PAPER ID: 20260201008

Chronic Kidney Disease: Current Challenges, Novel Biomarkers, Emerging Diagnostics, and Future Directions in Clinical Management

Ritika Gautam[1], Rishab Gupta[1], Isha Saini[2], Manisha Saini[3] and Sourabh Dalal[3]

[1]Student of B.Sc. Medical Laboratory Technology, Department of Allied & Healthcare Sciences, Jagannath University, Delhi NCR, Bahadurgarh

[2]Student of B.Sc. Anesthesia and Operation Theatre Technology, Department of Allied & Healthcare Sciences, Jagannath University, Delhi NCR, Bahadurgarh

[3]Assistant Professor, Department of Allied and Healthcare Sciences, Jagannath University, Delhi NCR, Bahadurgarh

Abstract: CKD is an insidious and slow disease, generally acting over many years to impact the structure and function of the kidneys. Most cases are a result of long-standing diseases, including diabetes, hypertension, inflammation, and other conditions brought about by lifestyle factors. Because the early signs and symptoms are rather nonspecific or may even be asymptomatic, most patients are usually diagnosed well after their kidneys have sustained critical damage. Research over the years has unraveled this progression: from subtle cellular injury and fibrosis to the impaired accumulation of toxins and repair mechanisms, leading progressively to diminished filtration capacity. With the discovery of newer biomarkers and better diagnostic tools, early detection has improved. Similarly, updated clinical guidelines have presented therapies capable of slowing disease progression and protecting kidney function. The mainstay of management now involves the use of drugs such as RAAS blockers and SGLT2 inhibitors, dietary modifications, and lifestyle changes. CKD is also associated with cardiovascular disease, bone disorders, and anemia, besides a considerable economic burden, and so it is a major public health priority. This review summarizes current knowledge about causes, biological mechanisms, diagnostic developments, treatment strategies, and overall impact. The goal is to emphasize how early screening, personalized care, and integrated management would provide important leverage in improving long-term outcomes.

Keywords: Chronic kidney disease, pathophysiology, diagnosis, biomarkers, management, complications, therapeutic approaches.

Introduction

Chronic Kidney Disease (CKD) is a major global health concern, affecting populations worldwide and contributing significantly to long-term morbidity and mortality. It is characterized by a gradual, irreversible loss of kidney function that develops over several months or years, often remaining undetected in its early stages. The most common risk factors associated with CKD include diabetes, hypertension, cardiovascular disorders, metabolic abnormalities, and lifestyle-related influences (2,7,23).

Scientific literature progress has given far-reaching insight into the biological mechanisms of CKD. Various interlinked pathways underlying chronic inflammation, oxidative stress, endothelial dysfunction, tubular injury, fibrosis, and accumulation of uremic toxins collectively facilitate renal damage (5, 15, 18). Since internal changes take place silently, CKD is often diagnosed in advanced stages, making treatment more difficult and complications more severe (1, 10).

Improvements in diagnostics, through the use of newer biomarkers like NGAL, Cystatin-C, and KIM-1, imaging, and risk-prediction models, have facilitated early detection strategies (4,9,12,19). At the same time, updates in clinical guidelines and therapeutic approaches-such as SGLT2 inhibitors, RAAS blockers, improved glycemic control, and dietary interventions-have imparted significant benefits in reducing disease progression and improving patient outcomes (3,11,14).

CKD is also associated with major systemic complications like cardiovascular disease, bone disorders, anemia, and increased mortality, thus further widening its clinical impact (8,16,17). Given the multisystemic involvement and escalating health burden, there is a definite need to know the causes, mechanisms, diagnostics, treatment, and consequences of CKD. This review synthesizes evidence from selected literature to present a clear and updated overview of CKD.

1.1. Epidemiology and Global Burden

CKD is now one of the major non-communicable diseases worldwide. Its prevalence is increasing due to rising rates of hypertension, diabetes, and ageing populations [1]. Because CKD often progresses without early symptoms, many cases remain undiagnosed until advanced stages[1].

Key Points:

- CKD is rising rapidly in both developed and developing countries.
- Late diagnosis increases treatment cost and complications.

- Healthcare systems face financial pressure due to dialysis, transplant, and long-term care [6].
- Global reviews show CKD has a growing economic burden on families and health systems [13]

1.2 Major Causes and Risk Factors

Diabetes and hypertension are the leading causes of CKD globally [2]. However, several additional factors contribute to kidney damage across populations.

Key Points:

- Diabetes causes glomerular injury and persistent albuminuria [11].
- Hypertension leads to nephron loss and vascular stiffness [2].
- Obesity and metabolic syndrome increase CKD risk significantly [14,22].
- Recurrent acute kidney injury can develop into CKD due to maladaptive tubular repair [15].
- Ageing, smoking, high-salt diet, and sedentary lifestyle also contributes.

1.3 Pathophysiology and Disease Mechanisms

CKD progression involves interconnected biological pathways leading to structural kidney damage.

Key Points:

- Chronic inflammation and oxidative stress accelerate nephron damage [15].
- Renal fibrosis is the final irreversible stage of tissue injury.
- Uremic toxins damage blood vessels and worsen anemia by impairing erythropoiesis [5,18].
- Cardiovascular complications are strongly linked with CKD progression [16,17,23].
- Declining GFR increases toxin accumulation, leading to multi-system effects.

1.4 Diagnostic Approaches and Emerging Biomarkers

Traditional markers like creatinine and GFR often detect CKD late. Therefore, modern research focuses on early biomarkers.

Key Points:

- Early detection improves outcomes significantly.
- Emerging biomarkers: NGAL, KIM-1, cystatin C, urine protein markers [9,12,19].
- Machine-learning models help predict CKD onset, progression, and treatment response more accurately [4].
- Advanced imaging and risk calculators support clinical decision-making.

1.5 Complications Associated with CKD

As CKD worsens, multiple organs and metabolic functions are affected.

Key Points:

- Toxin accumulation causes fatigue, anemia, acidosis, and fluid imbalance [18].
- CKD–MBD increases risk of osteoporosis and bone fractures [8].
- Cardiovascular diseases are the leading cause of death in CKD patients [16,17].
- Electrolyte disorders, especially high potassium levels, may become life-threatening.
- Mental fatigue and reduced mobility affect daily functioning.

1.6 Therapeutic Advances and Treatment Strategies

Modern treatment focuses on slowing disease progression and preventing complications.

Key Points:

- **SGLT2 inhibitors** improve kidney outcomes regardless of diabetes status [3].
- KDIGO guidelines recommend BP control, glycemic control, and lifestyle changes [7,11].
- Nutritional therapy: low-sodium, controlled protein intake, adequate hydration [14].
- Management of diabetes, hypertension, and cardiovascular disease is essential.
- Early referral to nephrologists improves long-term outcomes.

1.7 Psychosocial Impact and Quality of Life

CKD significantly affects mental and emotional health.

Key Points:

- Patients face stress due to dietary restrictions and frequent hospital visits [24].
- Persistent fatigue and lifestyle changes lower quality of life.
- Counselling, patient education, and support groups improve coping ability.
- Long-term medication burden affects motivation and mental well-being.

I. Methodology

This review follows a conceptual methodology, where previously published, scientific studies were analysed to understand how chronic kidney disease (CKD) begins, progresses, is diagnosed, and treated. No new experiments were performed; instead, key literature was reviewed to build a clear picture of the disease process.

2.1 Understanding How CKD Begins

CKD most commonly starts due to long-standing diabetes and hypertension, which slowly damage the nephrons, the filtering units of the kidneys. Studies show that persistent high glucose and pressure trigger inflammation, oxidative stress, and microvascular injury that set the foundation for CKD progression (2, 11, 23).

Over time, this early damage gradually reduces kidney function and leads to structural abnormalities (1, 7).

2.2 Biological Mechanisms Behind Disease Progression

To understand how CKD worsens, literature describing internal molecular pathways were reviewed.

Common mechanisms repeatedly highlighted include:

- Fibrosis and scarring of kidney tissue (15)
- Endothelial dysfunction caused by uremic toxins (5, 18)
- Tubular injury leading to incomplete repair (15)
- Inflammation and toxin accumulation worsening overall decline (5, 18)

These processes explain why CKD progresses silently for years before symptoms appear.

2.3 Diagnostic Approach in Literature

Published research and guidelines were reviewed to identify how CKD is commonly diagnosed.

Core diagnostic tools include:

- eGFR estimation (7, 20)
- Albuminuria and proteinuria analysis (7, 2)
- Imaging studies
- Biomarkers such as NGAL, KIM-1, Cystatin-C (9, 12, 19)
- Machine-learning–based prediction models (4)

These literature findings show that diagnosis has shifted from traditional tests toward more sensitive early-detection methods.

2.4 Treatment Strategies Identified from Literature

The methodology also included reviewing therapeutic research.

Core treatment themes from studies include:

- Blood pressure control & RAAS blockade (2, 7)
- SGLT2 inhibitors slowing CKD progression (3)
- Diabetes management in CKD patients (11, 25)
- Diet and lifestyle adjustments (14)
- Managing complications such as bone disease, cardiovascular risk, and anemia (8, 17, 18)

These findings help identify the most effective, evidence-based approaches used globally.

2.5 Early Conclusions Reported by Previous Studies

Across all reviewed literature, some common conclusions repeatedly appear:

- CKD progresses silently and often remains undetected for years (1, 2, 10).
- Early screening greatly reduces complications (9, 12).
- A combined management approach—medications + diet + lifestyle—works best (3, 11, 14).
- CKD increases cardiovascular and metabolic risk (16, 17).
- Late-stage CKD leads to high healthcare and financial burden (6, 13, 20).

These insights help build a unified, evidence-based understanding of CKD without conducting new experiments.

II. Results and Discussions

Current Challenges in Chronic Kidney Disease (CKD)

CKD is a major global health problem caused mainly by long-term diabetes and high blood pressure. Early detection is difficult because current tests often only identify kidney damage once it is advanced. Late diagnosis results in higher treatment costs and poorer patient outcomes.

3.1 Tables

Table 1: Limitations of Conventional Biomarkers

Traditional biomarkers like serum creatinine and estimated glomerular filtration rate (eGFR) are widely used, but they have limitations:

	Advantages	Limitations
Serum Creatinine	Widely available; inexpensive; routinely used in clinical practice	Rises only after significant kidney damage; influenced by age, muscle mass, diet, and hydration
eGFR	Standard method to estimate kidney function; useful for staging CKD	Not accurate in early kidney injury; affected by creatinine variability
Cystatin-C	More sensitive than creatinine; unaffected by muscle mass	Higher cost; limited availability in some settings
NGAL	Detects early tubular injury; useful in acute and chronic kidney disease	Can be elevated in infections and inflammation; expensive
KIM-1	Strong indicator of tubular damage; helpful in early detection	Not widely available; higher test cost
Albuminuria	Simple, quick test;	Can be affected by

	Advantages	Limitations
	predicts cardiovascular and renal risk	exercise, fever, and infections; not specific to structural damage

Novel Biomarkers Improving Early Detection

Recent research has identified novel biomarkers that can detect kidney injury earlier:

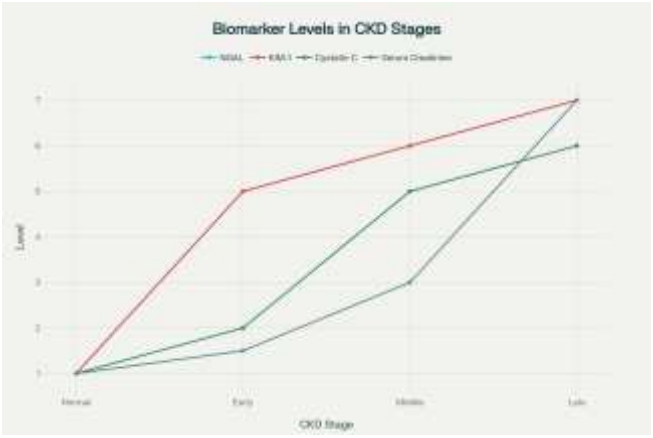
- **Cystatin C:** Less affected by muscle mass, offers improved estimation of kidney filtration.
- **NGAL (Neutrophil Gelatinase-Associated Lipocalin):** Rises shortly after tubular injury, signaling early damage.
- **KIM-1 (Kidney Injury Molecule-1):** Indicates damage to kidney tubules before changes in creatinine occur.

Table 2: Overview of Novel CKD Biomarkers

Biomarker	Type	Early Detection Capability	Clinical Use Status
Cystatin C	Filtration marker	Yes	Increasingly used
NGAL	Tubular injury marker	Yes	Research / emerging
KIM-1	Tubular injury marker	Yes	Research level

3.2 FIGURES

Fig 1 - Biomarker Levels Across Stages of Chronic Kidney Disease



This figure illustrates the changing levels of key biomarkers—NGAL, KIM-1, Cystatin C, and Serum Creatinine—across the progression of chronic kidney disease (CKD) from normal kidney function through early, middle, and late stages. NGAL and KIM-1 rise sharply in the early stages, signaling initial tubular injury. Cystatin C levels increase in the middle stages, reflecting declining glomerular filtration. Serum Creatinine elevates primarily in late stages, indicating significant kidney damage. Early detection through novel biomarkers like NGAL and KIM-1 can enable timely intervention and better patient outcomes

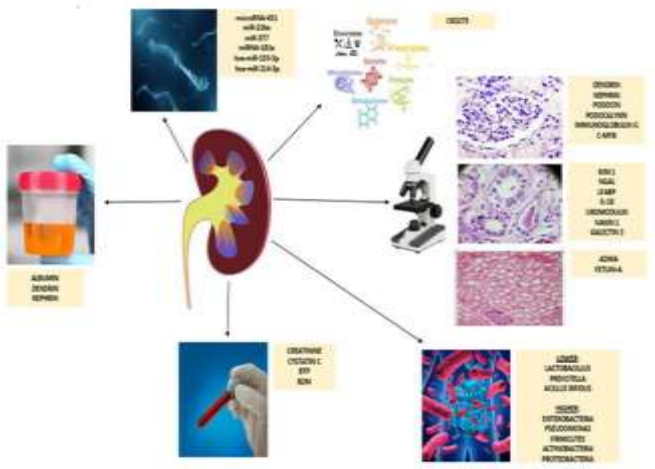
III. CONCLUSION

Chronic Kidney Disease continues to pose a serious global health challenge, largely driven by diabetes and hypertension. Early diagnosis is critical but remains difficult with conventional tests like serum creatinine and eGFR, which often miss early kidney damage. This underlines the importance of novel biomarkers such as Cystatin C, NGAL, and KIM-1 that provide earlier and more sensitive detection of kidney injury.

The integration of these advanced biomarkers, along with emerging technologies like multi-omics and artificial intelligence, offers promising opportunities to improve diagnosis, risk stratification, and personalized management of CKD. However, further research is needed to validate these biomarkers in diverse populations, standardize testing procedures, and make these tools affordable and accessible worldwide.

By focusing on early detection and biomarker-guided treatment, healthcare providers can better slow CKD progression, reduce complications, and enhance patient quality of life. This comprehensive approach has the potential to transform CKD care and alleviate the growing healthcare burden associated with this disease.

Fig:2



A schematic comparing traditional and novel biomarkers with respect to their capacity to detect kidney injury at various stages of CKD. This figure highlights how newer biomarkers such as NGAL and KIM-1 enable earlier detection compared to creatinine-based tests.

Source:

Mizdrak, M., Kumrić, M., Kurir, T., & Božić, J. (2022)[9]. Emerging Biomarkers for Early Detection of Chronic Kidney Disease. Journal of Personalized Medicine, 12. https://doi.org/10.3390/jpm12040548

ACKNOWLEDGEMENTS

THE AUTHORS EXPRESS THEIR SINCERE GRATITUDE TO THEIR MENTORS, COLLEAGUES, AND ALL THE RESEARCH PARTICIPANTS WHO CONTRIBUTED TO THIS STUDY. SPECIAL THANKS TO JAGANNATH UNIVERSITY FOR PROVIDING SUPPORT AND RESOURCES ESSENTIAL FOR COMPLETING THIS RESEARCH. ADDITIONALLY, THE AUTHORS ACKNOWLEDGE THE VALUABLE INPUT AND GUIDANCE FROM PEERS AND TECHNICAL STAFF DURING DATA COLLECTION AND ANALYSIS. THIS WORK WOULD NOT HAVE BEEN POSSIBLE WITHOUT THE DEDICATED EFFORTS OF EVERY INDIVIDUAL INVOLVED.

REFERENCES

1. Evans, M., Lewis, R., Morgan, A., Whyte, M., Hanif, W., Bain, S., Davies, S., Dashora, U., Yousef, Z., Patel, D., & Strain, W. (2021). A Narrative Review of Chronic Kidney Disease in Clinical Practice: Current Challenges and Future Perspectives. *Advances in Therapy*, 39, 33 - 43. https://doi.org/10.1007/s12325-021-01927-z
2. Chen, T., Knicely, D., & Grams, M. (2019). Chronic Kidney Disease Diagnosis and Management: A Review.. *JAMA*, 322 13, 1294-1304 . https://doi.org/10.1001/jama.2019.14745.
3. Mende, C. (2021). Chronic Kidney Disease and SGLT2 Inhibitors: A Review of the Evolving Treatment Landscape. *Advances in Therapy*, 39, 148 - 164. https://doi.org/10.1007/s12325-021-01994-2.
4. Sanmarchi, F., Fanconi, C., Golinelli, D., Gori, D., Hernandez-Boussard, T., & Capodici, A. (2023). Predict, diagnose, and treat chronic kidney disease with machine learning: a systematic literature review. *Journal of Nephrology*, 36, 1101 - 1117. https://doi.org/10.1007/s40620-023-01573-4
5. Harlacher, E., Wollenhaupt, J., Baaten, C., & Noels, H. (2022). Impact of Uremic Toxins on Endothelial Dysfunction in Chronic Kidney Disease: A Systematic Review. *International Journal of Molecular Sciences*, 23. https://doi.org/10.3390/ijms23010531.
6. Elshahat, S., Cockwell, P., Maxwell, A., Griffin, M., O'Brien, T., & O'Neill, C. (2020). The impact of chronic kidney disease on developed countries from a health economics perspective: A systematic scoping review. *PLoS ONE*, 15. https://doi.org/10.1371/journal.pone.0230512.
7. Levin, A. (2013). Evaluation and Management of Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline. *Annals of Internal Medicine*, 158, 825 - 830. https://doi.org/10.7326/0003-4819-158-11-201306040-00007.
8. Hsu, C., Chen, L., & Chen, K. (2020). Osteoporosis in Patients with Chronic Kidney Diseases: A Systemic Review. *International Journal of Molecular Sciences*, 21. https://doi.org/10.3390/ijms21186846.
9. Mizdrak, M., Kumrić, M., Kurir, T., & Božić, J. (2022). Emerging Biomarkers for Early Detection of Chronic Kidney Disease. *Journal of Personalized Medicine*, 12. https://doi.org/10.3390/jpm12040548.
10. Neale, E., Middleton, J., & Lambert, K. (2020). Barriers and enablers to detection and management of chronic kidney disease in primary healthcare: a systematic review. *BMC Nephrology*, 21. https://doi.org/10.1186/s12882-020-01731-x.
11. Boer, I., Caramori, M., Chan, J., Heerspink, H., Hurst, C., Khunti, K., Liew, A., Michos, E., Navaneethan, S., Olowu, W., Sadusky, T., Tandon, N., Tuttle, K., Wanner, C., Wilkens, K., Zoungas, S., & Rossing, P. (2020). KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.. *Kidney international*, 98 4S, S1-S115 . https://doi.org/10.1016/j.kint.2020.06.019.
12. Lousa, I., Reis, F., Beirão, I., Alves, R., Belo, L., & Santos-Silva, A. (2020). New Potential Biomarkers for

Chronic Kidney Disease Management—A Review of the Literature. *International Journal of Molecular Sciences*, 22. https://doi.org/10.3390/ijms22010043.

13. Jha, V., Al-Ghamdi, S., Li, G., Wu, M., Stafylas, P., Retat, L., Card-Gowers, J., Barone, S., Cabrera, C., & Sanchez, J. (2023). Global Economic Burden Associated with Chronic Kidney Disease: A Pragmatic Review of Medical Costs for the Inside CKD Research Programme. *Advances in Therapy*, 40, 4405 - 4420. https://doi.org/10.1007/s12325-023-02608-9.
14. Naber, T., & Purohit, S. (2021). Chronic Kidney Disease: Role of Diet for a Reduction in the Severity of the Disease. *Nutrients*, 13. https://doi.org/10.3390/nu13093277.
15. Yu, S., & Bonventre, J. (2020). Acute kidney injury and maladaptive tubular repair leading to renal fibrosis.. *Current Opinion in Nephrology & Hypertension*. https://doi.org/10.1097/mnh.0000000000000605.
16. Marassi, M., & Fadini, G. (2023). The cardio-renal-metabolic connection: a review of the evidence. *Cardiovascular Diabetology*, 22. https://doi.org/10.1186/s12933-023-01937-x.
17. Zoccali, C., Mallamaci, F., Adamczak, M., De Oliveira, R., Massy, Z., Sarafidis, P., Agarwal, R., Mark, P., Kotanko, P., Ferro, C., Wanner, C., Burnier, M., Vanholder, R., & Więcek, A. (2023). Cardiovascular complications in chronic kidney disease: a review from the European Renal and Cardiovascular Medicine Working Group of the European Renal Association. *Cardiovascular Research*, 119, 2017 - 2032. https://doi.org/10.1093/cvr/cvad083.
18. Hamza, E., Metzinger, L., & Meuth, V. (2020). Uremic Toxins Affect Erythropoiesis during the Course of Chronic Kidney Disease: A Review. *Cells*, 9. https://doi.org/10.3390/cells9092039.
19. Bidin, M., Shah, A., Stanslas, J., Seong, C., & Seong, C. (2019). Blood and urine biomarkers in chronic kidney disease: An update.. *Clinica chimica acta; international journal of clinical chemistry*, 495, 239-250. https://doi.org/10.1016/j.cca.2019.04.069.
20. Murton, M., Goff-Leggett, D., Bobrowska, A., Sanchez, J., James, G., Wittbrodt, E., Nolan, S., Sörstadius, E., Pecoits-Filho, R., & Tuttle, K. (2020). Burden of Chronic Kidney Disease by KDIGO Categories of Glomerular Filtration Rate and Albuminuria: A Systematic Review. *Advances in Therapy*, 38, 180 - 200. https://doi.org/10.1007/s12325-020-01568-8.
21. Pickkers, P., Darmon, M., Hoste, E., Joannidis, M., Legrand, M., Ostermann, M., Prowle, J., Schneider, A., & Schetz, M. (2021). Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intensive Care Medicine*, 47, 835 - 850. https://doi.org/10.1007/s00134-021-06454-7.
22. Lin, L., Tan, W., Pan, X., Tian, E., Wu, Z., & Yang, J. (2022). Metabolic Syndrome-Related Kidney Injury: A Review and Update. *Frontiers in Endocrinology*, 13. https://doi.org/10.3389/fendo.2022.904001.
23. Tonelli, M., Wiebe, N., Culleton, B., House, A., Rabbat, C., Fok, M., McAlister, F., & Garg, A. (2006). Chronic kidney disease and mortality risk: a systematic review.. *Journal of the American Society of Nephrology : JASN*, 17 7, 2034-47 . https://doi.org/10.1681/asn.2005101085.
24. Roberti, J., Cummings, A., Myall, M., Harvey, J., Lippiett, K., Hunt, K., Cicora, F., Alonso, J., & May, C. (2018). Work of being an adult patient with chronic kidney disease: a systematic review of qualitative studies. *BMJ Open*, 8. https://doi.org/10.1136/bmjopen-2018-023507.
25. SankarD.Navaneethan, M., SophiaZoungas, M., M.LuizaCaramori, M., , M., HiddoJ.L.Heerspink, M., , P., , B., Mbbs, M., , M., TamiSadusky, M., , M., , P., , M., Wilkens, M., Ms, R., BSc, M., MBChB, D., Tunnicliffe, P., Howell, P., Tonelli, P., , S., Earley, M., Rossing, B., D., D., & Khunti, K. (2020). Diabetes Management in Chronic Kidney Disease: Synopsis of the 2020 KDIGO Clinical Practice Guideline. *Annals of Internal Medicine*, 174, 385 - 394. https://doi.org/10.7326/m20-5938.
26. Poulianiti, K., Kaltsatou, A., Mitrou, G., Jamurtas, A., Koutedakis, Y., Maridaki, M., Stefanidis, I., Sakkas, G., & Karatzaferi, C. (2016). Systemic Redox Imbalance in Chronic Kidney Disease: A Systematic Review. *Oxidative Medicine and Cellular Longevity*, 2016. https://doi.org/10.1155/2016/8598253.
27. Cobo, G., Hecking, M., Port, F., Exner, I., Lindholm, B., Stenvinkel, P., & Carrero, J. (2016). Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis.. *Clinical science*, 130 14, 1147-63 . https://doi.org/10.1042/cs20160047.
28. ElHafeez, S., Bolignano, D., D'Arrigo, G., Dounousi, E., Tripepi, G., & Zoccali, C. (2018). Prevalence and burden of chronic kidney disease among the general population and high-risk groups in Africa: a systematic review. *BMJ Open*, 8. https://doi.org/10.1136/bmjopen-2016-015069.
29. Sato, Y., & Yanagita, M. (2018). Immune cells and inflammation in AKI to CKD progression.. *American journal of physiology. Renal physiology*, 315 6, F1501-F1512 . https://doi.org/10.1152/ajprenal.00195.2018.

30. Cosola, C., Rocchetti, M., Cupisti, A., & Gesualdo, L. (2018). Microbiota metabolites: Pivotal players of cardiovascular damage in chronic kidney disease. *Pharmacological Research*, 130, 132–142. https://doi.org/10.1016/j.phrs.2018.03.003.
31. Moody, E., Coca, S., & Sanders, A. (2018). Toxic Metals and Chronic Kidney Disease: a Systematic Review of Recent Literature. *Current Environmental Health Reports*, 5, 453 - 463. https://doi.org/10.1007/s40572-018-0212-1.
32. MacKinnon, H., Wilkinson, T., Clarke, A., Gould, D., O'Sullivan, T., Xenophontos, S., Watson, E., Singh, S., & Smith, A. (2018). The association of physical function and physical activity with all-cause mortality and adverse clinical outcomes in nondialysis chronic kidney disease: a systematic review. *Therapeutic Advances in Chronic Disease*, 9, 209 - 226. https://doi.org/10.1177/2040622318785575.
33. Bonner, A., Havas, K., Douglas, C., Thepha, T., Bennett, P., & Clark, R. (2014). Self-management programmes in stages 1-4 chronic kidney disease: a literature review.. *Journal of renal care*, 40 3, 194-204 . https://doi.org/10.1111/jorc.12058.
34. Jdiaa, S., Mansour, R., Alayli, A., Gautam, A., Thomas, P., & Mustafa, R. (2022). COVID–19 and chronic kidney disease: an updated overview of reviews. *Journal of Nephrology*, 35, 69 - 85. https://doi.org/10.1007/s40620-021-01206-8.
35. Gaut, J., & Liapis, H. (2020). Acute kidney injury pathology and pathophysiology: a retrospective review. *Clinical Kidney Journal*, 14, 526 - 536. https://doi.org/10.1093/ckj/sfaa142.
36. Mills, K., Xu, Y., Zhang, W., Bundy, J., Chen, C., Kelly, T., Chen, J., & He, J. (2015). A systematic analysis of world-wide population-based data on the global burden of chronic kidney disease in 2010. *Kidney international*, 88, 950 - 957. https://doi.org/10.1038/ki.2015.230.
37. Mikusic, N., Kouyoumdzian, N., & Choi, M. (2020). Gut microbiota and chronic kidney disease: evidences and mechanisms that mediate a new communication in the gastrointestinal-renal axis. *Pflügers Archiv - European Journal of Physiology*, 472, 303 - 320. https://doi.org/10.1007/s00424-020-02352-x.
38. Doshi, S., & Friedman, A. (2017). Diagnosis and Management of Type 2 Diabetic Kidney Disease.. *Clinical journal of the American Society of Nephrology : CJASN*, 12 8, 1366-1373 . https://doi.org/10.2215/cjn.11111016
39. Levey, A., Coresh, J., Balk, E., Kausz, A., Levin, A., Steffes, M., Hogg, R., Perrone, R., Lau, J., & Eknoyan, G. (2003). National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Annals of Internal Medicine*, 139, 137-147. https://doi.org/10.7326/0003-4819-139-2-200307150-00013.
40. Gregg, L., Bossola, M., Ostrosky-Frid, M., & Hedayati, S. (2021). Fatigue in CKD. *CJASN*, 16, 1445 - 1455. https://doi.org/10.2215/cjn.19891220
41. Evangelidis, N., Craig, J., Bauman, A., Manera, K., Saglimbene, V., & Tong, A. (2019). Lifestyle behaviour change for preventing the progression of chronic kidney disease: a systematic review. *BMJ Open*, 9. https://doi.org/10.1136/bmjopen-2019-031625.
42. Zadražil, J., & Horák, P. (2014). Pathophysiology of anemia in chronic kidney diseases: A review.. *Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia*, 159 2, 197-202 . https://doi.org/10.5507/bp.2013.093.
43. Salman, I. (2015). Cardiovascular Autonomic Dysfunction in Chronic Kidney Disease: a Comprehensive Review. *Current Hypertension Reports*, 17, 1-20. https://doi.org/10.1007/s11906-015-0571-z.
44. Sulaiman, M. (2019). Diabetic nephropathy: recent advances in pathophysiology and challenges in dietary management. *Diabetology & Metabolic Syndrome*, 11. https://doi.org/10.1186/s13098-019-0403-4.
45. Aiyegbusi, O., Kyte, D., Cockwell, P., Marshall, T., Keeley, T., Gheorghe, A., & Calvert, M. (2016). Measurement properties of patient-reported outcome measures (PROMs) used in adult patients with chronic kidney disease: A systematic review. *PLoS ONE*, 12. https://doi.org/10.1136/bmjopen-2016-012014.
46. Kadowaki, T., Maegawa, H., Watada, H., Yabe, D., Node, K., Murohara, T., & Wada, J. (2022). Interconnection between cardiovascular, renal and metabolic disorders: A narrative review with a focus on Japan. *Diabetes, Obesity & Metabolism*, 24, 2283 - 2296. https://doi.org/10.1111/dom.14829.
47. Nogueira, A., Pires, M., & Oliveira, P. (2017). Pathophysiological Mechanisms of Renal Fibrosis: A Review of Animal Models and Therapeutic Strategies.. *In vivo*, 31 1, 1-22. https://doi.org/10.21873/invivo.11019.
48. Pyram, R., Kansara, A., Banerji, M., & Loney-Hutchinson, L. (2012). Chronic kidney disease and diabetes.. *Maturitas*, 71 2, 94-103 . https://doi.org/10.1016/j.maturitas.2011.11.009.
49. Alebiosu, C., & Ayodele, O. (2005). The global burden of chronic kidney disease and the way forward.. *Ethnicity & disease*, 15 3, 418-23 .

50. Hager, M., Narla, A., & Tannock, L. (2017). Dyslipidemia in patients with chronic kidney disease. *Reviews in Endocrine and Metabolic Disorders*, 18, 29-40. https://doi.org/10.1007/s11154-016-9402-z
51. Stanifer, J., Von Isenburg, M., Chertow, G., & Anand, S. (2018). Chronic kidney disease care models in low- and middle-income countries: a systematic review. *BMJ Global Health*, 3. https://doi.org/10.1136/bmjgh-2018-000728.
52. Raiisi, A., Stewart, D., Fernandez-Llimos, F., Salgado, T., Mohamed, M., & Cunningham, S. (2019). Clinical pharmacy practice in the care of Chronic Kidney Disease patients: a systematic review. *International Journal of Clinical Pharmacy*, 41, 630 - 666. https://doi.org/10.1007/s11096-019-00816-4.
53. Etgen, T. (2015). Kidney disease as a determinant of cognitive decline and dementia. *Alzheimer's Research & Therapy*, 7. https://doi.org/10.1186/s13195-015-0115-4.
54. Taylor, D., Fraser, S., Dudley, C., Oniscu, G., Tomson, C., Ravanan, R., & Roderick, P. (2017). Health literacy and patient outcomes in chronic kidney disease: a systematic review. *Nephrology Dialysis Transplantation*, 33, 1545–1558. https://doi.org/10.1093/ndt/gfx293.
55. Defilippi, C., & Herzog, C. (2017). Interpreting Cardiac Biomarkers in the Setting of Chronic Kidney Disease.. *Clinical chemistry*, 63 1, 59-65 . https://doi.org/10.1373/clinchem.2016.254748.
56. Kaspar, C., Bholah, R., & Bunchman, T. (2016). Review of Pediatric Chronic Kidney Disease. *Blood Purification*, 41, 211 - 217.