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Immune dysfunction in patients with end stage kidney disease; Immunosenescence – Review

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Abstract. The body's defense against environmental factors is realized by physical barriers and cells of both the innate and adaptive immune systems. Patients with end stage kidney disease (ESKD), especially those treated by hemodialysis, have changes in both the function and the number or percent of different leukocyte subsets. Changes were described at the level of monocytes and lymphocyte subsets, which are associated with immunodeficiencies and pro-inflammatory status correlated with degenerative changes and increased cardiovascular risk. These abnormalities have been compared over the past years with alterations appearing as a result ageing. Also, similitudes regarding immunosenescence observed in ESKD patients, in combination with chronic inflammation, are described as the so-called "inflammaging syndrome".

Key words: end stage chronic kidney disease, GFR (glomerular filtration rate), hemodialysis, immunosenescence, immunosuppression, inflammaging syndrome.

What is new? What is important?

The presence of immune senescence and chronic inflammation in ESKD patients leading to cardiovascular and infectious diseases is important to be well understood by physicians in order to improve this condition and to find some measures capable of reverting the immune senescence, thymus involution and to stop or minimize chronic inflammation. In the past years various methods have been tried in order to reduce chronic inflammation: the biocompatibility of the membranes used in hemodialysis has increased, fewer patients are dialyzed using venous catheters, iron storage is well monetarized, and the efficiency of hemodialysis is on the rise. Regarding the complexity of the immune changes suffered by the ESKD patients we were wondering if there aren't any other possibilities to bring back the function of their immune system.

INTRODUCTION – GENERAL ASPECTS REGARDING THE IMMUNE SYSTEM

The body's defense against environmental factors consists of physical barriers, innate and adaptive immunity [1]. The organs involved in the immune systems are classified into primary and secondary lymphoid organs. The primary lymphoid organs include the bone marrow and the thymus. Here takes place the production as well as the release of white blood cells into the bloodstream. The secondary lymphoid organs take part in the coordination of the adaptive immune response and are represented by the spleen, lymph nodes and lymphatic tissue. While the cells of the innate immune system leave the bone marrow as mature cells, the adaptive immune system cells require a complementary development phase and the completion of functions that occurs in the secondary lymphoid organs [2].

White blood cells (WBC) are precisely identified by immunophenotyping with monoclonal antibodies against specific molecules found on the surface of cellular membranes through the process of flow cytometry. These surface markers have been classified in the CD nomenclature system (approximately 250 different protein structures) [3].

Flowcytometry is the best method to detect, by immunophenotyping, surface receptors at the investigated cell membrane's level.

Out of the cells involved in the immune response we will examine in this review monocytes and natural killer (NK) cells as representatives of innate immunity, and B and T cells as representatives of adaptive immunity.

Monocytes represent about 5% of all leucocytes. One of their main properties is that they migrate to different tissues where they become macrophages [3]. Other properties include phagocytic activity, the

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presentation of antigen to lymphocytes and the secretion of proinflammatory cytokines and components of the complement. Therefore, explaining their role in inflammation and the development of atherosclerosis [4].

Monocytes are classified based on the CD14 and CD16 expressions into three classes: CD14++/ CD16- (classical monocytes), CD14+/CD16+ (intermediary monocytes) and CD14low/CD16+ (non-classical monocytes). Of these, CD16+ monocytes, and especially the non-classical ones, have a higher capacity to produce proinflammatory cytokines and are commonly found in increasing numbers in the blood of patients diagnosed with inflammatory or infectious diseases [4,5].

Lymphocytes constitute approximately 20% of the total number of leucocytes. The main components are T cells, B cells and NK cells [3]. Prolonged exposure to a specific antigen induces the proliferation of a lymphocyte clone which will differentiate itself in effector and memory cells [1].

T cells, which account for 80% of the total number of lymphocytes, mature from their precursors in the thymus and eventually migrate into lymph nodes and lymphatic tissue [3].

Depending on the surface markers, there are different types of T cells: cytotoxic T cells (CD8) and helper T cells (CD4) [4]. CD8 positive T cells destroy virally infected cells, tumor cells as well as cells recognized as non-self-cells / tissues during transplantation [4]. CD4 positive T cells can release cytokines, stimulate proliferation, differentiate both B and T cells and activate monocytes [1]. Treg cells (regulatory T cells) are a subset of CD4 positive T cells that secrete cytokines that inhibit the immune response and inflammation, hence having an important role in the limitation of inflammation [4].

There are four different subclasses of T cells that can be identified in the blood, depending on the expression of CD45RA and CCR7 markers: naïve T cells CD45RA+/CCR7+; central memory T cells CD45RA-/CCR7+; effector memory T cells CD45RA-/CCR7- and TEMRA T cells CD45RA+/ CCR7- (especially for CD8+ T cells) [6]. Effector memory T cells are mostly found in the non-lymphoid tissue of the mucosal level, they rapidly produce cytokines at contact with the known pathogen agent and have an immediately effective function with a limited proliferation capacity. Contrarily, central memory T cells reside in the lymph tissue from which they proliferate quickly and strongly at pathogen recognition, being defined by their high proliferation capacity but reduced effective function [2,4,6]. Immunophenotypic T cell subsets are shown in Table 1.

Lastly, the TEMRA CD8+Tcells cells are considered by some authors to be “terminally differentiated effector cells” due to their capacity to secrete gamma interferon, high cytotoxicity, reduced proliferation capacity and higher sensitivity to apoptosis [6]. Even though TERMA CD4+T cells are not usually detected in blood, they appear in cases of infestation with certain viruses and are considered to fulfill a protective role [7].

Natural killer cells (NK), a type of cytotoxic lymphocyte, represent 5–15% of lymphocytes. These cells possess surface membrane receptors, through which their activity can be either inhibited or stimulated. Based on the intensity of the signals received from the virally infected cells or tumor cells, they activate and release cytotoxic granules that penetrate the targeted cells, inducing apoptosis [1,4].

B cells amount to 20% of the total number of lymphocytes and are produced in the bone marrow from precursors, migrate in the lymph nodes and populate lymph organs (lymph nodes, spleen, bowel, respiratory tract). Their primary role is to produce antibodies [3]. Depending on the surface markers of the B lymphocyte, in the peripheral blood, four subsets can be identified, each corresponding to a different growth stage: immature (transitional) B cells, naive B cells, memory B cells and plasmablasts [8]. Immunophenotypic profile is shown in Table 2.

Table 1

T cell subsets immunophenotype

T cell subsets	Immunophenotype
Naïve T lymphocytes	CCR7+ CD45RA+
Central memory	CCR7+ CD45RA- CD27+ CD28+
Effector memory (EM)	CCR7- CD45RA-
Early	CCR7- CD45RA- CD27- CD28+ Granzyme A- Granzyme B- Perforin-
Intermediate	CCR7- CD45RA-/+ CD27- CD28+ Granzyme A+ Granzyme B-/+ Perforin-
Late	CCD7- CD45RA+ CD27- CD28- Granzyme A+ Granzyme B+ Perforin+
TEMRA	CCR7- CD45RA+

Table 2

B cell subsets immunophenotype

B cell subsets	Immunophenotype
Immature	sIgM++ CD10+ CD19+ CD20+ CD27- CD38++
Naive	sIgM+ CD10- CD19+ CD20+ CD27- CD38-/+
Memory	sIgM-/+ CD10- CD19+ CD20+ CD27+ CD38-/+
Plasmablasts/Plasmacells	sIgM-/+ CD10- CD19+ CD20-/+ CD27++ CD38+++

The B-cell receptor (BCR – common receptor of B cells) is located on the surface membrane of B cells, consists of a immunoglobulin type component and can be activated by different soluble substances [2]. The immature B cells have an IgM type immunoglobulin, with the possibility of coexistence with IgD [2], these cells migrate from the bone marrow to the spleen as transitional B cells [9]. There they differentiate themselves into follicular B lymphocytes and marginal lymphocytes and after the process of differentiation, they are considered to be naive or mature. Marginal lymphocytes act fast, are independent of T cell antigen and mature into plasma cells with a short lifespan that produce IgM, whilst the follicular B cells are T cell antigen dependent and require the presence of the germinal center of the lymphoid follicle where lymphocytes proliferate, immunoglobulin class switching happens, and the development of memory B cells and plasma cells with a long lifespan that produce IgG, IgA or IgE takes place [2,9,10]. The switch process of immunoglobulin represents changing the production of Ig at the level of the lymphocytes' surface membrane from IgD and IgM (unswitched B cells) to IgG, IgA, IgE (switched B cells) [10].

Each component of the immune system plays a specific role in the defense of the body, thus, theoretically, by discovering the defects of one of these components, we can associate them with an increase in susceptibility to various infections or environmental factors [1].

PARTICULARITIES OF IMMUNODEFICIENCY ASSOCIATED WITH END STAGE KIDNEY DISEASE

Out of all pathologies associated with medical practice, one of the most frequent is renal disease. Renal dysfunction can be acute: AKI (Acute Kidney Injury) or chronic: CKD (chronic kidney disease), which is divided into 5 stages of evolution, depending on glomerular filtration rate (GFR) and albuminuria levels. The associated pathologies of patients with end stage kidney disease (ESKD) (GFR under 15ml/min) are most commonly cardiovascular diseases and infections, the later one appears as a consequence of a poor immune system.

Patients with chronic kidney disease suffer from chronic activation of the immune system which leads to atherosclerosis and an increased incidence of cardiovascular diseases at the same time. They are also susceptible to infections, secondary to a malfunction of the immune system [11]. Cardiovascular diseases can be present in patients regardless of chronic kidney disease stage. As kidney dysfunction progresses, the incidence of cardiovascular diseases increases, reaching a peak in patients with ESKD [12]. In the case of a GFR below 45ml/min/1.73 m^2 the risk of cardiovascular mortality increases with the decrease of the GFR [12].

When compared to the general population, patients that are chronically dialyzed have a 20-foldincreased cardiovascular disease mortality rate and an occurrence of infections that lead to clinical death in 12–22% of cases [12].

Patients with ESKD have cardiovascular diseases and infections as major causes of morbidity and mortality. Both conditions are associated with disorders that appear due to the imbalance of pro- and anti-inflammatory, and of pro- and anti-apoptotic events [13]. Systemic inflammation occurs during the evolution of CKD and causes the growth of oxidative stress, associated with atherosclerosis, vascular disease, cachexia and/or anemia [4]. In these patients the following have been noticed: a damaged immunity mediated by the T cells, variations in the number of naive and memory T cells, lack of the production of an adequate antibody titer, a rise in the production of cytokines and the generation of reactive oxygen species (ROS), the inhibition of the Treg's activity leading to a prevalence of pro-inflammatory factors compared to protective ones [1,4].

Ishani A. *et al.* show a bidirectional direct correlation, in a dialyzed patient, between the presence of sepsis or bacteriemia and the development of cardiovascular diseases. The favored link between them is the presence of inflammation in chronic hemodialysis patients [14].

The analysis by flow cytometry, over the course of time, of these three components of the immune system: monocytes, NK cells (innate immunity), B and T cells (adaptive immunity), shows concrete results regarding these cells' damaged number and functions in this type of patient as described in many reports.

The number of CD16+ monocytes is higher in patients with ESKD and could play a role in systemic inflammation and the growth of oxidative stress [4]. In dialyzed patients there is a positive correlation between the number of CD16+ monocytes and mortality, especially in the case of those patients who are also suffering from pre-existing cardiovascular diseases [15]. Particularly, there are studies in patients with chronic kidney disease, in which a correlation between the increasing number of intermediary monocytes and the occurrence of cardiovascular diseases has been established [16,17]. In the case of hemodialyzed patients a higher total number of intermediary monocytes seems to be an independent predictive mortality risk factor [12,15]. Chronic kidney disease alters the number, functions and distribution of monocyte subclasses and determines defects in the production of cytokines, phagocytosis and chemotaxis occur [15,18,19,20].

Raska K. Jr. *et al.* described a reduction in the number of T helper and suppressor cells in patients between 30 and 60 years, whilst only a reduction in the number of T helper cells in the age group of over 60 years was observed in 50 chronically dialyzed patients [21].

Xiang F.F. *et al.* report a drop in the total number of lymphocytes before the end stage of the disease in a batch of 472 patients suffering from CKD. These patients present, alongside the lower number of lymphocytes, a drop of B cell percentage, and a higher NK cell percentage, without being able to outline alterations regarding the total number of leucocytes, monocytes, CD4+ T cells, CD8+ T cells, or the CD4+/CD8+ ratio [11]. Lymphopenia has already been shown to be a predictor of overall mortality in chronic hemodialyzed patients, favoring infections and tumors [22].

In the case of uremic patients, and especially in the dialyzed ones, immunodeficiency occurs, which is characterized by a drop in the T cell response, a drop in the production of immunoglobulin as a response to stimuli, and an alteration of the monocyte and natural killer cell activity. These are associated with a misbalance between the production of pro-inflammatory cytokines and their inhibitors [23]. Descamps-Latscha and Chatenoud found that the anomalies in B and T cell levels aggravate as the chronic kidney disease advances and are exacerbated by means of hemodialysis [24].

A decrease in the total number of Tregs may be related to a reduction in anti-inflammatory activity in patients with ESKD. Studies show a decrease in the number of Treg, especially in patients with chronic hemodialysis with the accentuation of systemic inflammation and implicitly the appearance of cardiovascular complications in these patients [4].

Yoon *et al.* report that in patients with ESKD, there was a significant decrease in the CD4+/CD8+ ratio, and a decrease in the number of naive and central memory CD4+ and CD8+ cells, while the number of effector memory lymphocytes for both CD4+ and CD8+ T cells remained unchanged. The decreased number of naive and central memory lymphocytes was then attributed with the increased apoptosis of these cells. Results collected after dialysis sessions show that the dialysis procedure does not influence the total number of naive lymphocytes but there is a significant decrease in central memory CD8+ cells [25].

In patients with chronic ESKD B cells are significantly decreased in total number, although transitional B cells do not appear to be altered in number, thus: either uremia induces B cell apoptosis or uremia inhibits the transformation of the transitional B cells into a mature B cell [4]. Uremia is also responsible for reducing the number of naive and memory B cells [4]. Madeleine V. Pahl *et al.* showed a decrease in the number of all subpopulations of B cells except for transitional B cells in stable hemodialysis patients without being able to show an increase in apoptosis of B cells in the chronic hemodialysis patients compared to the nonuremic ones [26]. Kyoung Woon Kim *et al.* published a study comparing B cell subpopulations between patients undergoing chronic hemodialysis, with CKD in the predialysis stage and healthy volunteers. The results of the study showed that the percentage of B cells was not different in the three groups, the percentage of immature B cells was higher in the group of patients undergoing chronic hemodialysis versus predialysis patients, the percentage of memory B cells was higher in the group consisting of predialysis patients versus chronic hemodialysis patients, and there was a decrease in memory B cells in chronic dialysis patients compared to the control group [27]. According to the authors of this study, the decrease in immature B cells and the increase in memory B cells in patients in the predialysis stage would be the result of the imbalance between effector and regulatory actions [27].

Bouts AHM *et al.* show a decrease in the number of memory B cells in all 3 categories of children with kidney disease: those undergoing peritoneal dialysis, those undergoing hemodialysis and children with chronic kidney disease undergoing neither, in comparison to a control group that consists of healthy children. This finding can explain the decrease in immunoglobulin levels found in these patients and therefore the low efficacy of vaccination [28].

Maria Molina *et al.* report that the factors most frequently implicated in hemodialyzed patients' cardiovascular mortality are the low number of B cells below 100 cells/µl at initial determination and at 12 months, and a low number below 60 cells/µl NK cells at baseline, however, NK lymphopenia at 12 months does not appear to be significantly associated with mortality [22].

IMMUNOSENESCENCE

The profile of morbidity and mortality in patients with CKD seems to be very similar to that of the geriatric population, especially in terms of cardiovascular diseases or impaired immune profile, patients with ESKD present a premature ageing of the immune system [12,29]. We can see in younger hemodialyzed patients conditions like frailty, muscle wasting, cardiovascular diseases, osteoporosis which reminds of the pathology of the elderly and may appear secondary to oxidative stress, the accumulation of uremic toxins and chronic inflammation [30].

In the case of the elderly, the immune profile is characterized by the decrease of the number of naïve T cells and the increase of the number of highly differentiated memory T cells that have a proinflammatory effect with a role in destabilizing the atherosclerotic plaque and changes related to the aging of the immune system that have resulted in increased inflammation and decreased T cell function [7,12].

In the elderly, a slight degree of inflammation occurs and the cells of the immune system show some changes in their surface receptors, thus their functions become deficient leading to an increase in the incidence of diseases such as cardiovascular ones. The changes in the immune system related to ageing are called immunosenescence [29]

Immunosenescence will decrease the production of naïve T cells through the involution of the thymus, will reduce the palette of T cell receptors, and will decrease the quality of response to pathogens [31]. At the level of naive CD 4+ T cells, there is a proliferation that is not so high in the case of naive CD8+ T cells so that in old age the number of naive CD8+ cells become very low [32]. The number of naive CD8 + cells decrease, but the total number of CD8+ T cells remains unchanged due to the expansion of memory T cells [31]. The proportion of Treg cells may remain unchanged or even slightly increased [33]. The proportion of memory T cells increases with age and has more and more highly differentiated memory T cells such as TEMRA cells, contributing to a deficient immune response. The more differentiated memory T cells are, the more proinflammatory cytokines they will produce [34,35]. The increased number of memory T cells in the elderly is considered one of the factors contributing to the proinflammatory status and pathology of the elderly: Alzheimer's disease and cardiovascular disease. The notion of "inflammation-aging" also appears in literature [36,37,38].

The dialysis procedure by itself induces chronic inflammation, via multiple sources: extracorporeal circulation through bioincompatible membranes, prosthetic vascular access, dialysis solutions, etc. Studies showed an inverse correlation between CRP levels and naïve T cells in hemodialysis patients, which is additional proof of the correlation between inflammation and immune senescence. CKD patients present monocyte activation and overproduction of cytokines like Il-6 with an important proinflammatory action. ESKD patients can present T cell lymphopenia and T cell immune defect with an increase in susceptibility for infections, decreased response to vaccines and an inflammatory status, this association being referred to as "inflammaging" state of the elderly [30].

Chiu Y-L. *et al.* report in a study performed on 412 hemodialysis patients and 57 healthy patients that accelerated aging of T cells and monocytes characterized by a decrease in the number of naive CD4+ cells and CD8+ cells, and an increase in the number of proinflammatory monocytes (CD16+) in patients *vs* control subjects. These changes are associated with the age of the patients and the length of time they have been on dialysis [29]. This study assumes that chronic dialysis patients have many similarities related to physiological changes and increased morbidity and mortality similar to the elderly (including decreased muscle mass, decreased cognitive function, accelerated vascular disease, and increased risk of death) [29]. Chronic dialysis patients show a decrease in the percentage of naïve CD4+ and CD8+ T cells, an increase in the percentage of CD8+ effector memory, and high differentiated memory effector cells (TEMRA) [29].

The absolute number of CD4+ T cells is low in the uremic patient due to the decline of naïve and central memory lymphocytes [39]. Changes in lymphocyte subtypes in dialysis patients, similar to those associated with ageing, appear to be more pronounced in the CD8+ T cell compartment than in CD4+ T cells. Also, chronic dialysis patients have an absolutely high percentage and number of CD16+ monocytes, as in the case of elderly patients [29]. The conclusion of the study was that many of the immune changes that occur in the dialysis patients are similar to those seen with increasing age, leading to an increased susceptibility for various types of infections and a reduced response to vaccines [29].

Betjes M.G.H. publishes an article in which he also demonstrates that patients with CKD have an early ageing of the adaptive immune system with a decrease in the response to vaccination, and an increase in susceptibility to cancer and infections. One explanation would be the acceleration of thymus involution in uremic patients. It is possible that maintaining the function of the thymus as much as possible through a healthy, moving lifestyle, maintaining a normal weight, quitting smoking, as well as future regenerative therapies aimed at the thymus (cell therapies) will reduce the morbidity and mortality of patients with end stage kidney disease [31].

In patients with ESKD a decrease in the number of naive T cells is secondary to the involution of the thymus but these cells also have a proapoptotic profile, which contributes to a decrease in the number of naïve T cells [31]. The mechanism by which uremia causes a decrease in thymus function is not yet known, but the thymus has been shown to be sensitive to inflammation and oxidative stress that are increased in patients with chronic kidney disease [31].

Changes in T cells in the uremic patient are similar to those of a person at least 20 years older but without chronic end-stage renal disease [31]. Kidney transplantation is followed by relief of inflammation and oxidative stress in uremic patients, but no improvement in the T cell profile has been observed, with thymus involution caused by uremia appearing to be irreversible [31].

In the ESKD (GFR below 15 ml / min) and especially in dialysis patients, premature ageing of the immune system, loss of thymus function and expansion of memory T cells are important factors in the occurrence of secondary pathology in these patients due to immunosuppression [40,41,42].

In order to reverse or prevent immunosenescence in CKD patients there are several proven actions with positive results: increasing of physical activity leading to a modulation of cytokine release with anti-inflammatory proprieties, maybe long term administration of growth hormone in dialysis patients in order to reverse the thymopoiesis defect in these patients, administration of Recombimamt human interleukin-7 in order to reverse thymic involution, best controlling of microbiota by diet and probiotics knowing that dysbiosis may lead to inflammation, and dialysis procedures: using of biocompatible membranes, avoiding excessive iron load because an overload leads to sterile inflammation followed by tissue acute injury, neurotoxicity or ischemia-reperfusion injuries [30].

CONCLUSION

The immune system changes found in patients with ESKD are multiple and complex, and imply not only impaired immune changes, but also immunosenescence-like changes, correlated with increased cardiovascular risk. Further randomized controlled studies are needed to describe in-depth the premature aging in ESKD, and secondary to explore new therapeutic options for this special group of patients.

Apărarea organismului împotriva factorilor de mediu este realizată prin bariere fizice și celule ale sistemului imunitar moștenit și adaptativ. Pacienții cu boală renală în stadiu terminal (BRST), în special cei tratați prin hemodializă, prezintă modificări ale funcției, numărului sau procentului diferitelor subseturi de leucocite. Au fost descrise astfel modificări la nivelul monocitelor și subseturilor limfocitare, care sunt asociate atât cu sindroamele de imunodeficiență, cât și cu statusul proinflamator corelat cu modificările degenerative și riscul crescut cardiovascular. Aceste modificări, ce survin la pacienții cu BRST, au fost comparate în ultimii ani cu cele apărute ca urmare a procesului de îmbătrânire, observându-se similitudini cu procesul de imunosenescență.

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REFERENCES

1. DROPULIC L.K., LEDERMAN H.M. *Overview of Infections in the Immunocompromised Host*, Microbiol Spectr. 2016 Aug;4(4):10.1128
2. HOFFMAN R., BENZ E.J.Jr., SILBERSTEIN L.E., HESLOP H.E., WEITZ J.I., ANASTASI J., *et al.*, *HEMATOLOGY, BASIC PRINCIPLES AND PRACTICE*, seventh edition, Elsevier Inc, Aug 15, 2017
3. MALE D., *Immunology: An Illustrated Outline*, Fifth Edition, Garland Science, New York, 2014
4. VAZIRI N.D., PAHL M.V., CRUM A., NORRIS K., *Effect of Uremia on Structure and Function of immmune System*, J Ren Nutr, 2012 Jan;22(1):149–56
5. SANMARCO L.M., EBERHARDT N., PONCE N.E., CANO R.C., BONACCI G., AOKI M.P., *New Insights into the Immunobiology of Mononuclear Phagocytic Cells and Their Relevance to the Pathogenesis of Cardiovascular Diseases*, Front Immunol. 2018 Jan 9;8:1921.
6. VERMA K., OGONEK J., VARANASI P.R., LUTHER S., BUNTING I., THOMAY K., *et al.*, *Human CD8+CD57—TEMRA cells: TOO young to be called „old"*, PLoS One, 2017 May 8;12(5):e0177405.
7. KUMAR B.V., CONNORS T., FARBER D.L., *Human T cell development, localization, and* PEREZ-ANDRES M., PAIVA B., NIETO W.G., CARAUX A., SCHMITZ A., ALMEIDA J. *et al.*, and the Primary Health Care Group of Salamanca for the Study of MBL, *Human Peripheral Blood B-Cell Compartments A Crossroad in B-Cell Traffic*, Cytometry B Clin. Cytom. 2010;78 Suppl 1:S47-60.
8. PEREZ-ANDRES M., PAIVA B., NIETO W.G., CARAUX A., SCHMITZ A., ALMEIDA J. *et al.*, and the Primary Health Care Group of Salamanca for the Study of MBL, *Human Peripheral Blood B-Cell Compartments A Crossroad in B-Cell Traffic*, Cytometry B Clin. Cytom. 2010;78 Suppl 1:S47–60
9. SAPKOTA A., *B Cell [B Lymphocyte]- Definition, Types, Development, Applications.* https://microbenotes.com/b-cell-b-lymphocyte/ April 9, 2021.
10. BEMARK M., Translating *transitions-how to decipher peripheral human B cell development*, J Biomed Res 2015 Jul;29(4):264–84.
11. XIANG F-F., ZHU J-M., CAO X-S., SHEN B., ZOU J-Z., LIU Z-H., *Lymphocyte depletion and subset alteration correlate to renal function in chronic kidney disease patients*, Ren. Fail 2016;38(1):7–14.
12. COHEN G., *Immune Dysfunction in Uremia 2020*, Toxins [Basel] 2020 Jul 5;12(7):439.
13. COHEN G., HORL W.H., *Immune dysfunction in Uremia – An Update*, Toxins, [Basel], 2012 Oct 24;4(11):962–90.
14. ISHANI A., COLLINS A.J., HERZOG C.A., FOLEY R.N., *Septicemia, acces and cardiovascular diseases in dialysis patients: the URSDS wave 2 study*, Kidney International, 2005 Jul;68(1):311–8.
15. JENG Y., LIM P.S., WU M.Y., TSENG T-Y, CHEN C.H., CHEN H.P., *et al., Proportion of Proinflammatory Monocytes Are Important Predictors of Mortality Risk in Hemodialysed Patients*, Mediators Inflamm., 2017:1070959.
16. ROGACEV K.S., SEILER S., ZAWADA A.M., REICHART B., HERATH E., ROTH D., *et al. CD14++CD16+monocytes and cardiovascular outcome in patients with chronic kidney disease*, Eur. Heart J. 2011 Jan;32(1):84–92.
17. HEINE G.H, ULRICH C., SEIBERT E. SEILER S., MARELL J., REICHART B., *et al., CD14++ CD16+ monocytes but not total monocyte numbers predict cardiovascular events in dialysis patients*, Kidney International, 26 Dec 2007, 73(5):622–629.
18. LIM W. H., KIRETA S., LEEDHAM E., RUSS G.R., COATES P.T., *Uremia impairs monocytes and monocyte-derived dendritic cell function in hemodialysed patients*, Kidney Internatioanal, 2007, 72(9):1138–42.
19. HEINE G.H., ORTIZ A., MASSY Z.A. LINDHOLM B., WIECEK A., MARTINEZ-CASTELAO A. *et al., Monocyte subpopulations and cardiovascular risk in chronic kidney disease*, Nature Reviews Nephrology, 8:362–369 (2012).
20. GONCALVES S., PECOITS-FILHO R., PERRETO S., BARBERATO S.H., STINGHEN A.E.M., LIMA E.G.A., *et al., Associations between renal function, volume status and endotoxaemia in chronic kidney disease patients*, Nephrology, Dialysis, Transplantation, 2006 Oct;21(10):2788–94.
21. RASKA K.JR., RASKOVA J., SHEA S.M., FRANKEL L.M., WOOD R.H., LIFTER J. *et al. T cell subsets and cellular immunity in end-stage renal disease*, AM J Med 1983 Nov;75(5):734-40.
22. MOLINA M., ALLENDE L.M., GUTIERREZ E., PLEGUEZUELO D.E., HERNANDEZ E.R., RIOS F., *et al., CD19$^+$ B-Cells, a New Biomarker of Mortality in Hemodialysis Patients* Front Immunol 2018 Jun 15;9:1221.
23. DESCAMPS-LATSCHA B., HERBELIN A., NGUYEN A.T., JUNGERS P., CHATENOUD L., *Dysregulation of the immune system in chronic uremic and hemodialysed patients*, Presse Med, 1995, Feb 25;24(8):405–10.
24. DESCAMPS-LATSCHA B., CHATENOUD L., *T cells and B cells in chronic renal failure*, Semin Nephrol, 1996 May; 16(3):183–91.
25. YOON J-W., GOLLAPUDI S., PAHL M.V., VAZIRI N.D., *Naïve and central memory T-cell lymphopenia in end-stage renal disease* Kidney Int. 2006 Jul;70(2):371–6.
26. PAHL M.V., GOLLAPUDI S., SEPASSI L., GOLLAPUDI P., ELAHIMEHR R., VAZIRI N.D., *Effect of end-stage renal disease on B-lymphocyte subpopulations, IL-7, BAFF and BAFF* KIM K.W., CHUNG B.H., JEON E.J., KIM B.M., CHOI B.S., PARK C.W. *et al., B cell-associated immune profiles in patients with end-stage renal disease (ESRD)*, Exp. Mol. Med. 2012 Aug 31;44(8):465–7243.

27. KIM K.W., CHUNG B.H., JEON E.J., KIM B.M., CHOI B.S., PARK C.W. *et al*., *B cell-associated immune profiles in patients with end-stage renal disease (ESRD),* Exp. Mol. Med. 2012 Aug 31;44(8):465–7243.
28. BOUTS A.H.M., DAVIN J.C., KREDIET R.T., MONNENS L.A.H., NAUTA J., SCHRODER C.H., *Children with chronic renal failure have reduced numbers of memory B cells*, Clin Exp Immunol,2004 Sep;137(3):589–94.
29. CHIU Y-L., SHU K-H., YANG F-J., CHOU T-Y., CHEN P-M., LAY F-Y., *et al*., *A comprehensive characterization of aggravated aging-related changes in T lymphocytes and monocytes in end-stage renal disease: the iESRD study*, Immun. Ageing. 2018 Nov 8;15:27
30. DUCLOUX D., LEGENDRE M., BAMOULID J., SAAS P., COURIVAUD C., CREPIN T., *End-Stage Renal Disease-Related Accelerated Immune Senescence: Is Rejuvenation of the Immune System a Therapeutic Goal?* Front. Med., 2021 Sep 3:8:720402
31. BETJES M.G.H., *Uremia-Associated Ageing of the Thymus and Adaptive Immune Responses*, Toxins [Basel] 2020 Apr 3;12(4):224.
32. FAGNONI F.F., VESCOVINI R., PASSERI G., BOLOGNA G., PEDRAZZONI M., LAVAGETTO G., *et al., Shortage of circulating naive CD8[+] T cells provides new insights on immunodeficiency in aging*. Blood 2000 May 1;95(9):2860-8.
33. CICIN-SAIN L., SMYK-PEARSON S., CURRIER N., BYRD L., KOUDELKA C., ROBINSON T., *et al*., *Loss of naive T cells and repertoire constriction predict poor response to vaccination in old primates.* J. Immunol. 2010 Jun 15;184(12):6739–45.
34. SAULE P., TRAUET J., DUTRIEZ V., LEKEUX V., DESSAINT J.P., LABALETTE M. *Accumulation of memory T cells from childhood to old age: Central and effector memory cells in CD4[+] versus effector memory and terminally differentiated memory cells in CD8[+] compartment*. Mech. Ageing Dev. 2006 Mar;127(3):274–81.
35. NAISMITH E., PANGRAZZI L., GRASSE M., KELLER M., MIGGITSCH C., WEINBERGER B., *et al.*, Peripheral *antibody concentrations are associated with highly differentiated T cells and inflammatory processes in the human bone marrow*. Immun. & Ageing 2019 Aug 22;16:21.
36. BETJES M.G.H., MEIJERS R.W., DE WIT L.E., LITJENS N.H. *A killer on the road: Circulating CD4[+]CD28null T cells as cardiovascular risk factor in ESRD patients*. J. Nephrol. 2012 Mar–Apr;25(2):183–91.
37. BETJES M.G.H., WEIMAR W., LITJENS N.H. *Circulating CD4[+]CD28null T Cells May Increase the Risk of an Atherosclerotic Vascular Event Shortly after Kidney Transplantation*. J. Transplant. 2013;2013:841430.
38. BETJES M.G.H., DE WIT E.E., WEIMAR W., LITJENS N.H. *Circulating pro-inflammatory CD4posCD28null T cells are independently associated with cardiovascular disease in ESRD patients*. Nephrol. Dial. Transplant. 2010 Nov;25(11):3640–6.
39. GRUVER A.L., SEMPOWSKI G.D. *Cytokines, leptin, and stress-induced thymic atrophy*. J. Leukoc. Biol. 2008 Oct;84(4):915–23.
40. VERKADE M.A.; VAN DE WETERING J., KLEPPER M.; VAESSEN L.M.; WEIMAR W.; BETJES M.G.H. *Peripheral blood dendritic cells and GM-CSF as an adjuvant for hepatitis B vaccination in hemodialysis patients*. Kidney Int. 2004 Aug;66(2):614–21.
41. STEWARD J.H., VAJDIC C.M., VAN LEEUWEN M.T., AMIN J., WEBSTER A.C., CHAPMAN J.R., *et al*., *The pattern of excess cancer in dialysis and transplantation.* Nephrol. Dial. Transplant. 2009 Oct;24(10):3225–31.
42. LITJENS N.H., HUISMAN M., VAN DEN DORPEL M., BETJES M.G.H.*Impaired immune responses and antigen-specific memory CD4+ T cells in hemodialysis patients*. J. Am. Soc. Nephrol. 2008 Aug;19(8):1483–90.

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