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THE EFFECT OF DIALYSIS MODALITY AND MEMBRANE PERFORMANCE ON NATIVE IMMUNITY IN DIALYSIS PATIENTS

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ABSTRACT

Chronic Kidney Disease (CKD) is characterized by immune activation with development of chronic inflammation. However, immune deficiency also exists in CKD patients. The number and the activity of Natural Killer cells (NK-cells) are influenced by the biocompatibility of various dialysis membranes. In this study we investigated the effect of dialysis modality and membrane type on NK-cell number and on phagocytic activity of neutrophils in patients on different dialysis methods.

Sixty patients were included in the study and divided in three groups of 20 patients each. Patients on conventional hemodialysis using Low Flux membrane (cHD-LF) were included in Group I, patients on conventional dialysis using High Flux membrane (cHD-HF) were included in Group II and patients treated by on-line hemodiafiltration with High Flux polysulphone membrane (on-line HDF) were included in Group III. Native immunity was investigated using the number of NK-cells and the phagocytic activity of neutrophils.

NK-cells count was significantly lower ($p<0.001$) in the three groups of dialyzed patients in comparison to healthy subjects. However, no significant difference was observed in the NK-cells count among patients treated by conventional dialysis using Low or High Flux membrane and patients treated by on-line hemodiafiltration. Similarly, although the phagocytic activity of neutrophils was significantly decreased in all patients on dialysis ($p<0.001$), no difference related to the dialysis modality or membrane performance was observed. A strong positive correlation was recognized between parathormone blood levels and number of NK-cells ($r=0.305$, $p<0.01$).

In conclusion, an impairment of the native immunity represented by NK cell number and phagocytic activity of neutrophils is observed in patients on dialysis. Dialysis modality and membrane performance do not influence the native immunity of dialyzed patients. However, parathormone blood levels are possibly involved in the development of immune system disturbances in such patients.

Keywords: NK cells, phagocytosis, immunity, dialysis mode, membrane performance, parathormone

INTRODUCTION

The influence of chronic kidney disease (CKD) on immune system is characterized either by immune activation with development of chronic inflammation or by immune deficiency [1]. The immunodeficiency especially in patients on hemodialysis has an influence on all immune cells

(granulocytes, monocytes, T and B lymphocytes) [2] and leads to a higher incidence of infections and malignancies [3].

The subpopulation of Natural Killer cells (NK-cells) account for about 10-15% of peripheral blood lymphocytes and represent a first line of immune defense against any external or internal pathogen [4]. The activity of NK-cells in patients on chronic dialysis is depressed [5]. It has been shown that less biocompatible membranes (cuprophane, hemophane) have a greater suppressive effect on NK-cells in comparison to more biocompatible membranes (cellular acetate, polycarbonate, polyacrylonitrile, PMME) [6–10]. Furthermore, Raij et al showed that Low-Flux (Low Performance) membranes had a stronger depressive effect on NK cells in comparison to High-Flux (High Performance) membranes. It is of note that some studies showed reduction of NK cells subpopulation [6,11] while other studies showed increase of NK cells [12, 13] depending on the dialysis membrane that was used.

Uremic toxins of middle and higher molecular weight are implicated in the pathogenesis of immune system suppression in dialysis patients. This is more evident in patients treated with Low-Flux membranes who have lower rate of uremic toxins removal in comparison to patients treated with High-Flux membranes who show a better immune response.

The dialysis per se has been reported as another mechanism involved in the pathogenesis of immune dysfunction of patients on dialysis [6, 11]. However, the dialysis modality, in all previous mentioned studies was conventional hemodialysis (cHD). The on-line hemodiafiltration (on-line HDF) is a relatively new dialysis modality based on the production of ultrapure water (UPW) used for dialysate preparation just before the inflow of dialysate in the circuit. The use of UPW gives access to a virtually unlimited amount of sterile and non-pyrogenic solutions [14].

The aim of this study was to examine whether dialysis modality and type of dialyzer membrane have any influence on the number of NK cells and on phagocytic activity of neutrophilis in patients on chronic dialysis. In addition, the effect of parathyroid hormone (as a high molecular weight uremic toxin) on NK cells count and phagocytic activity of neutrophilis was investigated in this study.

PATIENTS – METHODS

Patients

Sixty (n=60) patients with end-stage renal disease on chronic hemodialysis program, clinically stable and without any hospitalization for the previous six months, were enrolled in the study. All patients showed no evidence of infection, during the period of the study. Patients with active inflammatory or autoimmune disease, HIV infection, hepatitis, malignancy, treatment with steroids or immunosuppressive regimen and blood transfusion over the last year were excluded.

Based on the above mentioned inclusion – exclusion criteria and the dialysis modality used, patients were divided in to three groups: Group I: Twenty (n=20) patients (12 males) with mean age of 56.8±10.8 years (range 36-70 years), were on conventional hemodialysis, treated with Low Flux dialyzer membrane (cHD-LF). The primary kidney disease was glomerulonephritis in 10, diabetes mellitus in 3, polycystic kidney disease in 1 and unknown in 6 patients. Group II: Twenty (n=20) patients, (11 males) with mean age of 62.7±13.4 years (range 27-85 years), were on conventional hemodialysis program, treated with High Flux dialyzer membrane (cHD-HF). The primary kidney disease was glomerulonephritis in 11, diabetes mellitus in 2, polycystic kidney disease in 2 and unknown in 5. Group III: Twenty (n=20) patients (10 males) with mean age of 65.5±15.3 years (range 38-92 years), were on on-line hemodiafiltration, using High Flux dialyzer membrane (on-line HDF). The primary kidney disease was glomerulonephritis in 9, diabetes mellitus in 3, polycystic kidney disease in 3 and unknown in 5.

The comorbidities in patients of groups I, II, III were heart failure [n=5, n=3, n=6], coronary artery disease [n=3, n=2, n=4] and hypertension [n=13, n=11, n=11], respectively.

Medication such as calcium channel blockers, b-blockers, angiotensin converted enzyme and statins were given at the same percentage of patients among the 3 groups. Phosphate binders were taken by 50-60% of patients in each group whereas all patients were treated by erythropoietin at similar doses (average dose: 3.500 IU [range 3.000-5.500]) on each dialysis session.

Forty (n=40) healthy subjects, (22 males) with mean age of 55.9±14.6 years (range 35-88 years) were used as control group.

All patient groups used bicarbonate as the dialysate solution. The composition of the dialysate was: sodium 137 mEq/l, potassium 2 mEq/L, bicarbonate 39 mEq/L, calcium 2.7 mEq/L, chloride 107 mEq/L, magnesium 1.0 mEq/L, acetate 4 mEq/L and dextrose 100 mg/dl (only in diabetic patients). Average blood flow values were 300 ml/min while dialysate flow was 500 ml/min. Dialysate conductivity was 14.0 mS/cm. Low molecular weight heparin was used in all patients as anticoagulant at a medium dose of 3.500 IU. All patients were dialysed three times per week for four hours at each session. The membrane type used in the study was Low and High Flux Polysulphone (Helixon, Fx 10 and Fx 80, Fresenius respectively]. None of the patients had residual renal function (urine output < 200 ml/day).

Laboratory measurements

Blood samples were collected from the arterial line, before the initiation of dialysis session [pre-dialysis (t0)] and at the end of dialysis [post-dialysis (t4)] session prior to the patient disconnection from the extracorporeal circuit.

The pre-dialysis sample was used to determine biochemical indexes (urea, creatinine, parathormone, etc) and for: 1) isolation of peripheral blood mononuclear cells, 2) isolation of white blood cells from the plasma, 3) determination of white blood cell types concentration, 4) determination of the percentage of NK cells and 5) study of phagocytosis

1) Isolation of the peripheral blood mononuclear cells (PBMC's)

Whole blood from every patient was collected in EDTA vacutainers tubes and 2.5 ml from each one was diluted with equal volume of RPMI 1640 medium (GIBCO BRL, Grand Island, NY, USA). Diluted samples were layered transferred onto 1.7 ml of Ficoll separating solution with 1.077 g/ml density (Biochrom AG, Berlin, Germany) and centrifuged at 1.000 g for 40 min at 250 C. Interface, containing peripheral blood mononuclear cells (PBMNs), was transferred in 5 ml phosphate buffered (PBS) and centrifuged at 1.000 g for 10 min at 250 C. Supernatant was removed and the sedimented PBMCs were resuspended in 1 ml of PBS. Same procedure was repeated once more and the number of the suspended PBMCs per ml of PBS was estimated by a hemocytometer.

2) Isolation of white blood cells

Human peripheral white blood cells (WBCs) were isolated from freshly donated heparinised whole blood after hypo-osmotic lysis of red blood cells with an ammonium chloride-based lysing solution (BD Pharm Lyse, San Diego, CA, USA). One volume of blood was mixed with five volumes of lysis buffer. Samples were then centrifuged at 200 g for 6 min at 25°C. Supernatant was aspirated and the same procedure was repeated once more. Sedimented WBCs were re-suspended in RPMI 1640 medium (GIBCO BRL, Grand Island, NY, USA).

3) Determination of the white blood cell types concentration

Whole blood samples were processed for typical hematologic tests to determine, among others, the percentages (%) of the white blood cell types: neutrophils and mononuclear cells (lymphocytes plus monocytes) (Cell DYNE automated hematological analyzer, ABBOTT, Illinois, USA).

4) Determination of the percentage of NK cells

The percentage of CD56+CD3- NK cells was estimated with flow cytometry using mouse anti-human CD3: RPE-Cy5 (MCA463C) and CD56: RPE (MCA1437PE) from AbD Serotee (Bavaria, Germany). PBMCs (105 cells) were incubated in 100 μl PBS, containing 3 μl anti-CD3 and 3 μl anti-CD56, for 20 min at 4o C. In each sample, 400 μl PBS were added and approximately 20,000 cells were analyzed in a Coulter EPICS-XL-MCL cytometer (Coulter, Miami, FL, USA). Data were analyzed using the XL-2 software and the percentage (%) of CD56+ CD3- NK-cells in the total PBMCs population was estimated.

5) Phagocytic activity of neutrophils

Human peripheral blood leukocytes (3x106 cells/ml) were incubated in 200 μl RPMI 1640 medium containing 20% plasma, with E. coli-FITC for 15 min, to estimate phagocytosis. Approximately 20,000 cells from each sample were analysed in a Coulter EPICS-XL-MCL cytometer (coulter, Miami, FL, USA), selecting the polymorphonuclear cell population with the appropriate gating. The XL-2 software was used to process the results. The phagocytic activity of neutrophils was determined in arbitrary fluorescent units (AFU) according to the median value of their fluorescence distribution.

We also studied the influence of biochemical indexes included the parathormone (PTH), a high molecular weight uremic toxin, on NK cells and phagocytosis of neutrophils.

Dialysis delivered dose

The dialysis delivered dose was estimated using the single and double (equilibrate) pool equations [15]:

spKt/(V= -ln(R-0,008×t)+(4-3,5R)×0,55 UF/V)

and

(eq or) dpKt/(V=spKt/(V+0,6((dpKt/V))/t))+0,03

Where:

R : the ratio ureat4/ureat0,
t : dialysis duration (hours),
UF : ultrafiltration volume (litres),
V : the urea distribution volume after the dialysis session

Dialysis efficacy

The dialysis delivered dose, as calculated with equations referred above, was for spKt/V 1.47±0.21 and for eqKt/V 1.26±0.32 (in normal acceptable range according to the K/DOQI).

Statistical analysis

The analysis was performed with using SPSS v 21.0. A post hoc power analysis was performed with the GPower 3.0 software for each of the two outcomes. Descriptions of categorical data were made using plurality, while the descriptions of continuous records with mean value and standard deviation. Single-breasted controls were performed with an independent t-test for independent samples or Mann Whitney test in case of rejection. Variance analysis was performed for multiple comparisons with the Tukey test. Correlation controls were analyzed with the Pearson correlation coefficient test. The results were used in two linear regression models for phagocytosis and for the percentage of NK. For the statistically significant effects, the interactions within the groups were also examined. Values of $p<0.05$ were accepted as statistically significant.

RESULTS

NK cells in healthy subjects and patients on dialysis

The percentage of CD56+CD3- NK cells was determined with flow cytometry and the NK-cells count was calculated based on the total white blood cell count. The average NK-cells count in healthy subjects was significantly higher in comparison to this of all patients on dialysis [(285±114 cells/μl (range 190-510 cells/μl) (8.1±1.8 %) vs. 136±87 cells/μl (range 22-310 cells/μl) (6.2±2.8 %), respectively ($p<0.001$) (Fig. 1)].

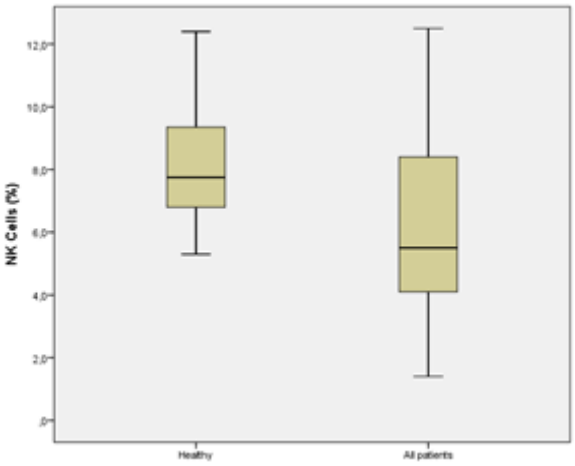

Figure 1. *Percentage (%) of NK cells in healthy and all dialysis patients (p<0.001)*

NK cells and dialysis modality

The average NK cells count was significantly decreased ($p<0.001$), in all three groups of dialysis patients: a) cHD-LF (group I) 157±226 cells/μl (range 22-1024 cells/μl) (6.0±2.7 %), b) cHD-HF (group II) 139±74 cells/μl (range 22-290 cells/μl) (6.9±3.3 %), c) on-line HDF (group III) 113±73 cells/μl (range 29-310 cells/μl) (5.6±2.6 %) in comparison to the healthy subjects group. However, no significant difference was observed among patients dialysed with different dialysis modalities [on-line HDF vs. cHD-HF, on-line HDF vs. cHD-LF and cHD-LF vs. cHD-HF]. Furthermore, no difference was observed in the NK cells between patients dialyzed with Low Flux or and High Flux membranes (data not shown).

Phagocytosis by neutrophils and dialysis modality

The average fluorescent units in all groups are presented in Table 1. A significant difference was observed between healthy subjects and all dialysis patients ($p<0.001$) (Fig 2), as well as healthy subjects vs. cHD-LF, cHD-HF and on-line HDF ($p<0.001$ respectively). However, no difference was observed in the phagocytosis capacity among patients dialyzed with different modalities of dialysis schedule and between patients dialyzed with either Low or High Flux membranes (data not shown).

Table 1. *The Phagocytic activity (AFU) of neutrophils in the study population*

Dialysis Mode	Fluorescent units (AFU)	Range
Healthy Subjects (n= 40)	16.6±1.5	3.80-20.75
All Dialysis Patients (n= 60)	10.1±2.8	4.30-15.20
Group I (cHD-LF) (n= 20)	11.2±2.5	7.30-14.60
Group II (cHD-HF) (n= 20)	7.9±2.4	4.30-12.80
Group III (on-line-HDF) (n= 20)	11.1±2.3	7.60-15.20

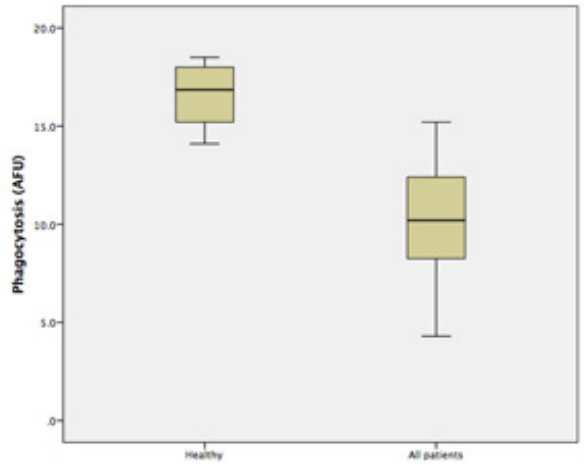

Figure 2. *Phagocytic activity (AFU) of neutrophils in healthy and all dialysis patients (p<0.001)*

NK cells, phagocytosis and parathormone

The blood levels of parathormone showed a strong positive linear correlation with the number of NK-cells (r=0.305, p=) (Fig 3). However, no correlation of blood parathormone levels with phagocytic activity of neutrophilis was observed (Fig 4).

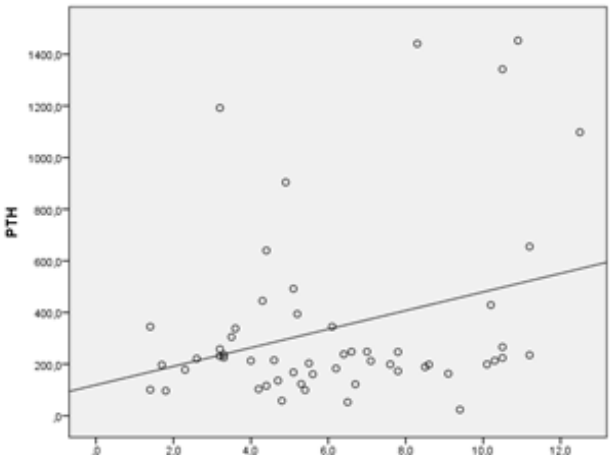

Figure 3. *Correlation of parathormone blood levels with percentage (%) of NK cells in all dialysis patients (r= 0.305, p=)*

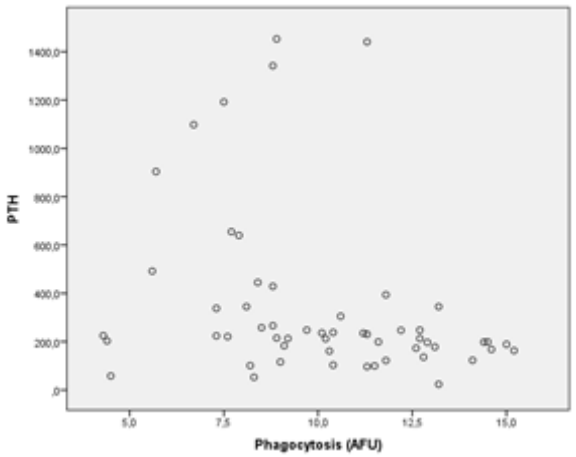

Figure 4. *Correlation of parathormone blood levels with phagocytic activity (AFU) of neutrophils in all dialysis patients (r=, p=NS)*

DISCUSSION

The effect of dialysis modality and type of dialysis membrane on the number of the NK-cells and on the phagocytic activity of neutrophils was investigated in this study in patients on different dialysis modalities. Although NK-cells number and phagocytic activity of polymorphonuclear cells were found to be reduced in patients on dialysis in comparison to healthy subjects, no correlation of the dialysis modality and membrane type was found with disturbances of natural immunity observed in these patients. The reduced number of NK-cells in patients on dialysis confirms the results of previous studies [6–9, 11, 16]. However, others reported [12] that the number of the NK-cells in dialyzed patients is increased if membranes with better biocompatibility are used [12]. The activity of NK-cells is also suppressed according to most studies [8, 9, 11, 13, 17]. Although in our study the activity of NK-cells was not investigated we can assume that it is also suppressed as the decreased activity of NK-cells is mainly associated with the reduced number of the NK-cells [11].

The modality of hemodialysis (cHD and online-HDF) seems not to have a remarkable impact on the number and indirectly on the activity of NK-cells. This is a novel finding, as the effect of the different hemodialysis modalities on NK-cells number is for first time addressed in this study. The comparison between online-HDF and cHD is chosen because in the former the dialysis solution entering the blood system of the patient is free from

microorganisms and endotoxins due to the purification process of the water [14].

Moreover, according to the results of this study the membrane's characteristics of the dialyzer did not had any effect on NK-cells numbers. It should be noted that all patients were dialyzed by polysulfone membrane which is one of the newer synthetic membranes with less electrical zeta potential of the membrane's material (-5mV) [18]. This might be the an explanation for the disagreement of these results with previous in vivo and in vitro studies showing that the number of the NK-cells is significantly reduced when a cellulose based membrane is used in comparison to other synthetic membranes (Polycarbonate, Cellulose acetate, Cuuprammonium, Polyacrylonitrile, Polymethylmethacrylate and Polysulfone)[6-10,13].

In the literature it is mentioned that chronic kidney disease, as a chronic inflammatory process, induces reduction of phagocytic ability of the polymorphonuclear cells and accelerates their apoptosis [19]. Among the factors involved in the development of oxidative stress and of chronic systematic inflammation are uremic toxins, the renin-angiotensin-aldosterone (RAAS) system, hypertension, infections, iron overload, antioxidant deficiency and the hemodialysis procedure per se.

Another interesting finding of this study was the strong positive correlation of parathormone blood levels with the number of NK-cells. PTH represents a uremic toxin with large molecular weight, (9500 Daltons). These results suggest that PTH might have an effect on T-lymphocytes but this is not clear. PTH promotes hemopoiesis which increases the activity of bone marrow, by acting indirectly in different populations of cells, through specific receptors (PPR) or directly by activation of cytokines like interleukin 6 (IL-6) [20]. The specific PP receptors of PTH in the populations of B and T-lymphocyte have been mentioned for first time by Yamamoto (1983) [21]. The mechanism of action of PTH on lymphocytes has not been clarified yet. It is postulated that the increment of intracellular calcium concentration activates the cellular adenylate cyclase. However, it has been mentioned that activation of PPR of lymphocytes by PTH can promote both stimulation [22] and suppression [23] of the cell function. The positive correlation of PTH levels with the number of NK-cells observed in this study agree with the results of Ozdemir et al [24] but are not supported by Angelini et al [25]. Although a strong positive correlation of PTH with the number of NK-cells was observed the phagocytic activity of neutrophils was not related to PTH levels.

In conclusion, impairment of the native immunity as represented by reduced NK cells numbers and phagocytic activity of neutrophils is observed in patients on dialysis. Dialysis modality and membrane type do not influence the native immunity of dialyzed patients. However, parathormone blood levels are possibly involved in the development of immune system disturbances in such patients.

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Резиме

ЕФЕКТОТ НА МОДАЛИТЕТОТ НА ДИЈАЛИЗА И ПЕРФОРМАНСИТЕ НА МЕМБРАНАТА ВРЗ ПРИРОДНИОТ ИМУНИТЕТ КАЈ ПАЦИЕНТИТЕ СО ДИЈАЛИЗА

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Хроничната бубрежна болест (CKD) се карактеризира со имуно активирање и со развој на хронично воспаление. Сепак, кај пациентите со CKD постои имунолошки дефицит. Бројот и активноста на клетките на природните убијци (NK-клетки) се под влијание на биокомпатибилноста на разни мембрани на дијализа. Во оваа студија го испитавме ефектот на модалитетот на дијализата и типот на мембраната врз бројот на NK-клетките и фагоцитната активност на неутрофилите кај пациентите на различни методи на дијализа.

Шеесет пациенти беа вклучени во студијата и беа поделени во три групи од по 20 пациенти. Пациентите на конвенционална хемодијализа што користеа мембрана со низок флукс (cHD-LF) беа вклучени во групата I, пациентите на конвенционална дијализа со употреба на мембрана со висока флукс (cHD-HF) беа вклучени во групата II и пациентите третирани преку онлајн хемодијафилтрација со полисулфонска мембрана со висок флукс (on-line HDF) беа вклучени во групата III. Се испитуваше природниот имунитет, користејќи го бројот на NK-клетки и фагоцитната активност на неутрофилите.

Бројот на NK-клетките беше значително понизок ($p < 0,001$) во трите групи пациенти на дијализа во споредба со здравите субјекти. Сепак, не е забележана значителна разлика во бројот на NK-клетките кај пациентите третирани со конвенционална дијализа со употреба на ниска или висока флукс мембрана и пациентите третирани преку онлајн хемодијафилтрација. Слично на тоа, иако фагоцитната активност на неутрофилите беше значително намалена кај сите пациенти на дијализа ($p < 0,001$), не беа забележани никакви разлики поврзани со модалитетот на дијализата или мембранската изведба. Беше препозната силна позитивна корелација меѓу нивото на паратормон во крвта и бројот на NK-клетките ($r = 0,305$, $p < 0,01$).

Како заклучок, беше забележано нарушување на природниот имунитет претставен со бројот на NK-клетки и фагоцитната активност на неутрофили кај пациентите на дијализа. Модалитетот на дијализа и перформансите на мембраната не влијаат врз природниот имунитет на пациенти на дијализа. Сепак, нивото на паратормон во крвта е веројатно вклучено во развојот на нарушувањата на имунолошкиот систем кај таквите пациенти.

Клучни зборови: NK-клетки, фагоцитоза, имунитет, режим на дијализа, перформанс на мембрана, паратормон