POBOROWSKA, Dominika, KAHAN, Weronika, SZAFRAŃSKA, Weronika, POLAŃSKA, Katarzyna, WOJACZEK, Marta, NIEDBAŁ, Piotr, KOSIŃSKA, Agnieszka, KRAS, Magdalena, LELEK, Katarzyna and ŁATA, Marcin. Physical activity in diabetic nephropathy-protective and preventive effects on the occurrence of diabetic complications. Quality in Sport. 2024;19:54020. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.19.54020
https://apcz.umk.pl/QS/article/view/54020

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 02.08.2024. Revised: 02.08.2024. Accepted: 12.08.2024. Published: 19.08.2024.

Physical activity in diabetic nephropathy-protective and preventive effects on the occurrence of diabetic complications

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Abstract

Introduction and purpose

Nephropathy is characterized by a gradual increase in blood pressure, urinary albumin excretion and cardiovascular risk. It is associated with a decrease in glomerular filtration rate (GFR) resulting in end-stage renal failure. It lowers the standard of living and leads to premature death in patients with this complication of diabetes. The purpose of this article is to present the problem of diabetic nephropathy, possible diagnostic methods, treatment methods with emphasis on the effect of physical activity on improving and alleviating diabetic nephropathy.

State of knowledge

This article reviews the literature on type 1 and type 2 diabetes, diabetic complications with special attention to diabetic nephropathy and the effect of exercise on the frequency and progression of this complication. The number of people with diabetes and the associated complications of diabetes are steadily increasing. Proper diet and physical activity can maintain

normal blood glucose levels and slow the progression of diabetic nephropathy as well as other diabetic complications.

Material and method

The literature available in "PubMed" and Google Schoolar was reviewed. The focus was on the problem of complications of diabetes mellitus with a special emphasis on diabetic nephropathy, pathogenesis, diagnosis, treatment methods and prevention of nephropathy through the beneficial effects of exercise in diabetic patients.

Summary

In our review, we managed to show how diabetic nephropathy is a big problem in diabetic patients. Based on a number of studies, we were able to prove the beneficial effects of physical activity on reducing the incidence of diabetes complications. Through a variety of modalities and mechanisms, exercise helps control blood sugar and blood pressure and reduce serum creatinine and albuminuria, thereby alleviating kidney damage.

Keywords: Diabetic nephropathy; Physical activity; Type 1 and type 2 diabetes; Diabetes complications

Introduction

Diabetes is a metabolic disease of civilization. There are two types of diabetes. Type I diabetes leads to insulin deficiency as a result of an autoimmune process, causing the destruction of pancreatic β-cells. Type II is the most common form of the disease, characterized by decreased insulin secretion and insulin resistance.[1] The disease causes a number of chronic serious complications, including diabetic nephropathy. This is a dangerous complication that is highly likely to lead to kidney failure. About one in three adults with diabetes develops chronic kidney disease.[2] The mortality rate for people with diabetic nephropathy is about 30 times higher compared to diabetic patients without kidney damage.[3]

Purpose

The purpose of this study is to show how important in preventing or delaying complications of diabetes are normal blood glucose levels, which can be normalized by proper diet and regular physical activity. In our work, we want to point out how big a problem diabetic nephropathy is for diabetic patients, the methods of diagnosis, treatment, and classification of nephropathy by analyzing the scientific literature and relevant studies.

Material and methods

Diabetes is one of the socially significant epidemic diseases. According to the International Diabetes Federation, there are currently 537 million people with diabetes and it is estimated that this number will rise to 784 million in 2045.[4] There are social and economic burdens that are determined by the development of microvascular and macrovascular complications, which are the cause of early disability and mortality for patients.[5] Diabetic nephropathy occurs in about 40% of diabetic patients, according to recent data.[6] Chronic renal failure resulting from diabetic nephropathy is one of the leading causes of mortality among patients with type 1 diabetes.[7] In patients with type 2 diabetes, diabetic nephropathy ranks 3rd among causes of death due to diabetes complications.[8] Therefore, diabetic nephropathy is a serious public health problem. In our work, we will look at treatment methods, including attention to physical activity as a method of treatment, prevention and progression of this diabetic complication. To do this, we review publicly available article databases such as PubMed and Google Schoolar.

Results

In our review, we were able to present the diagnostic differentiation, classification and summarize the forms of treatment of diabetic nephropathy. By reviewing a number of articles, we became convinced of the positive aspect of physical activity as one of the methods of treating and preventing diabetic complications. Our analysis showed that physical activity has a beneficial effect in reducing the risk of diabetic nephropathy and causes a decrease in severity in patients who have this complication.

Nephropathy

Diabetic nephropathy is recognized as a significant complication of both type I and type II diabetes. It is the most common cause of end-stage renal failure.[9] The mechanism of this complication is very complex and not fully understood, which translates into poor therapeutic outcomes. Unfortunately, it has also been shown that standard therapy, combined with restrictive blood glucose control and blood pressure control, is unable to halt the progression of the disease. Therefore, it is necessary to look at new non-standard methods by which we are able to slow down this microangiopathic process.

Epidemiology and pathogenesis

Diabetic nephropathy is diagnosed in 20-40% of people with diabetes. Even after 15 years of the disease, we can show albuminuria, we can demonstrate albuminuria, which is an important screening biomarker of renal function because it reflects glomerular damage.[10-11]

Racial groups such as African-Americans and Native Americans are particularly burdened. In this regard, studies show that genetics also play a significant role in the development of this complication.[12]

A number of factors are known to adversely affect the development of diabetic kidney disease and include prolonged hyperglycemia, high serum lipid levels, hypertension, smoking, male gender, a high-sodium and high-protein diet and genetic predisposition.[13-14]

A very complex process leads to diabetic kidney disease. Chronic hyperglycemia and dyslipidemia play a major role in the pathogenesis. In addition, many mediators such as oxidative stress, chronic inflammation and excessive activation of the renin- angiotensin-aldosterone system influence the occurrence and progression.

Long-term hyperglycemia induces excessive production of reactive oxygen species and is the main culprit of cell damage in diabetes and its complications. Reduced antioxidant capacity leads to the release of inflammatory mediators and increased levels of cytokines and chemokines, including IL-6, MCP-1, TGF-beta and VEGF.[15]

The cascade leads to changes in the structure and function of the glomeruli. In addition, intraglomerular pressure increases, by increasing renal flow and constricting the vessels draining the glomeruli. Clinically, this manifests itself as increased albumin seepage and subsequent proteinuria. With the duration of the whole process, glomerular vitrification and fibrosis of the interstitial tissue occur, and in the final stage, renal failure .[16-17]

Diagnosis

Diabetic nephropathy is defined as persistent albuminuria found two or more times, at least three months apart, in urine samples taken in the morning. Significant albuminuria is more than 30 mg per day or greater than 200 micrograms of albumin excretion per minute. Moderately increased albuminuria occurs when the rate of albumin excretion reaches 30 - 300 mg/24h. This is a marker of early diabetic nephropathy. It is also necessary to rule out urinary tract infections, which can potentially cause increased albumin excretion. Symptoms of nephropathy appear when structural and functional damage to the glomeruli is at an advanced level (stage III CChN according to Mogensen). They usually concern feelings of fatigue and swelling of the feet. Patients also observe foaming of urine. This is usually accompanied by other microvascular complications of diabetes, such as high blood pressure, coronary artery disease and retinopathy.[18,10]

Classification

The division of diabetic nephropathy can be presented according to Mogensen.

Period I occurs from the beginning of the disease. In this phase, albumin excretion is normal (more than 30 mg/day), however, there is an enlargement of the size of the kidneys. GFR reaches a value of 160 ml/min. Changes in this phase are reversible.

Period II is the interval from 2-5 years of diabetes. Histological changes are found (including thickening of the basement membrane of capillaries). Albumin excretion is usually at the upper limit of normal or periodically elevated.

Period III is considered the onset of latent nephropathy. It occurs between 5 and 10-15 years of the disease. Further progression of histopathological changes is observed, over and above this albumin excretion reaches values of 30-300 mg/24 h (gradually increasing microalbuminuria), and GFR decreases from 160 to 130 ml/min. In some patients, blood pressure increases.

In the fourth period, clinically overt diabetic nephropathy occurs. It occurs after 15-25 years of disease duration. In this phase there is macroalbuminuria (more than 300 mg /24h), and most patients have hypertension, edema and lipid disorders.

The fifth period is the stage of end-stage renal failure, after 25-30 years of diabetes. By closing the renal glomeruli, there is a reduction in proteinuria, but also a significant reduction in GFR (less than 10 ml/min). The structural changes are irreversible.

Treatment

The treatment of diabetic nephropathy is primarily aimed at slowing the progressive process of impairment of kidney function and structures. In the treatment of people with diabetes, nephroprotective treatment should be started at an early stage of the disease. It is based primarily on strict control of blood glucose levels, blood pressure, as well as maintaining adequate serum lipid levels. The therapy also uses new drugs that target the pathomechanisms of oxidative stress and inflammation.[19] ACEIs AND ARBs, or drugs that inhibit the RAA system. Blockade of this system through the use of Captopril has shown effective nephroprotective effects, and when used at an early enough stage can inhibit the progression of the complication. Mineralocorticoid Receptor Antagonists is another group that, in addition to regulating sodium balance, has shown positive effects on inhibiting inflammation and fibrosis

taking place in the interstitial tissue of the kidney. 1,25-Dihydroxyvitamin D3 is a hormonal form of vitamin D with various physiological functions, used in diabetic nephropathy it shows anti-inflammatory and nephroprotective effects. Another important group are drugs used especially in type II diabetes. SGLT2 (the phlogazines) and GLP-1 receptor agonists in their action, in addition to the absence of risk of hypoglycemia, also slow the progression of diabetic kidney disease , and reduce the risk of cardiovascular events.[20-23]

Physical activity and its impact on the risk of diabetic nephropathy

There is growing evidence that exercise can mitigate the progression of kidney damage in patients with diabetic nephropathy. It is recommended that patients with diabetic nephropathy undertake exercise that mobilizes major muscle groups throughout the body.

Hawley et al. showed that physical training can improve insulin sensitivity in people with insulin resistance due to increased expression of proteins associated with glucose metabolism, insulin transduction and increased lipid oxidation in muscle.[24] A controlled study of 99 subjects with an average GFR of 33 million/min/1.73m2, among whom 59% had diabetes and 29% had coronary artery disease, showed that long-term physical training leads to improved cardiorespiratory fitness in patients with chronic kidney disease. This is accompanied by a reduction in albuminuria and an increase in GFR.[25] Another study analyzed renal parameters in 19,664 patients with diabetes and 11,648 patients without diabetes, with a follow-up period of 56 months.[26] Those who engaged in physical activity 2-6 times a week had a 43% lower risk of adverse renal outcomes compared to those who did not engage in physical activity.

A meta-analysis involving 38,991 participants showed that physical activity increased GFR and decreased urine albumin/creatinine ratio in patients with diabetes.[27]

Pongrac Barlovic et al.[28] have shown that regular moderate to vigorous exercise reduces the likelihood of the onset and development of kidney disease. It is also associated with a reduced risk of cardiovascular incidents. A 10-year follow-up study involving 2,180 people with type 1 diabetes confirmed that taking exercise, especially high-intensity exercise reduces the risk of diabetic nephropathy.[29] Karstoft et al.[30] divided patients into two groups, intermittent walking training and continuous walking training. All participants exercised these activities 5 times a week in 60-minute sessions for 4 months, and found that interval walking was more effective than continuous walking matched in terms of energy expenditure in improving physical fitness, body composition and glycemic control. Pechter et al.[31] showed that all patients with chronic kidney disease participating in water exercise showed a significant reduction in proteinuria and serum cystatin C levels compared to the sedentary lifestyle group, confirming the improvement

of renal function through physical activity. Wilkinson et al.[32] proved that exercise that can continuously mobilize the major muscle groups of the whole body is most effective in alleviating chronic kidney disease. Costantini-Nascimento et al.[33] showed that exercise can regulate the immune system to develop an anti-inflammatory effect on diabetes-induced kidney damage, and exercise can reduce the expression of inflammatory factors and TGF-β and alleviate oxidative stress to alleviate diabetes-induced kidney damage. Therefore, exercise can reduce inflammatory and fibrotic factors and alleviate oxidative stress in the kidney, thus playing a protective role. Baião et al.[34] showed that long-term physical activity decreased levels of C-reactive protein (CRP) and pro-inflammatory cytokines such as IL-6 in patients with chronic kidney disease and increased levels of IL-10, suggesting that exercise may mitigate kidney damage by alleviating inflammation.

Discussion

Diabetic nephropathy has become one of the leading causes of mortality and disability in diabetic patients. Lack of dietary adherence, lack of physical activity and the associated lack of blood glucose control are associated with a high risk of diabetic complications including the diabetic nephropathy in question. Promoting a healthy, active lifestyle of a balanced diet, as well as maintaining blood glucose at normal levels and periodic monitoring of renal parameters, are crucial to mitigating and inhibiting diabetic nephropathy.

Conclusion

In this work, we have demonstrated the positive effect of physical activity on the prevention of kidney damage, that is, on the development of diabetic nephropathy. Daily physical activity contributes to normalization of blood glucose, but also reduces albuminuria, which is a biomarker of kidney function. For patients suffering from diabetes, it is important not to lead to the progression of disorders of the structure and function of the glomeruli, through the ongoing inflammatory process and fibrosis, which is also benefited by exercise. Studies are proving the role of physical activity as a form of adjunctive treatment for newly diagnosed diabetes and chronic hyperglycemia with vascular complications.

DISCLOSURE

Author's contribution

Conceptualization, Dominika Poborowska and Weronika Kahan; methodology, Weronika Szafrańska; software, Katarzyna Polańska; check, Marta Wojaczek and Magdalena Kras; formal analysis, Agnieszka Kosińska and Piotr Niedbał; investigation, Marcin Łata and Katarzyna Lelek; resources, Dominika Poborowska; data curation, Weronika Kahan; writing - rough preparation,Katarzyna Polańska; writing - review and editing, Marta Wojaczek; visualization, Magdalena Kras; supervision, Agnieszka Kosińska and Piotr Niedbał; project administration, Marcin Łata and Katarzyna Lelek ; receiving funding - no specific funding.

All authors have read and agreed with the published version of the manuscript.

Financing statement

The study received no specific funding

Institutional Review Board Statement

Not applicable – Not required

Informed Consent Statement

Not applicable – Not required

Data Availability Statement

The data presented in this study is available upon request from the correspondent author.

Conflict of interest

The authors deny any conflict of interest

References:

1. Choudhury AA, Devi Rajeswari V. Gestational diabetes mellitus - A metabolic and reproductive disorder. Biomed Pharmacother. 2021 Nov;143:112183. doi: 10.1016/j.biopha.2021.112183. Epub 2021 Sep 21. PMID: 34560536.
2. US Department of Health and Human Services, Centers for Disease Control and Prevention. *National Chronic Kidney Disease Fact Sheet: General Information and National Estimates on Chronic Kidney Disease in the United States, 2010.* US Department of Health and Human Services, Centers for Disease Control and Prevention; Atlanta, GA, USA: 2010.
3. Sagoo MK, Gnudi L. Diabetic nephropathy: a review. Diabet. *Nephrop.* 2020; 2067 :3–7.
4. Sun H., Saeedi P., Karuranga S., Pinkepank M., Ogurtsova K., Duncan BB, Stein C., Basit A., Chan JCN, Mbanya JC i in. Atlas of diabetes IDF: global, regional and national diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res. Clin. Pract.* 2022; 183 :109119. doi: 10.1016/j.diabres.2021.109119.
5. Mauricio D., Alonso N., Gratacòs M. Chronic complications of diabetes: the need to go beyond classical concepts. *Trends Endocrinol. Metab.* 2020; 31 :287–295. doi: 10.1016/j.tem.2020.01.007.
6. Li KX, Ji MJ, Sun HJ Updated pharmacological insights into resveratrol in the treatment of diabetic nephropathy. *Gene.* 2021; 780 :145532. doi: 10.1016/j.gene.2021.145532.
7. Thomas B. Global burden of diabetic kidney disease: time trends and gender differences. *Curr. Diab. Rep.* 2019; 19:18 . doi: 10.1007/s11892-019-1133-6.
8. González-Pérez A., Saez M., Vizcaya D., Lind M., Rodriguez LG Prevalence and risk factors for mortality and end-stage renal disease in people with type 2 diabetes and diabetic kidney disease: a population-based cohort study in the United Kingdom. *BMJ Open Diabetes Res. Care*. 2021; 9 :e002146. doi: 10.1136/bmjdrc-2021-002146.
9. Lu Y, Liu D, Feng Q, Liu Z. Diabetic Nephropathy: Perspective on Extracellular Vesicles. Front Immunol. 2020 Jun 3;11:943. doi: 10.3389/fimmu.2020.00943. PMID: 32582146; PMCID: PMC7283536.
10. Samsu N. Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. Biomed Res Int. 2021 Jul 8;2021:1497449. doi: 10.1155/2021/1497449. PMID: 34307650; PMCID: PMC8285185.

11. Thipsawat S. Early detection of diabetic nephropathy in patient with type 2 diabetes mellitus: A review of the literature. *Diabetes and Vascular Disease Research*. 2021;18(6). doi:10.1177/14791641211058856
12. Varghese RT, Jialal I. Diabetic Nephropathy. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534200/
13. Opazo-Ríos L, Mas S, Marín-Royo G, Mezzano S, Gómez-Guerrero C, Moreno JA, Egido J. Lipotoxicity and Diabetic Nephropathy: Novel Mechanistic Insights and Therapeutic Opportunities. Int J Mol Sci. 2020 Apr 10;21(7):2632. doi: 10.3390/ijms21072632. PMID: 32290082; PMCID: PMC7177360.
14. Saini DC, Kochar A, Poonia R. Clinical correlation of diabetic retinopathy with nephropathy and neuropathy. Indian J Ophthalmol. 2021 Nov;69(11):3364-3368. doi: 10.4103/ijo.IJO_1237_21. PMID: 34708806; PMCID: PMC8725070.
15. Luis F. Hernandez, Natsuki Eguchi, David Whaley, Michael Alexander, Ekamol Tantisattamo, Hirohito Ichii. Anti-Oxidative Therapy in Diabetic Nephropathy. Front. Biosci. (Schol Ed) 2022, 14(2), 14. https://doi.org/10.31083/j.fbs1402014
16. Jin Q, Liu T, Qiao Y, Liu D, Yang L, Mao H, Ma F, Wang Y, Peng L, Zhan Y. Oxidative stress and inflammation in diabetic nephropathy: role of polyphenols. Front Immunol. 2023 Jul 21;14:1185317. doi: 10.3389/fimmu.2023.1185317. PMID: 37545494; PMCID: PMC10401049.
17. Yang J, Liu Z. Mechanistic Pathogenesis of Endothelial Dysfunction in Diabetic Nephropathy and Retinopathy. Front Endocrinol (Lausanne). 2022 May 25;13:816400. doi: 10.3389/fendo.2022.816400. PMID: 35692405; PMCID: PMC9174994.
18. Lyssenko V, Vaag A. Genetics of diabetes-associated microvascular complications. Diabetologia. 2023 Sep;66(9):1601-1613. doi: 10.1007/s00125-023-05964-x. Epub 2023 Jul 14. PMID: 37452207; PMCID: PMC10390394.
19. Hu Q, Chen Y, Deng X, Li Y, Ma X, Zeng J, Zhao Y. Diabetic nephropathy: Focusing on pathological signals, clinical treatment, and dietary regulation. Biomed Pharmacother. 2023 Mar;159:114252. doi: 10.1016/j.biopha.2023.114252. Epub 2023 Jan 13. PMID: 36641921.
20. Elendu C, John Okah M, Fiemotongha KDJ, Adeyemo BI, Bassey BN, Omeludike EK, Obidigbo B. Comprehensive advancements in the prevention and treatment of diabetic

nephropathy: A narrative review. Medicine (Baltimore). 2023 Oct 6;102(40):e35397. doi: 10.1097/MD.0000000000035397. PMID: 37800812; PMCID: PMC10553077.

21. Natesan V, Kim SJ. Diabetic Nephropathy - a Review of Risk Factors, Progression, Mechanism, and Dietary Management. Biomol Ther (Seoul). 2021 Jul 1;29(4):365-372. doi: 10.4062/biomolther.2020.204. PMID: 33888647; PMCID: PMC8255138.
22. Tuttle KR, Agarwal R, Alpers CE, Bakris GL, Brosius FC, Kolkhof P, Uribarri J. Molecular mechanisms and therapeutic targets for diabetic kidney disease. Kidney Int. 2022 Aug;102(2):248-260. doi: 10.1016/j.kint.2022.05.012. Epub 2022 Jun 3. PMID: 35661785.
23. Delanaye P, Scheen AJ. EMPA-KIDNEY : l'empagliflozine dans la maladie rénale chronique [EMPA-KIDNEY: empagliflozin in chronic kidney disease]. Rev Med Liege. 2023 Jan;78(1):24-28. French. PMID: 36634063.
24. Hawley J.A., Lessard S.J. Exercise training-induced improvements in insulin action. *Acta Physiol.* 2008;192:127–135. doi: 10.1111/j.1748-1716.2007.01783.x.
25. Weiner D.E., Liu C.K., Miao S., Fielding R., Katzel L.I., Giffuni J., Well A., Seliger S.L. Effect of Long-term Exercise Training on Physical Performance and Cardiorespiratory Function in Adults With CKD: A Randomized Controlled Trial. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* 2023;81:59–66. doi: 10.1053/j.ajkd.2022.06.008.
26. Bohm M., Schumacher H., Werner C., Teo K.K., Lonn E.M., Mahfoud F., Speer T., Mancia G., Redon J., Schmieder R.E., et al. Association between exercise frequency with renal and cardiovascular outcomes in diabetic and non-diabetic individuals at high cardiovascular risk. *Cardiovasc. Diabetol.* 2022;21:12. doi: 10.1186/s12933-021-01429-w.
27. Cai Z., Yang Y., Zhang J. Effects of physical activity on the progression of diabetic nephropathy: A meta-analysis. Biosci. Rep. 2021;41:BSR20203624. doi: 10.1042/BSR20203624.
28. Pongrac Barlovic D., Tikkanen-Dolenc H., Groop P.H. Physical Activity in the Prevention of Development and Progression of Kidney Disease in Type 1 Diabetes. *Curr. Diabetes Rep.* 2019;19:41. doi: 10.1007/s11892-019-1157-y.
29. Pongrac Barlovic D., Harjutsalo V., Groop P.H. Exercise and nutrition in type 1 diabetes: Insights from the FinnDiane cohort. *Front. Endocrinol.* 2022;13:1064185. doi: 10.3389/fendo.2022.1064185.

30. Karstoft K., Winding K., Knudsen S.H., Nielsen J.S., Thomsen C., Pedersen B.K., Solomon T.P. The effects of free-living interval-walking training on glycemic control, body composition, and physical fitness in type 2 diabetic patients: A randomized, controlled trial. *Diabetes Care.* 2013;36:228–236. doi: 10.2337/dc12-0658.
31. Pechter U., Ots M., Mesikepp S., Zilmer K., Kullissaar T., Vihalemm T., Zilmer M., Maaroos J. Beneficial effects of water-based exercise in patients with chronic kidney disease. *Int. J. Rehabil. Res.* 2003;26:153–156.
32. Wilkinson T.J., Shur N.F., Smith A.C. "Exercise as medicine" in chronic kidney disease. *Scand. J. Med. Sci. Sports.* 2016;26:985–988. doi: 10.1111/sms.12714.
33. Costanti-Nascimento A.C., Brelaz-Abreu L., Bragança-Jardim E., Pereira W.O., Camara N.O.S., Amano M.T. Physical exercise as a friend not a foe in acute kidney diseases through immune system modulation. *Front. Immunol.* 2023;14:1212163. doi: 10.3389/fimmu.2023.1212163.
34. Baião V.M., Cunha V.A., Duarte M.P. Effects of Exercise on Inflammatory Markers in Individuals with Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *Metabolites.* 2023;13:795. doi: 10.3390/metabo13070795.