BJMHR
British Journal of Medical and Health Research
Journal home page: www.bjmhr.com

Immune parameters in patients with end-stage renal disease on hemodialysis

Susmitha Karunasree Perumalla[1]*, Girish Namagondlu[2], M.S. Gireesh[3], John Antony Jude Prakash[4], Siddharth Jhunjhunwala[5]

1. BioSystems Science and Engineering, Indian Institute of Science, Bangalore, Karnataka, India.
2.Nephrologist, Medstar Speciality Hospital, Bangalore, Karnataka, India
3. Dept of Nephrology, Ramaiah Medical College, Bangalore. Karnataka, India
4.Professor, Clinical, Microbiology, Christian, Medical College,Vellore
5. Centre for BioSystems Science and Engineering, Indian Institute of Science, Bangalore, Karnataka, India.

ABSTRACT

Renal failure because of chronic kidney disease (CKD) leads to increased accumulation of uremic toxins due to decreased glomerular filtration rates. This in turn has a bearing on other metabolic functions in the body. Hemodialysis in end stage renal disease helps in elimination of toxic metabolites but long-term dialysis and the underlying chronic inflammation could affect immune cell activity, one of the main factors contributing to CKD associated complications and mortality. In this review, we tried to compile the important immune cell types and their different parameters that are altered in hemodialysis patients and the downstream impact of such alterations.

Keywords: Uremia, CKD, hemodialysis, immune cells, cytokines

*Corresponding Author Email: susmitha1297@gmail.com
Received 12 April 2023, Accepted 11 May 2023

Please cite this article as: Perumalla SK *et al.*, Immune parameters in patients with end-stage renal disease on hemodialysis. British Journal of Medical and Health Research 2023.

INTRODUCTION

Chronic kidney disease is a severe health condition contributing to decreased quality of life and a heavy economic burden[1]. Though asymptomatic in the initial stages, several complications develop as it progresses to end-stage renal disease (ESRD). ESRD is characterized by irreversible compromise in glomerular filtration, which results in the accumulation of uremic toxins that have profound deteriorating effects on the body.

Uremic toxins are very heterogenous, and more than 100 have been identified. They have been classified into three categories based on their physicochemical properties; free water-soluble low molecular weight solutes, protein-bound solutes, and middle molecules [2]. Removing these toxins from the body is the chief concern of the clinician, and with the lack of availability of suitable donors for transplants, dialysis remains the only option for many individuals suffering from ESRD.

Hemodialysis (HD) is the most common form of dialysis that helps remove uremic toxins. HD apparatus consists of a dialyzer, dialysis solution (dialysate), tubing to transport blood and dialysate, and a machine to power and monitor the procedure. Dialyzers are commonly made of polyurethane shell within which hollow fibres are suspended in a dialysate. Vascular access is created, through which blood flows out of the body into the dialyzer, where waste products and excess water are removed. The purified blood is returned to the body.

Though dialysis helps in reducing the accumulating toxins and metabolites, the repeated contact of circulating immune cells with dialysis instruments, the constant general low-grade uremic milieu, decreased plasma bicarbonate levels before dialysis, and other factors result in a state of immune activation and chronic inflammation in these individuals. Increased oxidative stress is a hallmark of such immune activation, and oxidative stress predicts survival in HD patients [3]. It leads to increased levels of oxidized lipids and advanced oxidation protein products (AOPPs), which are pro-inflammatory. While these responses can help combat infections and harmful stimuli, they can also become deleterious if uncontrolled. Antioxidant responses gradually diminish with advancing renal failure [4].

Uremic conditions result in compromised intestinal barrier integrity and early onset protein energy malnutrition, which results in generalized malnutrition- inflammation complex syndrome [5]. All these can give rise to auto antigens against the kidneys [6]. The kidney dependent metabolic and hormonal functions are also affected due to reduced production of vitamin D, renin, and erythropoietin, which in turn have a bearing on the functioning of immune cells. [7]. In addition, dysfunctional apoptosis of cells during renal failure causes defective immune responses [8]. Put together, these changes in immune cells add to the pre-existing complications of ESRD and are thought to increase morbidity and mortality.

Mortality is due to the compounded effect of risk factors like older age group, co-morbid conditions resulting in dialysis-associated complications, and a progressive decline of the immune system. It is well known that mortality in ESRD is mainly due to cardiovascular diseases CVD followed by infections [9,10]. Though the usual risk factors of CVD like hypertension, diabetes mellitus, and dyslipidemia are present in CKD patients, the not-so-usual risk factors like malnutrition, volume overload, anemia, and oxidative stress associated with CKD accelerate CVD progression in CKD [11]. Hypercytokinemia is strongly associated with CVD and poor outcome in ESRD. Mortality due to sepsis was observed to be about 100 to 300 times more likely in individuals on hemodialysis than the general population [9,10]. Similarly, CKD mortality due to sepsis was higher than any other chronic medical condition [12]. Patients with eGFR levels as low as 30mL/min/1.73m2 and below but not started on dialysis have increased risk of blood stream infections and sepsis [13]. One reason for increased number of infections could be the decreased phagocytic ability of immune cells [14]. This review focuses on the changes that immune cells undergo in patients on hemodialysis.

Immune parameters deregulated in hemodialysis

Cytokines

The roles of TNFα and IL-6 have been extensively studied in CKD patients including those undergoing dialysis. The levels of TNFα and IL6 are increased in pre-dialysis uremic patients when compared to healthy subjects [15]. Both cytokines are pro inflammatory, and the resulting renal inflammation is likely to lead to a pro-fibrotic state in ESRD [16]. They also alter the phenotype of vascular smooth muscle cells and promote vascular calcification [17] through various metabolic and coagulant mechanisms [18] thus accelerating atherogenesis [19]. In addition to these cytokines, the accumulation of others, such as IL1β, also adds to the systemic low-grade inflammation. They are incriminated in acute symptoms like fever and hypotension during dialysis. This hypotension could cause a compromise in tissue perfusion leading to organ complications. Gut hypoperfusion can lead to systemic endotoxemia, which contributes to the beginning of chronic inflammation in dialysis [20].

Apoptosis and release of cell free DNA in dialysis patients has been shown to trigger the release of pro-inflammatory cytokines (IL-6) from monocytes [21]. IL10 is an anti-inflammatory cytokine, and defective IL10 synthesis seen in endotoxin stimulated peripheral blood mononuclear cells (PBMCs) of HD patients is suggestive of a deficient feedback inhibition of proinflammatory cytokines, which could add to the chronic inflammatory state [22]. IL18, another proinflammatory cytokine, has been shown to be increased in HD [23]. The overall increase in cytokines is responsible for changes in many downstream effects tipping the balance usually maintained in the body.

Other factors that add to the deteriorating situation are erythropoeitin resistance [24] leading to anemia, an increase in migration inhibitory factor (MIF) that activates macrophages to release pro inflammatory cytokines, and increase in NFκB signalling [25]. Cytokine levels are affected by more than one parameter, such as residual renal function, type of dialyzer used, variable ultrafiltration rates, existing co-morbid conditions, and patient's current medications [26]. A study conducted on a cohort of dialysis patients to arrive at immunological variables associated with survival and mortality over a 3-year mean follow-up period revealed that increased IL-2, IL-4, IL-5, and IL-12 improved survival, while an increase in IL-1, TNF-α, IL-6, and IL-13 levels were associated with higher relative mortality risk [26]. Since these cytokines are intricately connected, mere associations should not be taken in isolation when assessing the overall status of the individual. Instead, these results should be interpreted with caution, and the rise or fall of upstream or downstream cytokines must be considered.

Neutrophils and NK cells

The etiology of infections that cause mortality in dialysis patients is commonly bacterial [27]. The barrier mechanisms in place and the action of innate immune cells can usually combat common bacteria. But they may be compromised in individuals with CKD, including individuals undergoing dialysis. In fact, in dialysis, the acute phase immune responses are commonly due to bio-incompatible membranes and contamination of dialysate fluid [28,29]. On encountering the dialysis equipment, neutrophils can set off the first inflammatory response in the uremic setting through spontaneous activation, ROS production and NET formation [30]. A concomitant apoptosis is set up to combat the excess inflammatory response. The balance between this spontaneous activation and apoptosis could become erratic, complicating the immune response to infections [31,32]. Neutrophil activation is also dependent on intracellular Ca2+ concentration, and increasing concentrations of intracellular Ca2+ in HD patients is responsible for decreased reactivity of neutrophils upon stimulation [33].

One form of cell death in neutrophils is by forming neutrophil extracellular traps (NETs). NETosis releases DNA histone complexes, and when cell-free DNA levels were compared pre and post dialysis; they were found to be elevated in the latter. These results also correlated with increased apoptosis markers [34]. Thus, the level of cell-free DNA has been established as an independent predictor of all-cause mortality in HD patients. One of the most common co morbid conditions contributing to chronic renal failure is diabetes mellitus, and elevated glucose levels can trigger NETosis. Additionally, reactive oxygen species (ROS) can be induced by advanced glycation end products (AGEs) in DM, increasing NETosis. Over a period of time, immune exhaustion takes over, leading to premature aging and tissue degeneration [8]. Neutrophils in HD are marked by decreased chemotactic, phagocytic and

bactericidal capacity in dialysis patients [35,36] and this decrease in functional ability likely results in increased infections.

In a study investigating the effect of dialysis modality and membrane type on NK cells and neutrophils which are representative of innate immunity, it was observed that NK cell numbers and neutrophil phagocytic ability decreased irrespective of the modality or membrane type [37]. Also, many studies have shown that NK cell cytotoxicity decreased in HD patients. In vitro studies that used the uremic serum on NK cells from healthy donors showed decreased NK cell cytotoxicity [38]. Uremia is marked by a state of constant oxidative stress and inflammation. This down regulates the signalling mechanism when receptor ligands are engaged on the surface of the cells [39]. This decrease in the numbers and functional ability of NK cells in uremia could lead to an increased propensity for viral infections [40].

Dendritic cells, Monocytes, and Macrophages

Dendritic cells are the major antigen presenting cells linking innate and adaptive immunity. The differentiation of monocytes to dendritic cells (DCs) is impaired in HD patients. In vitro experiments to evaluate the function of DCs derived from monocytes have suggested that these cells in uremic sera showed decreased endocytosis and maturation. At the same time, there was an increase in apoptotic and necrotic mechanisms [41]. Grindt *et al.* showed that HLA DR expression on monocytes did not differ between HD patients and controls (patients with chronic renal failure but not on dialysis). Still, there is a marked decrease in the expression of CD86 in the monocytes of patients on dialysis. While HLA DR represents the first signal in T cell activation, CD86 represents the co-stimulatory signal. Thus, a decrease in the up regulation of co stimulatory molecules was observed, leading to a compromise in the quality of T cell response [42].

The alterations in co stimulatory molecules during the immune response that result in decreased antigen presentation are thought to be due to a decrease in TLR expression in uremia [43]. TLR expression is seen to have been decreased in predialysis conditions; repeated exposure to endotoxins in HD is believed to reduce TLR expression. In such patients, a decrease in TLR 4 during LPS challenge is associated with decreased levels of TNFα, IL1β, IL6 and IL8 [44,45]. Decreased TLR expression may lead to an increased propensity for infection.

IL12 is a pro-inflammatory cytokine predominantly produced by monocytes and DCs, stimulating the production of IFNγ by T cells. Higher levels of IL12 and IFNγ were observed in patients on HD. Under normal conditions, contact with any membrane results in cell activation where there is increased expression of adhesion molecules which results in initial cell proliferation and subsequent exhaustion and apoptosis. It is speculated that there exists a pre activated state of monocytes in dialysis patients owing to the presence of high levels of

IL1β, IL6, IL12 and TNFα in them[46]. To support this suggestion, there are in vitro studies that showed spontaneous apoptosis on contact with dialysis membranes [47]without having to go through classical immune activation, exhaustion, and apoptosis. In dialysis, there are both apoptotic and anti apoptotic phenomena at play. For example, some of the uremic retention solutes like Ig light chains delay apoptosis, but apoptotic factors like AGEs counter this, oxidized LDL and TNFα [48–50]. The evidence for this is also seen in studies that show an increase in transcript levels of apoptotic and anti-apoptotic genes in dialysis patients. [51]. Another school of thought attributes it to the dialysis membranes, which, irrespective of their biocompatibility, can activate complement, and initiate the recruitment of cells of acute inflammation. This is supported by studies on apoptotic markers like cell free DNA, annexin V expression, etc., which have not yielded consistent results in patients on HD [52]. Thus, a consensus could not be reached if it is dialysis per se or the uremic state that is responsible for apoptosis.

The uremic environment up regulates macrophage scavenger receptors (CD36) to help fight pathogens and, in the process, clean up oxidized LDL. This could lead to the formation of foam cells, the initial step in atherogenesis, which results in accelerated subsequent mortality [53]. In CAPD subjects, the phenomenon of peritoneal fibrosis could be determined to an extent by the type of dialysate used. It has been shown that high glucose concentration of dialysate solution polarized macrophages to M2 phenotype, which may contribute to PD related fibrosis [54]. Monocytes and macrophages from PD patients showed an overall hyporeactivity to stimulation and decreased cytokine secretion (IL 1B and TNFα) compared to their HD counterparts [55].

T and B lymphocytes

There is an intricate crosstalk between innate and adaptive immunity. A constant state of uremia may dampen and compromise this phenomenon [8]. CD4+ helper cells can differentiate into multiple functional states defined by the cytokines produced. IL 12, which is produced in response to antigen stimulation by APCs of the innate arm, helps in the differentiation of naïve T cells into Th1 cells. The Th1/ Th2 ratio is higher in HD patients, which could be due to increased levels of pro inflammatory IL12 which triggers the production of IFNγ by T cells and suppressing IL4 [56]. Also, the balance between Th1 and Th2 responses determines the development and progression of atherosclerosis [57]. The net proliferation of T cells in uremic patients is balanced by the rate of apoptosis which could eventually move toward reduced numbers of T cells [51]. However, it has also been shown that HD restores T cell proliferation and co-stimulatory molecule expression in uremic patients, showcasing why dialysis is essential in these patients.

A three-year follow-up study on parameters indicating survival in HD patients showed that improved T cell number and function are associated with improved survival [26].

B lymphocyte numbers could decrease in HD due to the down regulation of B cell activating factor (BAFF) or increased apoptosis [58]. However, antibody production is more or less maintained constant in dialysis patients [24].

Eleftheraides *et al.* mention that the role of acquired immunity in ESRD is best understood in the context of response to vaccines, viral, mycobacterial infections, and delayed type hypersensitivity. In vaccines with protein antigens, the antibody response was much lesser when compared to those with polysaccharide antigens [24]. This highlights the role of T cells in aiding B cells to mount antibody response wherein protein antigen presentation is a T dependent phenomenon, and polysaccharides can do it without the help of T cells. The relative risk of acquiring active TB in HD patients is high [59,60]. Since T lymphocyte interaction with macrophages is responsible for the pathogenesis, a defect in T cell responses is thought to be the reason. Besides, in any delayed type hypersensitivity reactions like the tuberculin skin test in HD patients, the positivity is much lower than the predicted value [61,62].

SUMMARY AND FUTURE DIRECTIONS

Our goal was to provide a concise summary of studies that relate to how specific immune components directly change in ESRD, specifically in individuals undergoing dialysis. From these studies, it is evident that various immune cells and cytokines are considerably altered in ESRD patients undergoing dialysis. However, the literature is inconsistent on the precise dynamical and functional changes among immune cells over the course of dialysis, and hence further research is required. Specifically, studies incorporating analysis of cells both pre- and post-dialysis will help in arriving at meaningful conclusions. In addition, changes to immune cells in the occurrence of infections in patients undergoing dialysis need to be studied in prospective studies where results can be compared to pre dialytic stage taking into consideration the existing co-morbid conditions. Similarly, the mechanics of dialysis procedure involving the various physical components, like the material used in tubing, dialyzer membrane, the flux changes and their bearing on immune cells is another aspect where manipulations can be made towards better outcomes in dialysis patients.

REFERENCE

1. Hill, N.R., Fatoba, S.T., Oke, J.L., Hirst, J.A., O'Callaghan, C.A., Lasserson, D.S., and Hobbs, F.D.R. (2016). Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One *11*, e0158765. 10.1371/journal.pone.0158765.

2. Duranton, F., Cohen, G., Smet, R.D., Rodriguez, M., Jankowski, J., Vanholder, R., Argiles, A., and Group, on behalf of the E.U.T.W. (2012). Normal and Pathologic Concentrations of Uremic Toxins. JASN *23*, 1258–1270. 10.1681/ASN.2011121175.
3. Suvakov, S., Jerotic, D., Damjanovic, T., Milic, N., Pekmezovic, T., Djukic, T., Jelic-Ivanovic, Z., Savic Radojevic, A., Pljesa-Ercegovac, M., Matic, M., et al. (2019). Markers of Oxidative Stress and Endothelial Dysfunction Predict Haemodialysis Patients Survival. AJN *50*, 115–125. 10.1159/000501300.
4. Duni, A., Liakopoulos, V., Roumeliotis, S., Peschos, D., and Dounousi, E. (2019). Oxidative Stress in the Pathogenesis and Evolution of Chronic Kidney Disease: Untangling Ariadne's Thread. Int J Mol Sci *20*, E3711. 10.3390/ijms20153711.
5. Achinger, S.G., and Ayus, J.C. (2013). Inflammation from dialysis, can it be removed? Nephrol Dial Transplant *28*, 770–773. 10.1093/ndt/gfs480.
6. Darrah, E., and Andrade, F. (2012). NETs: the missing link between cell death and systemic autoimmune diseases? Front Immunol *3*, 428. 10.3389/fimmu.2012.00428.
7. Cohen, G. (2020). Immune Dysfunction in Uremia 2020. Toxins (Basel) *12*, 439. 10.3390/toxins12070439.
8. Sharif, M.R., Chitsazian, Z., Moosavian, M., Raygan, F., Nikoueinejad, H., Sharif, A.R., and Einollahi, B. (2015). Immune Disorders in Hemodialysis Patients. *9*, 13.
9. Gansevoort, R.T., Correa-Rotter, R., Hemmelgarn, B.R., Jafar, T.H., Heerspink, H.J.L., Mann, J.F., Matsushita, K., and Wen, C.P. (2013). Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet *382*, 339–352. 10.1016/S0140-6736(13)60595-4.
10. Sarnak, M.J., and Jaber, B.L. (2000). Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney Int *58*, 1758–1764. 10.1111/j.1523-1755.2000.00337.x.
11. Sarnak, M.J., Levey, A.S., Schoolwerth, A.C., Coresh, J., Culleton, B., Hamm, L.L., McCullough, P.A., Kasiske, B.L., Kelepouris, E., Klag, M.J., et al. (2003). Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation *108*, 2154–2169. 10.1161/01.CIR.0000095676.90936.80.
12. Mansur, A., Mulwande, E., Steinau, M., Bergmann, I., Frederik Popov, A., Ghadimi, M., Beissbarth, T., Bauer, M., and Hinz, J. (2015). Chronic kidney disease is associated with a higher 90-day mortality than other chronic medical conditions in patients with sepsis. Sci Rep *5*, 10539. 10.1038/srep10539.

13. James, M.T. (2008). Risk of Bloodstream Infection in Patients With Chronic Kidney Disease Not Treated With Dialysis. Arch Intern Med *168*, 2333. 10.1001/archinte.168.21.2333.
14. Chonchol, M. (2006). Neutrophil dysfunction and infection risk in end-stage renal disease. Semin Dial *19*, 291–296. 10.1111/j.1525-139X.2006.00175.x.
15. Tetta, C., Camussi, G., Turello, E., Salomone, M., Aimo, G., Priolo, G., Segoloni, G., and Vercellone, A. (1990). Production of cytokines in hemodialysis. Blood Purif *8*, 337–346. 10.1159/000169988.
16. Tang, P.C.-T., Zhang, Y.-Y., Chan, M.K.-K., Lam, W.W.-Y., Chung, J.Y.-F., Kang, W., To, K.-F., Lan, H.-Y., and Tang, P.M.-K. (2020). The Emerging Role of Innate Immunity in Chronic Kidney Diseases. Int J Mol Sci *21*, 4018. 10.3390/ijms21114018.
17. 17. Schlieper, G., Schurgers, L., Brandenburg, V., Reutelingsperger, C., and Floege, J. (2016). Vascular calcification in chronic kidney disease: an update. Nephrol Dial Transplant *31*, 31–39. 10.1093/ndt/gfv111.
18. Yudkin, J.S., Kumari, M., Humphries, S.E., and Mohamed-Ali, V. (2000). Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis *148*, 209–214. 10.1016/s0021-9150(99)00463-3.
19. Stenvinkel, P., Heimbürger, O., and Jogestrand, T. (2002). Elevated interleukin-6 predicts progressive carotid artery atherosclerosis in dialysis patients: association with Chlamydia pneumoniae seropositivity. Am J Kidney Dis *39*, 274–282. 10.1053/ajkd.2002.30546.
20. McIntyre, C.W., Harrison, L.E.A., Eldehni, M.T., Jefferies, H.J., Szeto, C.-C., John, S.G., Sigrist, M.K., Burton, J.O., Hothi, D., Korsheed, S., et al. (2011). Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. Clin J Am Soc Nephrol *6*, 133–141. 10.2215/CJN.04610510.
21. Atamaniuk, J., Kopecky, C., Skoupy, S., Säemann, M.D., and Weichhart, T. (2012). Apoptotic cell-free DNA promotes inflammation in haemodialysis patients. Nephrol Dial Transplant *27*, 902–905. 10.1093/ndt/gfr695.
22. Perianayagam, M.C., Jaber, B.L., Guo, D., King, A.J., Pereira, B.J.G., and Balakrishnan, V.S. (2002). Defective Interleukin-10 Synthesis by Peripheral Blood Mononuclear Cells among Hemodialysis Patients. BPU *20*, 543–550. 10.1159/000066958.
23. Gangemi, S., Mallamace, A., Minciullo, P.L., Santoro, D., Merendino, R.A., Savica, V., and Bellinghieri, G. (2002). Involvement of Interleukin-18 in Patients on Maintenance Haemodialysis. AJN *22*, 417–421. 10.1159/000065269.

24. Eleftheriadis, T., Antoniadi, G., Liakopoulos, V., Kartsios, C., and Stefanidis, I. (2007). Disturbances of acquired immunity in hemodialysis patients. Semin Dial *20*, 440–451. 10.1111/j.1525-139X.2007.00283.x.
25. Zaza, G., Pontrelli, P., Pertosa, G., Granata, S., Rossini, M., Porreca, S., Staal, F.J.T., Gesualdo, L., Grandaliano, G., and Schena, F.P. (2008). Dialysis-related systemic microinflammation is associated with specific genomic patterns. Nephrol Dial Transplant *23*, 1673–1681. 10.1093/ndt/gfm804.
26. Kimmel, P.L., Phillips, T.M., Simmens, S.J., Peterson, R.A., Weihs, K.L., Alleyne, S., Cruz, I., Yanovski, J.A., and Veis, J.H. (1998). Immunologic function and survival in hemodialysis patients. Kidney Int *54*, 236–244. 10.1046/j.1523-1755.1998.00981.x.
27. Abbott, K.C., and Agodoa, L.Y. (2001). Etiology of bacterial septicemia in chronic dialysis patients in the United States. Clin Nephrol *56*, 124–131.
28. Hernández, M.R., Galán, A.M., Cases, A., Lopez-Pedret, J., Pereira, A., Tonda, R., Bozzo, J., Escolar, G., and Ordinas, A. (2004). Biocompatibility of cellulosic and synthetic membranes assessed by leukocyte activation. Am J Nephrol *24*, 235–241. 10.1159/000077395.
29. Opatrný, K., Jr (2003). Clinical importance of biocompatibility and its effect on haemodialysis treatment. Nephrology Dialysis Transplantation *18*, v41–v44. 10.1093/ndt/gfg1044.
30. Kim, J.-K., Hong, C.-W., Park, M.J., Song, Y.R., Kim, H.J., and Kim, S.G. (2017). Increased Neutrophil Extracellular Trap Formation in Uremia Is Associated with Chronic Inflammation and Prevalent Coronary Artery Disease. J Immunol Res *2017*, 8415179. 10.1155/2017/8415179.
31. Cendoroglo, M., Jaber, B.L., Balakrishnan, V.S., Perianayagam, M., King, A.J., and Pereira, B.J. (1999). Neutrophil apoptosis and dysfunction in uremia. J Am Soc Nephrol *10*, 93–100. 10.1681/ASN.V10193.
32. Sela, S., Shurtz-Swirski, R., Cohen-Mazor, M., Mazor, R., Chezar, J., Shapiro, G., Hassan, K., Shkolnik, G., Geron, R., and Kristal, B. (2005). Primed peripheral polymorphonuclear leukocyte: a culprit underlying chronic low-grade inflammation and systemic oxidative stress in chronic kidney disease. J Am Soc Nephrol *16*, 2431–2438. 10.1681/ASN.2004110929.
33. Immler, R., Simon, S.I., and Sperandio, M. (2018). Calcium signaling and related ion channels in neutrophil recruitment and function. Eur J Clin Invest *48*, e12964. 10.1111/eci.12964.

34. Korabecna, M., and Tesar, V. (2017). NETosis provides the link between activation of neutrophils on hemodialysis membrane and comorbidities in dialyzed patients. Inflamm Res *66*, 369–378. 10.1007/s00011-016-1010-6.
35. Lewis, S.L., Van Epps, D.E., and Chenoweth, D.E. (1988). Alterations in chemotactic factor-induced responses of neutrophils and monocytes from chronic dialysis patients. Clin Nephrol *30*, 63–72.
36. Vanholder, R., and Ringoir, S. (1992). Polymorphonuclear cell function and infection in dialysis. Kidney Int Suppl *38*, S91-95.
37. Dimitrios, G.S. (2019). The Effect of Dialysis Modality and Membrane Performance on Native Immunity in Dialysis Patients. PRILOZI *40*, 25–32. 10.2478/prilozi-2019-0011.
38. Asaka, M., Iida, H., Izumino, K., and Sasayama, S. (1988). Depressed natural killer cell activity in uremia. Evidence for immunosuppressive factor in uremic sera. Nephron *49*, 291–295. 10.1159/000185078.
39. Eleftheriadis, T., Kartsios, C., Yiannaki, E., Kazila, P., Antoniadi, G., Liakopoulos, V., and Markala, D. (2008). Chronic inflammation and CD16+ natural killer cell zeta-chain downregulation in hemodialysis patients. Blood Purif *26*, 317–321. 10.1159/000130068.
40. Nagai, K. (2021). Dysfunction of natural killer cells in end-stage kidney disease on hemodialysis. Ren Replace Ther *7*, 8. 10.1186/s41100-021-00324-0.
41. Lim, W.H., Kireta, S., Leedham, E., Russ, G.R., and Coates, P.T. (2007). Uremia impairs monocyte and monocyte-derived dendritic cell function in hemodialysis patients. Kidney International *72*, 1138–1148. 10.1038/sj.ki.5002425.
42. Girndt, M., Sester, M., Sester, U., Kaul, H., and Köhler, H. (2001). Defective expression of B7-2 (CD86) on monocytes of dialysis patients correlates to the uremia-associated immune defect. Kidney Int *59*, 1382–1389. 10.1046/j.1523-1755.2001.0590041382.x.
43. Girndt, M., Trojanowicz, B., and Ulrich, C. (2020). Monocytes in Uremia. Toxins (Basel) *12*, 340. 10.3390/toxins12050340.
44. Ando, M., Shibuya, A., Tsuchiya, K., Akiba, T., and Nitta, K. (2006). Reduced expression of Toll-like receptor 4 contributes to impaired cytokine response of monocytes in uremic patients. Kidney Int *70*, 358–362. 10.1038/sj.ki.5001548.
45. Kuroki, Y., Tsuchida, K., Go, I., Aoyama, M., Naganuma, T., Takemoto, Y., and Nakatani, T. (2007). A study of innate immunity in patients with end-stage renal disease: special reference to toll-like receptor-2 and -4 expression in peripheral blood monocytes of hemodialysis patients. Int J Mol Med *19*, 783–790.

46. Girndt, M., Köhler, H., Schiedhelm-Weick, E., Schlaak, J.F., Meyer zum Büschenfelde, K.H., and Fleischer, B. (1995). Production of interleukin-6, tumor necrosis factor alpha and interleukin-10 in vitro correlates with the clinical immune defect in chronic hemodialysis patients. Kidney Int *47*, 559–565. 10.1038/ki.1995.70.
47. Carracedo, J., Ramírez, R., Martín-Malo, A., Rodríguez, M., Madueño, J.A., and Aljama, P. (2001). Role of adhesion molecules in mononuclear cell apoptosis induced by cuprophan hemodialysis membranes. Nephron *89*, 186–193. 10.1159/000046066.
48. Cohen, G., Haag-Weber, M., and Hörl, W.H. (1997). Immune dysfunction in uremia. Kidney Int Suppl *62*, S79-82.
49. Galle, J., Schneider, R., Heinloth, A., Wanner, C., Galle, P.R., Conzelmann, E., Dimmeler, S., and Heermeier, K. (1999). Lp(a) and LDL induce apoptosis in human endothelial cells and in rabbit aorta: role of oxidative stress. Kidney Int *55*, 1450–1461. 10.1046/j.1523-1755.1999.00351.x.
50. Kettritz, R., Falk, R.J., Jennette, J.C., and Gaido, M.L. (1997). Neutrophil superoxide release is required for spontaneous and FMLP-mediated but not for TNF alpha-mediated apoptosis. J Am Soc Nephrol *8*, 1091–1100. 10.1681/ASN.V871091.
51. Friedrich, B., Janessa, A., Schmieder, R., Risler, T., and Alexander, D. (2008). Acute effects of haemodialysis on pro-/anti- apoptotic genes in peripheral blood leukocytes. Cell Physiol Biochem *22*, 423–430. 10.1159/000185486.
52. Atamaniuk, J., Ruzicka, K., Stuhlmeier, K.M., Karimi, A., Eigner, M., and Mueller, M.M. (2006). Cell-free plasma DNA: a marker for apoptosis during hemodialysis. Clin Chem *52*, 523–526. 10.1373/clinchem.2005.058883.
53. Chmielewski, M., Bryl, E., Marzec, L., Aleksandrowicz, E., Witkowski, J.M., and Rutkowski, B. (2005). Expression of Scavenger Receptor CD36 in Chronic Renal Failure Patients. Artificial Organs *29*, 608–614. 10.1111/j.1525-1594.2005.29097.x.
54. Lin, Y.-F., Chang, D.-M., Shaio, M.-F., Lu, K.-C., Chyr, S.-H., Li, B.-L., and Sheih, S.-D. (1996). Cytokine Production during Hemodialysis: Effects of Dialytic Membrane and Complement Activation. Am J Nephrol *16*, 293–299. 10.1159/000169012.
55. Ando, M., Shibuya, A., Yasuda, M., Azuma, N., Tsuchiya, K., Akiba, T., and Nitta, K. (2005). Impairment of innate cellular response to in vitro stimuli in patients on continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant *20*, 2497–2503. 10.1093/ndt/gfi048.
56. Sester, U., Sester, M., Hauk, M., Kaul, H., Köhler, H., and Girndt, M. (2000). T-cell activation follows Th1 rather than Th2 pattern in haemodialysis patients. Nephrol Dial Transplant *15*, 1217–1223. 10.1093/ndt/15.8.1217.

57. Stenvinkel, P., Ketteler, M., Johnson, R.J., Lindholm, B., Pecoits-Filho, R., Riella, M., Heimbürger, O., Cederholm, T., and Girndt, M. (2005). IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia--the good, the bad, and the ugly. Kidney Int *67*, 1216–1233. 10.1111/j.1523-1755.2005.00200.x.
58. Fernández-Fresnedo, G., Ramos, M.A., González-Pardo, M.C., de Francisco, A.L., López-Hoyos, M., and Arias, M. (2000). B lymphopenia in uremia is related to an accelerated in vitro apoptosis and dysregulation of Bcl-2. Nephrol Dial Transplant *15*, 502–510. 10.1093/ndt/15.4.502.
59. Chia, S., Karim, M., Elwood, R.K., and FitzGerald, J.M. (1998). Risk of tuberculosis in dialysis patients: a population-based study. Int J Tuberc Lung Dis *2*, 989–991.
60. Simon, T.A., Paul, S., Wartenberg, D., and Tokars, J.I. (1999). Tuberculosis in hemodialysis patients in New Jersey: a statewide study. Infect Control Hosp Epidemiol *20*, 607–609. 10.1086/501679.
61. Fang, H.-C., Chou, K.-J., Chen, C.-L., Lee, P.-T., Chiou, Y.-H., Hung, S.-Y., and Chung, H.-M. (2002). Tuberculin skin test and anergy in dialysis patients of a tuberculosis-endemic area. Nephron *91*, 682–687. 10.1159/000065031.
62. Smirnoff, M., Patt, C., Seckler, B., and Adler, J.J. (1998). Tuberculin and anergy skin testing of patients receiving long-term hemodialysis. Chest *113*, 25–27. 10.1378/chest.113.1.25.