-	Male	Yes	No	-	Yes	Yes	WBC = 3.38 Neu = 2.61 Lymph = 0.53	61
7	79	Male	No	Yes	-	Yes	No	Before HDF WBC = 8.59 Lymph = 0.92 After HDF WBC = 7.90 Lymph = 0.74	62
8	40	Female	No	No	-	Yes	Yes	Before HDF WBC = 15.49 Lymph = 1.01 After HDF WBC = 5.68 Lymph = 0.58	62
9	74	Male	No	Yes	-	No	No	WBC = 3.27 Lymph = 0.43	63
10	76	Female	No	No	-	No	No	WBC = 5.02 Lymph = 0.58	63
11	48	Female	No	No	-	No	No	WBC = 6.57 Lymph = 1.33	63
12	69	Male	No	No	-	No	No	WBC = 6.95 Lymph = 0.86	63
13	35	Male	No	No	-	No	No	WBC = 6.36 Lymph = 0.98	63

HDF: hemodiafiltrations

diagnosed with COVID-19 (9 cases, 16.09%). From 37 COVID-19 HD patients, 72% represented no obvious clinical symptoms, 11% had a fever, 8% experienced fatigue, and 3% had a dry cough. Unlike the non-HD COVID-19 patients, the main mortality causes of HD COVID-19 patients were cardiovascular and cerebrovascular diseases rather than typical pneumonia. Moreover, HD patients with COVID-19 had lower levels of TNF-α and IL-6 pro-inflammatory cytokines compared with non-HD COVID-19 patients.[30] In a study performed by Fontana *et al.*[31] in Italy, it has been shown that age is a determining factor in the incidence of COVID-19 in HD patients. The average age of HD patients with COVID-19 was 75.96 ± 11.09. The COVID-19 positive cases consisted a total of 5% of all HD patients that were mainly male with a body mass index (BMI) of 25.18 ± 4.In the case of the co-morbidities, hypertension consisted 93% and diabetes 53% of all diseases. In a study carried out in Spain, Goicoechea *et al.*[32] explained 36 COVID-19 cases among HD patients that after 7 days, 11 patients out of them were expired. Elderly patients exhibited a trend for higher mortality. On the other hand, patients undergoing hemodiafiltration exhibited a relatively lower mortality rate. In the follow-up study, characteristics such as high LDH, high CRP, and low lymphocyte count were separately associated with a higher mortality rate. In further examination, 61% demonstrated bilateral peripheral ground-glass opacity, 19% exhibited unilateral complication, and 19% had a normal chest. This study reported the mortality rate of COVID-19 in HD patients equal to 30.5% that is much higher than the reported mortality rate for other COVID-19 patients.[33–35] Li *et al.*[36] carried out a double-center study in Wuhan, China. In the first center, 10% of maintenance HD patients and 6% of staff were suspected of COVID-19 that 1.7% of the patients and 2.9% of the staff were PCR-confirmed. In the second center, 46 patients out of 244 HD patients were suspected of COVID-19 that only 7 cases were PCR-confirmed. Among the 46 suspected patients, 6.5% experienced fever, 8.7% had fatigue, and 4.3% had cough while 87% did not show any presentations. There is a report that the incidence of COVID-19 in HD patients is higher than the peritoneal dialysis patient.[37] Yau *et al.*[38] explained 11 HD patients with COVID-19 in Canada that aged between 63 and 72 years, mainly male. They had at-least one comorbidity including hypertension (100%), cardiovascular disease (64%), and diabetes (91%). Patients had a median WBC count of 4.72×10^3 /μL and the median lymphocyte count equal to 0.54×10^3 / μL. In paraclinical evaluation, 100% of patients exhibited high CRP and 83% of them demonstrated active pneumonia in chest radiography. In a study conducted by us, we demonstrated that the patients with a kidney failure etiology of hypertension and those with blood group AB^+ had lower incidence of COVID-19 while lupus nephropathy cases and those with blood group A^+ had higher morbidity rate. We also demonstrated that HD patients with COVID-19 had higher WBC and neutrophil counts compared with other COVID-19 patients.[39]

CONCLUDING REMARKS

Although the impact of COVID-19 on renal damage is not widely accepted,[40] HD-associated immune-dysregulations described above are likely to exacerbate the morbidity and mortality of COVID-19. Considering the elevated incidence of co-morbidities, age status and regular admission to dialysis units and clinics, the morbidity and mortality of COVID-19 in HD patients is comparatively higher. Some case studies have identified a worse path of COVID-19 in HD patients. Inflammatory situation and high immune system activity in HD patients can devastate the immunopathogenic state of COVID-19. Higher baseline inflammatory cytokines lead to quicker and probably stronger CS, which increases the risk of ARDS and multi-organ injury in this population. With regard to the complexity of COVID-19 physiopathology in HD patients, it is important to further examine the effect of HD-associated immune dysregulations on susceptibility to COVID-19.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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