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SIGNIFICANCE AND APPLICABILITY OF SOME INFLAMMATORY MARKERS IN PATIENTS UNDERGOING HEMODIALYSIS

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Abstract. Introduction: *Patients with end-stage renal disease treated with hemodialysis are increasing worldwide, and the main reasons for their shortened survival are cardiovascular and infectious events.* ***Aim:*** *The aim of our study was to monitor the levels of the most commonly used inflammatory markers in practice and to clarify their applicability in this subgroup of patients.* ***Materials and methods:*** *We studied the values of C-reactive protein, interleukin-6, procalcitonin, ferritin, and uric acid in 69 patients treated with hemodialysis for more than 90 days. Those who had clinical evidence of infection or active neoplasm were excluded from the study. We compared the data with sex, age, main diagnosis, and vascular access. By age, patients were divided into those under and over 65 years of age. The data were processed with Statistical Package for Social Sciences (SPSS), version 20.0 (IBM Corp., Armonk, NY). Statgraphics Plus, version 2.1, and EXCEL for Windows.* ***Results:*** *We found that the data for procalcitonin, interleukin-6, ferritin, and uric acid were significantly higher than the reference values for healthy individuals. The only indicator that showed comparable values with healthy individuals was CRP. At the same time, the results for CRP and IL-6 were significantly higher in the groups over 65 years of age (0.025 and 0.006, respectively).* ***Conclusion:*** *According to our results, the only well-correlated and significant indicator in patients on hemodialysis treatment is CRP. Other markers should be used primarily to monitor the effect of the treatment.*

Key words: *end-stage renal failure, hemodialysis, infectious complications, CRP, procalcitonin, IL-6, ferritin, uric acid*

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INTRODUCTION

Chronic kidney disease (CKD) is a growing public health problem, affecting many people, and is becoming a huge financial burden [1]. Estimates show that by 2017, the number of people affected by kidney disease exceeded 850 million people [2], and it is expected that by 2040, CKD "will go from being the third fastest-growing cause of death worldwide to becoming the fifth most common cause of death" [3].

Life expectancy for patients on hemodialysis is significantly reduced compared to the general population. According to the United States Renal Data System,

40- to 45-year-old men and women without dialysis have a life expectancy of about 40 years, while those on dialysis have a life expectancy of no more than 10 years [4].

The progressive loss of renal function is associated with impaired immunity in patients. The clinical consequences of this acquired immune deficiency in patients with chronic kidney disease, both in terms of morbidity and mortality, are significant. These patients are more susceptible to infections, respond poorly to vaccinations, and have an increased risk of developing atherosclerotic changes and various neoplasms [5].

According to data cited in 2011 by T. Eleftheriadis et al., the annual mortality rate due to bacteremia is 100-300 times higher in hemodialysis patients compared to the general population. Even when age, race, sex, presence of diabetes mellitus, and possible technical errors are taken into account, the mortality rate due to bacteremia is still 50 times higher [6].

In 2021, one-third of Medicare spending for beneficiaries with end-stage renal disease was for inpatient care. Nearly 25% of these costs were related to infection management. Total Medicare spending for care for beneficiaries with end-stage renal disease was over $52 billion in 2021 [7, 8].

The aim of our study was to investigate four biomarkers that are considered sufficiently sensitive and specific for the inflammatory process in the general population, and to establish their level in patients with end-stage renal failure treated with hemodialysis, and to what extent they may be applicable in the early diagnosis of infectious conditions in this subpopulation.

MATERIALS AND METHODS

The study was conducted on a total of sixty-nine patients treated with hemodialysis, with a mean age of 62.0 ± 13.957 years, 30 (43.5%) of whom were women. The study was performed after obtaining permission from the Research Ethics Committee at the relevant medical university (Decision No.851/2025), and it included all patients with chronic hemodialysis who did not meet the exclusion criteria and had signed an informed consent for participation. Exclusion criteria were: refusal to participate, presence of a neoplastic process, anamnestic and clinical data for an inflammatory condition at the time of examination, confirmed by blood count data: leukocytosis with neutrophilia. The proportion of patients studied was 86.7% of the total number of patients treated with hemodialysis at that time. CRP, Procalcitonin, Ferritin, interleukin 6 (IL-6), and uric acid were tested. The results were compared with normal values for the general population, as well as with the sex, age, underlying disease, and vascular access of the patients. Statistical Package for Social Sciences (SPSS), version 20.0 (IBM Corp., Armonk, NY) was used to process the results. Statgraphics Plus, version 2.1, and EXCEL for Windows. Normal distribution for hypothesis testing: Analysis of Variance (ANOVA) – LSD.

Non-parametric tests for non-normal distributions to test hypotheses: *chi-squares, Pearson test, Kruskal-Wallis test, Mann-Whitney (Wilcoxon)*.

Student's t-test was used in the dynamic tracking of results.

A $p\text{-value} < 0.05$ is considered statistically significant.

RESULTS

The distribution of patients by age and underlying disease are shown in the following graph – Figure 1, with statistical significance being established for the relationship between age and chronic glomerulonephritis as the main cause of end-stage renal failure (Chi-Square, $\chi^2 = 4.455$, df = 1, p = 0.035).

Only 18.8% of patients on chronic dialysis treatment have a native AV fistula for vascular access; the rest mainly refuse to construct one due to cosmetic reasons, fear of needles, and only 11.3% of patients with a tunneled catheter have exhausted the possibility of constructing an anastomosis.

Procalcitonin tests showed a mean value of 0.290 ng/ml (0.395 ± 0.452 ng/ml) with a normal value of < 0.05 ng/ml, with an elevated value being reported in all patients. No significant difference was found by age (p = 0.957).

The values we determined for CRP were 3.34 mg/l (10.24 ± 22.179 mg/l), with a laboratory norm of < 5.0 mg/l, and the differences in the data in the groups under and over 65 years of age (2.46 vs 4.97 mg/l, respectively) proved to be significant (p = 0.025).

Serum ferritin data showed – 392.30 ng/ml (576.11 ± 494.03 ng/ml), with a normal range of 4.6 to 204 ng/ml, with no significant differences found according to the age of the patients (p = 0.133).

IL-6 had a mean value of 9.0 pg/ml (12.6 ± 10.741 pg/ml), with a normal value of < 7.0 pg/ml; its mean value was increased regardless of age, but in the group over 65 years of age, this increase was more pronounced (8 vs 10 pg/ml, respectively) and the difference was significant (p = 0.006).

Uric acid (UA) levels were elevated in 81.2% of patients (> 420 µmol/l), with no significant difference found in the two age groups, p = 0.342.

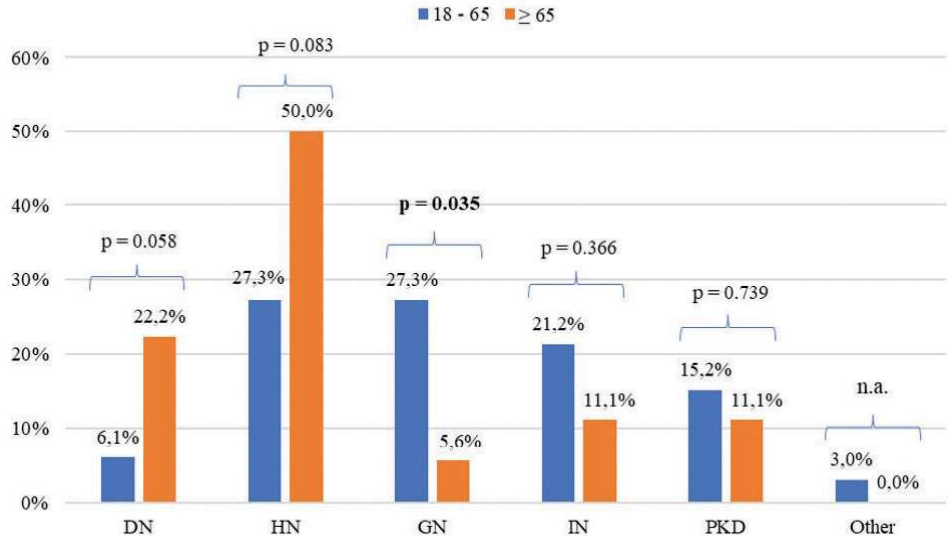

Fig. 1. Distribution of patients by age and underlying disease
(DN – diabetic nephropathy, HN – hypertensive nephropathy, GN – glomerulonephritis, IN – interstitial nephropathy, PKD – polycystic kidney disease)

DISCUSSION

In addition to the basic changes in the immunity of patients with arterial hypertension, diabetes mellitus, hyperlipidemia, metabolic syndrome, etc., factors specific to dialysis methods are added, leading to an increased availability of free oxygen radicals, pro-inflammatory markers, uremic environment, which accelerate the processes of atherosclerosis, carcinogenesis, and immunosuppression. Ultimately, patients treated with dialysis methods end up with an increased frequency of hospitalizations, mortality, and economic pressure on the healthcare system [9, 10].

C-reactive protein (CRP). CRP is an acute-phase protein synthesized in the liver in response to inflammation and is often measured to monitor the response to therapy in patients with acute and chronic inflammatory conditions. Because of its availability, reproducibility, and low cost, serum CRP levels are a convenient marker for the diagnosis of sepsis. Discovered by W. Tillett and T. Francis in 1930, its name is associated with its identification as a substance in the serum of patients with acute inflammation that reacts with the “C”-carbohydrate antigen of the pneumococcal capsule. C-reactive protein (CRP) is a member of the pentraxin family and probably exists in at least two conformationally distinct forms: native pentameric CRP (pCRP) and monomeric CRP (mCRP). Its production is induced primarily by the action of IL-6 on the gene responsible for its transcription during the acute phase of an infectious process. Therefore, it can be argued that the increase in this biomarker parallels the levels of IL-6 in serum. The detection of CRP values > 8.7 mg/dl has a sensitivity and specificity of 93.4% and 86.1%, respectively. However, its examination is recommended more as a marker for monitoring the effect of treatment than for accurate diagnosis of the infectious process [11, 12, 13]. J. Li et al. considered that the simultaneous examination of CRP and procalcitonin has sufficient sensitivity and specificity in sepsis [14].

CRP was the only biomarker for infection that showed normal values in dialysis patients who had no clinical evidence of inflammation. However, its values were significantly higher in those over 65 years of age, which corresponded to a similar trend in the results for IL-6, confirming the relationship between these indicators.

Procalcitonin (PCT). In today’s clinical practice, procalcitonin (PCT) has become a promising marker for the early diagnosis of bacterial infections. It is a precursor of the hormone calcitonin, with 116 amino-acid residues, to which Le Moullec et al. [15] first drew attention in 1984. Almost 10 years later, M. Assicot et al. established a correlation between its serum levels and proven bacterial infections and sepsis [16]. Procalcitonin can also be synthesized in the liver, kidneys, pancreas, leukocytes, etc., but its levels usually increase mainly under the influence of pro-inflammatory cytokines, such as IL-6, tumor necrosis factor (TNF)-alpha, and viral infections reduce its production [17]. In addition to its high specificity with respect to the bacterial etiology of inflammation, pro-

calcitonin is a very convenient indicator for monitoring the effect of antibiotic treatment [18].

In our study, PCT levels were significantly elevated in all patients studied, almost six times above the reference value, which is why, in our opinion, this indicator does not have sufficient sensitivity in the diagnosis of infectious conditions in hemodialysis patients, but it may be considered for monitoring the effect of the treatment.

Interleukins (IL). Cytokines are chemokines produced by the host immune system in response to infection or injury that play a role in the complex pathophysiology of sepsis. Interleukin-6 (IL-6), IL-8, and IL-10 are the most widely studied cytokines for the diagnosis of sepsis, as well as for the assessment of the inflammatory response, and help determine patient prognosis. IL-6 is a prototypical proinflammatory cytokine, IL-8 is a major chemokine, and IL-10 is an important anti-inflammatory cytokine [5, 9, 19].

None of the cytokine markers has shown to be more sensitive or specific than PCT or CRP [20].

Ryuzo Abe et al. found in their study that blood levels of CRP and IL-6 were significantly higher in cases of gram-negative sepsis [20].

In our study, IL-6 levels were above the average reference range, and this increase was reported in over 81% of the subjects, which also makes it an insufficiently sensitive indicator of infection, as is PCT. We should also note the significantly higher values of this indicator in the over-65 age group – a difference which should be taken into account when interpreting laboratory data.

Ferritin. Understanding the biology of ferritin has traditionally focused on its role in iron storage and homeostasis, with low ferritin levels indicating deficiency and high levels indicating primary or secondary hemochromatosis. During infection, elevated ferritin levels represent an important host defense mechanism that deprives bacterial growth of iron and protects immune cell function. It may also be protective, limiting free radical production and mediating immunomodulation. Furthermore, hyperferritinemia is a key acute-phase reactant used by clinicians as an indication for therapeutic intervention aimed at controlling inflammation in high-risk patients. Others have argued that ferritin is a key mediator of immune dysregulation, particularly in extreme hyperferritinemia, through direct immunosuppressive and proinflammatory effects [21].

In our study, serum ferritin values were significantly higher than the reference values, but we should pay attention to the fact that most of the patients treated with hemodialysis also receive iron preparations, which makes the increase in this indicator difficult to interpret. However, in our opinion, it can be taken into account in the complex of indicators for monitoring the effect of the treatment.

Uric acid is the end product of purine breakdown in humans, but in other mammals, it is further metabolized to allantoin by uricase. It exerts antioxidant effects by scavenging free radicals and chelating metal ions. In fact, uric acid is known to have a protective effect against neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. It activates both the innate and adaptive immune systems, which is why we can say that uric acid is an indicator of the inflammatory status of the examined person. However, in patients with renal failure, its levels increase as a manifestation of impaired elimination [22-24].

Uric acid was elevated in 81.2% of the studied patients, which is mainly related to the underlying disease, but although it is an unreliable inflammatory marker in such a population, we should not ignore its pathogenetic importance as a factor for accelerated atherosclerosis and impaired general immunity in hemodialysis patients.

CONCLUSION

Our study found that serum CRP levels are a sufficiently inexpensive, comparable, and reliable marker for the presence of an infectious condition in patients treated with hemodialysis. Other markers, such as IL-6, PCT, and ferritin, are better suited to be used as treatment outcome monitoring indicators in this population.

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Informed Consent From Participants: *Written informed consent was obtained from all participants prior to inclusion in the study.*

REFERENCES

1. Neuen BL, Chadban SJ, Demaio AR, et al. Chronic kidney disease and the global NCDs agenda. BMJ Glob Health. 2017 Jul 6;2(2):e000380. doi: 10.1136/bmjgh-2017-000380.
2. Jager KJ, Kovesdy C, Langham R, et al. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. Kidney Int. 2019 Nov;96(5):1048-1050. doi: 10.1016/j.kint.2019.07.012.

3. Bello AK, Okpechi IG, Osman MA, et al. Epidemiology of haemodialysis outcomes. Nat Rev Nephrol. 2022;18(6):378-395.
4. United States Renal Data System. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. (National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020). https://usrds-adr.niddk.nih.gov/2022
5. Borisov B, Doroteya K. Changes in innate immunity in patients with chronic kidney disease. Current Trends in Immunology. 2021, 2, 35-41.
6. Eleftheriadis T, Liakopoulos V, Leivaditis K, et al. Infections in hemodialysis: a concise review - Part 1: bacteremia and respiratory infections. Hippokratia. 2011;15(1):12-17.
7. Johansen K, Gilbertson D, Shuling L, et al. US Renal Data System 2023 Annual Data Report: Epidemiology of Kidney Disease in the United States. American Journal of Kidney Diseases. 2024;83(4):A8-A13.
8. Silberzweig, J. Reducing Infections in Outpatient Hemodialysis: The Impact of Human Factors. American Journal of Kidney Diseases. 2024;84(1):4-5
9. Espi M, Koppe L, Fouque D, Thaunat O. Chronic Kidney Disease-Associated Immune Dysfunctions: Impact of Protein-Bound Uremic Retention Solutes on Immune Cells. Toxins (Basel). 2020;12(5):300.
10. Espi M, Charmetant X, Fusil F, et al. Chronic Kidney Disease-Associated Defect in Humoral Immune Response Is Driven by Inflammation. Toxins 2026, 18, 104.
11. Fan SL, Miller NS, Lee J, Remick DG. Diagnosing sepsis – The role of laboratory medicine. Clin Chim Acta. 2016; 460:203-210.
12. Jungen MJ, Ter Meulen BC, van Osch T, et al. Inflammatory biomarkers in patients with sciatica: a systematic review. BMC Musculoskelet Disord. 2019;20(1):156.
13. Luan YY, Yao YM. The Clinical Significance and Potential Role of C-Reactive Protein in Chronic Inflammatory and Neurodegenerative Diseases. Front Immunol. 2018;9:1302.
14. Li J, Hu L, Li L. C-Reactive Protein, Procalcitonin, and a Novel Pathogenesis and Therapeutic Target of Thrombocytopenia in Sepsis. Emerg Med Int. 2022; 2022:2498435.
15. Le Moullec JM, Jullienne A, Chenais J, et al. The complete sequence of human preprocalcitonin. FEBS Lett. 1984;167(1): 93-97.
16. Assicot M, Gendrel D, Carsin H, et al. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993; 341(8844): 515-518.
17. Lippi G, Sanchis-Gomar F. Procalcitonin in inflammatory bowel disease: Drawbacks and opportunities. World J Gastroenterol. 2017; 23(47): 8283-8290.
18. Kip MMA, van Oers JA, Shajiei A, et al. Cost-effectiveness of procalcitonin testing to guide antibiotic treatment duration in critically ill patients: results from a randomised controlled multicentre trial in the Netherlands. Crit Care. 2018; 22(1): 293.
19. Ivanov N, Mihailova S, Bilyukov R, et al. Changes in the cytokine profile in patients during COVID-19 infection. Acta Medica Bulgarica, 2023, 50 (4):5-12.
20. Abe R, Oda S, Sadahiro T, et al. Gram-negative bacteremia induces greater magnitude of inflammatory response than Gram-positive bacteremia. Crit Care. 2010;14(2): R27.
21. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol. 2017;29(9):401-409.
22. Gupta J, Mitra N, Kanetsky PA, et al. CRIC Study Investigators. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. Clin J Am Soc Nephrol. 2012;7:1938–1946.
23. Isaka Y, Takabatake Y, Takahashi A, et al. Hyperuricemia-induced inflammasome and kidney diseases. Nephrol Dial Transplant. 2016;31(6):890–896.
24. Gavrailova M, Elenkova A, Robeva R. Differences in metabolic parameters in patients with different degrees of obesity. Acta Medica Bulgarica, 2026, 53 (2):22-28.