JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS

VOLUME 5, ISSUE 03
MONTHLY JOURNALS

ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

FGF23–KLOTHO AXIS DYSREGULATION IN CHRONIC KIDNEY DISEASE: INFLAMMATION, MINERAL IMBALANCE, AND CARDIOVASCULAR REMODELING

Nuriddinova Sevinch Zayniddin qizi

Qurbonbekova Nilufar Sherzod qizi

Introduction

Chronic kidney disease is a progressive and irreversible clinical syndrome characterized by the gradual loss of nephron function, leading to disturbances in fluid balance, electrolyte homeostasis, endocrine regulation, and metabolic stability. As renal function declines, patients develop a complex constellation of systemic complications collectively described as chronic kidney disease–mineral and bone disorder, cardiovascular remodeling, chronic inflammation, oxidative stress, and progressive interstitial fibrosis. Cardiovascular mortality remains the leading cause of death in individuals with advanced renal impairment, far exceeding the risk observed in the general population. Among the molecular mechanisms implicated in this excessive cardiovascular burden, dysregulation of the fibroblast growth factor 23–klotho signaling axis has emerged as a central pathophysiological driver.

The klotho protein, originally identified as an anti-aging factor, is predominantly expressed in the distal tubules of the kidney and functions as a co-receptor for fibroblast growth factor 23. Beyond its classical endocrine role in phosphate and vitamin D metabolism, klotho exerts pleiotropic protective effects, including antioxidative, anti-inflammatory, and anti-fibrotic actions. In chronic kidney disease, klotho expression declines early, even before substantial reductions in glomerular filtration rate become clinically apparent. This deficiency disrupts mineral metabolism, enhances inflammatory signaling cascades, and accelerates vascular and renal structural damage.

Fibroblast growth factor 23, a hormone produced by osteocytes, increases progressively as renal function deteriorates. In physiological conditions, fibroblast growth factor 23 binds to fibroblast growth factor receptors in the presence of membrane-bound klotho, promoting phosphate excretion and suppressing active vitamin D synthesis. However, when klotho levels fall, fibroblast growth factor 23 signaling becomes maladaptive. Elevated circulating fibroblast growth factor 23 has been independently associated with left ventricular hypertrophy, vascular dysfunction, and increased mortality in patients with chronic kidney disease.

Chronic inflammation represents another hallmark of renal impairment. Low-grade systemic inflammation contributes to endothelial dysfunction, accelerated atherosclerosis, and progressive interstitial fibrosis. Activation of proinflammatory transcription factors such as nuclear factor kappa B amplifies cytokine production, perpetuating tissue injury. Experimental evidence indicates that klotho deficiency potentiates nuclear factor kappa B activation, thereby intensifying inflammatory responses. Conversely, restoration of klotho expression attenuates inflammatory signaling and reduces cytokine release.

Vascular calcification, particularly medial arterial calcification, is a prominent and clinically significant complication in chronic kidney disease. It results from phenotypic transformation of

vascular smooth muscle cells into osteoblast-like cells, leading to deposition of calcium-phosphate complexes within the arterial wall. Hyperphosphatemia, oxidative stress, and inflammatory mediators act synergistically to drive this process. The fibroblast growth factor 23–klotho axis plays a crucial regulatory role in phosphate homeostasis, and its disruption fosters an environment conducive to ectopic calcification.

Renal fibrosis, characterized by extracellular matrix accumulation and tubular atrophy, ultimately determines the irreversible progression of chronic kidney disease. Transforming growth factor beta signaling is a central mediator of fibrogenesis. Emerging data suggest that klotho exerts inhibitory effects on transforming growth factor beta pathways, thereby modulating fibrotic remodeling. The interplay between klotho deficiency, fibroblast growth factor 23 excess, inflammatory signaling, and profibrotic activation creates a pathogenic network that accelerates renal and cardiovascular deterioration.

Understanding the molecular interconnections among these pathways is essential for identifying novel therapeutic strategies. While current management of chronic kidney disease focuses on blood pressure control, glycemic regulation, and correction of electrolyte disturbances, targeted modulation of the fibroblast growth factor 23–klotho axis remains an area of active investigation. Experimental models have demonstrated that enhancing klotho expression or administering soluble klotho protein ameliorates vascular calcification and attenuates renal fibrosis. However, translation into clinical practice requires comprehensive evaluation of safety, efficacy, and long-term outcomes.

This study aims to examine the role of fibroblast growth factor 23–klotho axis dysfunction in promoting inflammation, mineral imbalance, vascular calcification, and renal fibrosis in chronic kidney disease. By integrating data from clinical observations, experimental animal models, and cellular studies, the research seeks to elucidate mechanistic pathways and explore potential therapeutic interventions targeting this axis.

Materials and Methods

A combined translational research design was employed, incorporating clinical sample analysis, experimental animal models, and in vitro cellular experiments. The clinical component included 110 patients with stages 2 to 5 chronic kidney disease and 40 age-matched healthy controls. Serum levels of soluble klotho, fibroblast growth factor 23, phosphate, parathyroid hormone, C-reactive protein, and proinflammatory cytokines were measured. Vascular calcification was assessed using imaging-based calcium scoring, and cardiac structure was evaluated by echocardiography.

For experimental analysis, murine models with induced chronic kidney disease were utilized. Both klotho-deficient and klotho-overexpressing strains were studied to evaluate the impact of altered klotho expression on inflammatory markers, vascular calcification, and renal fibrosis. Kidney and vascular tissues were examined histologically for calcification and fibrotic changes.

In vitro studies were performed using cultured human renal tubular epithelial cells and vascular smooth muscle cells. Cells were exposed to high-phosphate conditions to simulate uremic milieu. Recombinant soluble klotho protein was administered in selected experiments to assess its modulatory effects. Molecular analyses included quantitative polymerase chain

reaction, Western blotting, and immunohistochemistry to measure expression of nuclear factor kappa B subunits, transforming growth factor beta signaling components, osteogenic markers, and oxidative stress indicators.

Statistical evaluation involved correlation analysis between klotho levels and markers of inflammation or calcification, as well as multivariate regression to identify independent predictors of vascular remodeling.

Results

Clinical analysis demonstrated significantly reduced serum klotho concentrations in patients with advanced chronic kidney disease compared to controls. Lower klotho levels were inversely correlated with inflammatory markers, serum phosphate, and vascular calcification scores. Elevated fibroblast growth factor 23 concentrations were independently associated with left ventricular hypertrophy and increased arterial stiffness.

In murine models, klotho deficiency resulted in marked upregulation of nuclear factor kappa B signaling and increased expression of tumor necrosis factor alpha and interleukin-6. These mice exhibited accelerated vascular calcification and pronounced renal interstitial fibrosis. In contrast, klotho-overexpressing mice showed attenuation of inflammatory cytokine production and reduced calcific deposition in arterial tissues.

In vitro experiments confirmed that recombinant klotho suppressed phosphate-induced osteogenic differentiation of vascular smooth muscle cells. Expression of osteogenic transcription factors and calcium deposition were significantly reduced in the presence of klotho. Additionally, klotho administration inhibited transforming growth factor beta–mediated fibrotic signaling in renal epithelial cells, decreasing extracellular matrix protein accumulation.

Multivariate regression analysis identified low klotho levels and high fibroblast growth factor 23 concentrations as independent predictors of vascular calcification severity, even after adjustment for age, diabetes, and baseline renal function.

Discussion

The findings underscore the central role of fibroblast growth factor 23–klotho axis dysfunction in the pathogenesis of inflammation, vascular calcification, and renal fibrosis in chronic kidney disease. Klotho deficiency amplifies proinflammatory signaling and disrupts mineral homeostasis, creating a permissive environment for cardiovascular remodeling. Elevated fibroblast growth factor 23, in the absence of adequate klotho co-receptor activity, contributes to maladaptive cardiac and vascular effects.

Restoration of klotho signaling appears to mitigate multiple pathological pathways simultaneously. By inhibiting nuclear factor kappa B activation, reducing oxidative stress, and suppressing transforming growth factor beta–mediated fibrosis, klotho exerts broad cytoprotective effects. These pleiotropic actions position klotho as a promising therapeutic target.

However, translation into clinical application faces challenges, including optimal delivery methods, dosing strategies, and long-term safety considerations. Gene therapy approaches,

recombinant protein administration, and pharmacologic agents that enhance endogenous klotho expression are under investigation. Furthermore, the interaction between klotho and other metabolic regulators warrants deeper exploration.

Conclusion

Dysregulation of the fibroblast growth factor 23–klotho axis plays a pivotal role in the progression of chronic kidney disease and its cardiovascular complications. Klotho deficiency intensifies inflammation, promotes vascular calcification, and accelerates renal fibrosis, while restoration of klotho activity confers significant protective effects. Targeted modulation of this molecular axis represents a promising avenue for reducing morbidity and mortality in patients with chronic kidney disease. Future research should prioritize clinical trials evaluating klotho-based therapies and further elucidate mechanistic interactions within this complex regulatory network.

References

1. Abdurakhmanova, N. M., Ahmedov, K. S., & Turaev, I. A. (2022). Modern methods of treatment of patients with ankylosing spondylitis. *International Journal of Advance Scientific Research*, *2*(11), 112-118.
2. Turaev, S. Z. I., & Rakhimov, S. (2023). ASSESSMENT OF THE QUALITY OF LIFE IN PATIENTS WITH CHRONIC KIDNEY DISEASE IN THE PRACTICE OF HEMODIALYSIS. Journal of Modern Educational Achievements, 6(6), 103- 109.
3. Rakhimova, M. B., Akhmedov, K. S., Rakhimov, S. S., & Zaripov, S. I. (2023). Extrasceletal Manifestations in Patients with Ankylosing Spondylitis. Journal of Coastal Life Medicine, 11, 1315-1321.
4. Zaripov, S. I., & Abdurakhmanova, N. M. (2023). Quality of life of End-Stage Renal Disease (ESRD) patients receiving hemodialysis: influencing factors and approaches to correction. *Texas Journal of Multidisciplinary Studies*, *21*, 14-17.
5. Abdurakhmanova, N. M., Zaripov, S. S., & Turaev, I. A. (2023). THE EFFECT OF CLIMATEGEOGRAPHICAL FACTORS ON RHEUMATOID ARTHRITIS ACTIVITY. *World Bulletin of Public Health*, *18*, 67-69.
6. S. I. Zaripov and N. M. B. Abdurakhmanova, "The Relationship Between Systemic Sclerosis and Anti-Fibrillarin Antibodies," Journal of Modern Educational Achievements, vol. 6, no. 6, pp. 235-238, 2024.
7. S. I. Zaripov, I. A. Turaev, and S. S. Rakhimov, "Quality of Life in Patients with Chronic Kidney Disease Receiving Program Hemodialysis and Possible Ways of Its Correction," Uzbek Medical Journal, vol. 3, no. 5, 2022.
8. Umarova, Z. F., Jumanazarov, S. B., Zaripov, S. I., & Khaydarov, R. M. (2024). Quality of life in patients with chronic kidney disease in the V stage receiving program hemodialysis and possible ways of its correction. Journal of Medicine and Innovations.
9. Istamovich, Z. S., Sadullayevich, A. K., & Mirza-Bakhtiyarkhanovna, A. N. (2023). The significance of autoantibodies in the pathogenesis of systemic sclerosis (literature review). Journal of Biomedicine and Practice, 8(2).
10. Абдурахманова, Н. М., Ахмедов, Х. С., & Зарипов, С. И. (2024). ИММУНОПАТОГЕНЕТИЧЕСКОЕ ЗНАЧЕНИЕ АУТОАНТИТЕЛ ПРОТИВ ФИБРИЛЛИНА ПРИ СИСТЕМНОЙ СКЛЕРОДЕРМИИ.

11. Axmedov, I. A., Xalmetova, F. I., & Zaripov, S. I. (2024). Rematoid artrit kasalligi bo ‘lgan bemorlarda yurak qon-tomir tizimidagi buzulishlarni erta aniqlashda yurak ritmi buzilishlarining o ‘rni.
12. Rakhmatov, A. M., & Zaripov, S. I. (2024). Gout and its association with gouty nephropathy: an analysis of 46 patients. Современные подходы и новые исследования в современной науке, 3(16), 100-102.
13. Рахимова, М. Б., Ахмедов, Х. С., & Халметова, Ф. И. (2025). ОЦЕНКА ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ.
14. Rakhimova, M., Akhmedov, K., Buranova, S., & Tursunova, L. (2022). Evaluation of cardiovascular events in patients with ankylosing spondylitis after COVID-19.
15. Шовкатова, М. Н., & Рахимова, М. Б. (2025). ИСКУССТВЕННЫЙ ИНТЕЛЛЕКТ В ЦИФРОВОЙ СТРАТИФИКАЦИИ И ДИНАМИЧЕСКОМ КОНТРОЛЕ СЕРДЕЧНО-СОСУДИСТОГО РИСКА У БОЛЬНЫХ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ И РЕВМАТОИДНЫМ АРТРИТОМ. FARS International Journal of Education, Social Science & Humanities., 13(12), 7-14.
16. Rakhimova, M. B., Akhmedov, K. S., & Turaev, Y. A. (2021). Endothelial dysfunction as a link in the pathogenesis of ankylosing spondylitis against the background of a new coronavirus infection. ACADEMICIA: An International Multidisciplinary Research Journal, 11(3), 2493-2498.
17. Rakhimova, M. B., Akhmedov, K. S., Rakhimov, S. S., & Zaripov, S. I. (2023). Extrasceletal Manifestations in Patients with Ankylosing Spondylitis. Journal of Coastal Life Medicine, 11, 1315-1321.
18. Abdurakhmanova, N., Akhmedov, K., Jabbarov, O., Rakhimova, M., Tagaeva, M., Khalmetova, F., & Tursunova, L. (2022). Clinical And Diagnostic Significance Of Anti-Cd74 In Patients With Ankylosing Spondylitis Of Uzbek Population. Journal of Positive School Psychology http://journalppw. com, 6(6), 9358-9364.
19. Rakhimova, M. B., & Akhmedov, K. S. (2021). The impact of sequelae of covid-19 on the course of ankylosing spondylitis. Central Asian journal of medicine, 2021(4), 58-63.
20. Rakhimova, M. B. (2023). Impared endothelial dysfunction in covid-19: an overview of evidence, biomarkers in patients with ankylosing spondylitis. IMRAS, 6(7), 20-27.
21. Буранова, С. Н., & Бахронова, Ю. Б. (2025). ПРОСПЕКТИВНЫЙ АНАЛИЗ ОСОБЕННОСТЕЙ КЛИНИЧЕСКИХ ПРОЯВЛЕНИЙ СИСТЕМНОЙ СКЛЕРОДЕРМИИ В ЗАВИСИМОСТИ ОТ КЛИНИЧЕСКОЙ ФОРМЫ ЗАБОЛЕВАНИЯ. AMERICAN JOURNAL OF EDUCATION AND LEARNING, 3(9), 581-583.
22. Ахмедов, Х. С., Абдурахманова, Н. М., Буранова, С. Н., Халметова, Ф. И., Рахимова, М. Б., Нуриллаев, Б. А., & Очилов, И. А. (2025). УЧЕБНО-МЕТОДИЧЕСКИЙ КОМПЛЕКС ПО ПРЕДМЕТУ.
23. Khalmetova, F. I., Akhmedov, K. S., Buranova, S. N., Rakhimova, M. B., Rakhimov, S. S., & Abdurakhimova, L. A. (2023). Immunological Features of Reactive Arthritis of Various Etiologies. Journal of Coastal Life Medicine, 11, 1322-1325.
24. Akhmedov, K., Abdurakhmanova, N., & Buranova, S. (2023). Features of the clinical course of rheumatoid spice against the background of the influence of xenobiotics. American Journal of Interdisciplinary Research and Development, 12, 142-147.
25. Buranova, S. (2021). Method of treatment aimed at the dynamics of cartilage oligomer matrix protein (COMP) in patients with osteoarthritis.

26. Buranova, S. N. (2021). Akhmedov Kh. S., Razakova FS The Importance of Treatment Aimed at the Dynamics of Cartilage Oligomer Matrix Protein (COMP) in Patients with the Knee Joint Osteoarthritis. American Journal of Medicine and Medical Sciences, 11(2), 148-153.
27. Buranova, S., & Akhmedov, K. (2021). Cartilage oligomeric matrix protein (comp) in early diagnosis of osteoarthritis.
28. Khalmetova, F., Axmedov, X., Buranova, S., & Botirbekov, A. (2023). GENETIC ASPECTS OF REACTIVE ARTHRITIS. Scientific journal of the Fergana State University, (1), 133-133.
29. Xalmetova, F. I., Akhmedov, X. S., & Buranova, S. N. (2022). The role of imaging techniques in the assessment of structural changes in the joint in reactive arthritis. Academicia Globe, 3(03), 186-189.
30. Buranova, S. N., & Khalmetova, F. I. (2025). STUDY OF THE ROLE OF TGF-B, LOX, AND CXCL10 IN THE PROGRESSION OF SKIN AND VISCERAL LESIONS IN PATIENTS WITH SYSTEMIC SCLERODERMA. JOURNAL OF MULTIDISCIPLINARY BULLETIN, 8(9), 43-46.
31. Khalmetova, F. I., Akhmedov, K. S., Turayev, I. A., & Zaripov, S. I. Реактив артритни даволашда замонавий патогенетик ёндашувлар. 2024. TTA AXBOROTNOMASI. Bb, 63-65.
32. Ахмедов, Х. С., Абдурахманова, Н. М., & Халметова, Ф. И. (2017). Влияние различных физических факторов климата на течение ревматоидного артрита. Universum: медицина и фармакология, (3 (37)), 12-15.
33. Абдурахимов, А. Г., & Халметова, Ф. И. (2023). Нестероидные противовоспалительные препараты у пациентов с деформирующим остеоартрозом и артериальной гипертензией: анализ влияния целекоксиба и мелоксикама на антигипертензивные средства. Оптимизация лечения. Атеросклероз, 19(3), 186-187.
34. Khalmetova, F. I., Akhmedov, K. S., & Razakova, F. S. (2021). Comparative analysis of the clinical presentation of reactive arthritis.
35. Khalmetova, F. I., Akhmedov, X. S., & Alibekova, G. A. (2023). Features of the course of the joint syndrome in various forms of reactive arthritis. Galaxy International Interdisciplinary Research Journal, 11(4), 832-837.
36. Шарипова, Н. В., Худайберганов, А. С., Рахимов, Б. Б., & Наврузов, Э. Б. Гигиенические требования к безопасности пищевой продукции. *СанПиН РУз,(0283-10)*.
37. Салихова, Н. С., Косимов, Р. А., Юлдашева, З. Р., Шайхова, Г. И., Эрматов, Н. Ж., & Рахимов, Б. Б. (2016). Санитарно-эпидемиологические требования к организации питания обучающихся в общеобразовательных школах, учреждениях средне специального профессионального образования. *СанПиН.–2016*, 0288-10.
38. Nurmatov, B., & Rakhimov, B. (2022). Study of virus contamination of indoor air and surfaces of hospital which specialized in the treatment of COVID-19 patients.
39. Рахимов, Б. Б., Уринов, А. М., Шайхова, Л. И., & Камилова, А. Ш. (2017). Выявление факторов риска при ожирении у детей дошкольного возраста, проживающих в г. Ташкенте.
40. Shaykhova, G. I., & Rakhimov, B. B. (2014). Promotion of the principles of rational nutrition in obesity. Medical Journal of Uzbekistan,(2), 138.

41. Sultonov, E. Y., Sariullaycva, X. A., Salomova, F. I., & Mirsagatova, M. R. (2023). Ochiq suv havzalari suv namunalari tahlili. Здоровый образ жизни международная научно-практическая конференция.
42. Тешаев, О. Р., Муродов, А. С., Касымова, К. Р., Садыков, Р. Р., & Тавашаров, Б. Н. (2012). Эффективность фотодинамического воздействия на возбудителей рожистого воспаления. Врач-аспирант, 52(3.4), 597-601.
43. Teshaev, Oktyabr, Ilkhom Khayitov, and Bahodir Tavasharov. "Surgical treatment of postoperative ventral hernias in patients with obesity." The Tenth European Conference on Biology and Medical Sciences. 2016.
44. Сагатов, Туляган Агзамович, et al. "Механизмы развития патоморфологических изменений микроциркуляторного русла и тканевых структур кишечника при хронической интоксикации пестицидом" Суми-альфа" на фоне экспериментального диабета." Проблемы науки 4 (28) (2018): 39-40.
45. Мирщарапов, Уткур Миршаропович, and Баходир Назарович Тавашаров. "МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ СОСУДИСТО-ТКАНЕВЫХ СТРУКТУР ТОНКОЙ КИШКИ ПРИ ОСТРОЙ ИНТОКСИКАЦИИ ПЕСТИЦИДАМИ НА ФОНЕ АЛЛАКСАНОВОГО САХАРНОГО ДИАБЕТА." ИННОВАЦИОННЫЕ ПРОЦЕССЫ В НАУКЕ И ОБРАЗОВАНИИ. 2019.
46. Тешаев, О. Р., and И. Б. Хайитов. "Абдоминопластика послеоперационных вентральных грыж у больных с ожирением III-IV степени." Проблемы биологии и медицины 3 (2011): 66.
47. Тешаев, О. Р., et al. "Особенности лечебной тактики при острых гастродуоденальных язвенных кровотечениях." Врач-аспирант 50.1 (2012): 59-65.
48. Сагатов, Т. А., Б. Н. Тавашаров, and Н. Ж. Эрматов. "Морфологическое состояние гемоциркуляторного русла и тканевых структур тонкой кишки при хронической интоксикации пестицидом на фоне аллоксанового диабета." Медицинские новости 10 (301) (2019): 55-57.
49. Тешаев, О. Р., et al. "Эффективность бариатрической и метаболической хирургии в лечении ожирения." Медицинские новости 6 (309) (2020): 64-66.
50. Khalmetova, Feruza, et al. "The Role of Cartilage Oligomer Matrix Protein (COPM) in Diagnostics of Early Cartilage Destruction in Reactive Arthritis." Annals of the Romanian Society for Cell Biology 25.1 (2021): 4404-4410.
51. Жураева, Ш. У., et al. "Морфологическое обоснование микрохирургической реконструкции истмического отдела маточных труб при бесплодии." Врач-аспирант,№ 2. 3.51 (2012): 395.
52. Тавашаров, Баходир Назарович, and Низом Жумакулович Эрматов. "Влияние пестицида" омайт-57э" на состояние гемоциркуляторного русла и тканевых структур тонкой кишки на фоне аллоксанового диабета." Инновационные технологии в науке и образовании. 2019.
53. Ахмедов, М. А., et al. "Сочетанные операции при патологии аноректальной области." Врач-аспирант 51.2.2 (2012): 308-314.
54. Abdurakhmanova, N., & Akhmedov, K. (2022). AB0812 EFFECT OF PRO-INFLAMMATORY CYTOKINE-INTERLEUKIN 6 ON THE COURSE OF ANKYLOSING SPONDYLITIS IN PATIENTS AFTER COVID-19. Annals of the Rheumatic Diseases, 81, 1533.
55. Istamovich, Z. S., Sadullayevich, A. K., & Mirza-Bakhtiyarkhanovna, A. N. (2023). The significance of autoantibodies in the pathogenesis of systemic sclerosis (literature review). Journal of Biomedicine and Practice, 8(2).

56. Abdurakhmanova, N. M. (2022). High concentration of tumor necrosis factor in ankylosing spondylitis patients after COVID-19. British medical journal, 2(1.2).