WIECZOREK, Olga Beata, ALEKSANDROWICZ, Daria, GŁĄBIEŃ, Marta, JAKUBCZAK, Zofia, MIŁKOWSKI, Pawel, ZIMNIAK, Maria Weronika, KONDRATOWICZ, Aneta, ŚLIWIAK, Patryk, KUSIAK, Karolina and KUŚNIERZ , Anna. Current Approaches to Treatment and Protein Intake Management in Pre-Dialysis Chronic Kidney Disease: Impact on Physical Exercise . Quality in Sport. 2024;22:54956 eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.22.54956
https://apcz.umk.pl/QS/article/view/54956

The journal has had 20 points in 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: 06.09.2024. Revised: 28.09.2024. Accepted: 15.10.2024. Published: 18.10.2024.

Current Approaches to Treatment and Protein Intake Management in Pre-Dialysis Chronic Kidney Disease: Impact on Physical Exercise

Olga Wieczorek 1, Daria Aleksandrowicz 2, Marta Głąbień 3, Anna Kuśnierz 4, Zofia Jakubczak 5, Paweł Miłkowski 6, Maria Zimniak 7, Aneta Kondratowicz 8, Karolina Kusiak 9, Patryk Śliwiak 10

1. **Olga Wieczorek**
   Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Łódź, 22 dr. Stefan Kopciński Street, 90-153 Lodz, Poland
   https://orcid.org/0009-0002-1973-6547
   olgawieczorek2997@gmail.com
2. **Daria Aleksandrowicz**
   Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Łódź, 22 dr. Stefan Kopciński Street , 90-153 Lodz, Poland
   https://orcid.org/0009-0004-5249-6092
   daria.aleksandrowicz97@gmail.com

3. **Marta Głąbień**

Central Clinical Hospital named after Military Medical Academy in Łódź, 113 S.Żeromskiego Street, 90-549 Lodz, Poland

https://orcid.org/0009-0003-8910-7647

marta.glabien@gmail.com

4. **Zofia Jakubczak**

Central Clinical Hospital of Medical University of Lodz, 251 Pomorska Street, 92-213 Lodz, Poland

https://orcid.org/0009-0002-8166-330X

zofia.jakubczak8@gmail.com

5. **Paweł Miłkowski**

Provincial Multidisciplinary Center of Oncology and Traumatology named after M. Copernicus University in Łódź, 62 Pabianicka Street, 93-513 Lodz, Polan

https://orcid.org/0009-0005-5470-1261

pawelmilkowski97@gmail.com

6. **Maria Weronika Zimniak**

Independent Public Health Care Facility of the Ministry of Internal Affairs and Administration, 42 Polnocna Street, 91-425 Lodz, Poland

https://orcid.org/0009-0005-6048-7791

mw.zimniak@gmail.com

7. **Aneta Kondratowicz**

K. Jonscher Hospital, 14 Milionowa Street, 93-113 Lodz, Poland

https://orcid.org/0009-0002-6548-2525

anetakondratowiczpl@gmail.com

8. **Patryk Śliwiak**

K. Jonscher Hospital, 14 Milionowa Street, 93-113 Lodz, Poland

https://orcid.org/0009-0000-7484-8045

patryksliwiak98@gmail.com

9. **Karolina Kusiak**

Central Clinical Hospital of the Medical University of Lodz, 251 Pomorska Street, 92-213 Lodz, Poland

https://orcid.org/0009-0008-0667-8097

kusiakkarolina46@gmail.com

10. Anna Kuśnierz

Provincial Multidisciplry Center of Oncology and Traumatology named after M. Copernicus University in Łódź, 62 Pabianicka Street, 93-513 Lodz, Poland

https://orcid.org/0009-0005-2983-4986
annakusnierz7@gmail.com

Abstract

Chronic kidney disease (CKD) is the 8th most common condition in the modern world. Unfortunately, it becomes more and more frequent and constitutes a significant global health problem, affecting millions of people worldwide. Therefore, its treatment is an important topic among researchers all over the world. It has been the subject of many trials, so it will eventually be as effective, secure, and comfortable for patients as it possibly can be. That is why updating and assembling current knowledge is the key to organizing information. This paper focuses on pharmacological treatment and nutritional guidelines for CKD pre-dialysis patients, as well as physical activity outcomes. It aims to summarize this knowledge, educate, and help doctors in their daily clinical work.

Material and methods

This is a paper review based on articles found on PubMed by using keywords like "chronic kidney disease," "protein intake in chronic kidney disease," "chronic kidney disease treatment," "consequences of chronic kidney disease," and "nutritional principles in chronic kidney disease."

Keywords: "chronic kidney disease" ; "flozines" ; "finerenone" ; "angiotensin-converting enzyme inhibitor" ; "angiotensin receptor blocker" ; "GLP-1 analog" ; "protein intake in kidney disease."

Conclusion

There are various methods of chronic kidney disease treatment, both pharmacological and included in renal replacement therapy, that are always accompanied by a proper diet. While nephroprotection and casual treatment followed by dialysis or kidney transplant are all important issues, dietary principles such as protein or phosphorus intake are also significant. Treatment selection for a patient is complex and depends on the individual's needs. However, there are principles that should be followed to achieve the most optimal effect of therapy and thus not only improve the quality but also the length of the patient's life.

Introduction

[30] Chronic kidney disease (CKD), according to KDIGO (Kidney Disease Improving Global Outcomes), is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. The most common ethiopathologies are, among others, diabetes, hypertension, obesity, acute kidney injury (AKI), and cardio-renal syndrome (CRS). The clinical picture includes weakness, fatigue, and hypothermia along with skin symptoms, circulatory disorders, respiratory disorders, digestive disorders, neuromuscular disorders, hormonal and metabolic disorders, electrolyte and acid-base disorders, hematopoietic and immune system disorders, and mineral and bone disorders. The therapy includes pharmacological treatment of the underlying pathology, slowing down the destruction process of the kidney, treating the CKD sequelae, and if it does not improve the patient’s clinical state, renal replacement therapy (RRT), which includes hemodialysis, peritoneal dialysis, or kidney transplant. Last but not least, parallel to the above methods, patients need to follow a certain diet to both slow the progression of the disease and avoid malnutrition caused by occurring catabolic processes.

Slowing down the acceleration of CKD and prevention of complications

Apart from managing the causal factors, it is equally important to prevent kidneys from further destruction. To achieve that, we implement treatment with neuroprotective drugs. Those are renin-angiotensin system (RAS) inhibitors, including angiotensin-converting enzyme (ACE) inhibitors (ACEI) and angiotensin receptor blockers (ARB), sodium-glucose

cotransporter-2 (SGLT2) inhibitors, also known as flozines, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RA), also known as GLP-1 analogs, and finerenon, which is a non-steroidal selective mineralocorticoid receptor antagonist. All the above groups have different mechanisms and protect kidneys in different ways. Furthermore, individual drugs within those groups also vary from each other.

Renin-angiotensin system inhibitors

ACEIs and ARBs are very popular drugs, mainly used for hypertension treatment. While it is true that these are first-line drugs for managing high blood pressure, they are also well known as nephroprotective medicines. [11] By blocking receptors of angiotensin II, which primarily causes vasoconstriction in the efferent arterioles, leading to elevated intraglomerular pressure and proteinuria. This can result in tubular damage and the activation of pro-inflammatory and fibrotic chemokines and cytokines. That is why RAS inhibitors slow down the loss of estimated glomerular filtration rate (eGFR) and the progression of mild or moderate chronic kidney disease. To better understand the role of RAS inhibitors, it is crucial to be aware of differences between ACEIs and ARBs. [12,13] Angiotensin II binds to receptors in numerous organs, including the brain, kidneys, heart, adrenal glands, and the vascular wall. There are two subtypes of angiotensin II receptors: AT1 and AT2. The activation of AT1 causes vasoconstriction and is linked to hypertrophy of the left ventricle (LV) and arteries, while the AT2 receptor plays a more limited role but has been linked to the stimulation of arterial wall growth. Angiotensin II can activate both AT1 and AT2 receptors. Therefore, ACEIs block both receptor subtypes. In contrast, ARBs specifically block only the AT1 receptor. [14] Additionally, ACE plays a key role in kinin metabolism, and inhibiting ACE increases kinin levels. Elevated kinin levels are thought to contribute to the blood pressure-lowering effects of ACEIs by releasing nitric oxide from vascular endothelial cells. [15] This also plays an important role because research shows elevated kinin levels may also enhance insulin sensitivity, thereby aiding in the reduction of blood glucose levels in patients with type 2 diabetes mellitus (T2DM), which are another group of individuals at increased risk of developing CKD. This shows that initiating ACEI treatment may yield better results in such a group in comparison to incorporating ARBs. What is more, managing hypertension itself is one of the mainstays of treating CKD, as patients suffering from high blood pressure have a higher risk of developing cardiac diseases. [8] The reason why is that as chronic kidney disease advances, the likelihood of developing cardiovascular conditions significantly rises, with 50%

of patients in late-stage CKD (stages 4–5) already having cardiovascular disease. [9] These in turn, as research shows, may lead to death even before reaching end-stage kidney disease (ESKD). [10] According to another research, the occurrence of heart failure (HF) was three times greater in individuals with an eGFR below 60 ml/min per 1.73 m² compared to those in the reference group with an eGFR of 90 ml/min per 1.73 m² or higher. This shows how important cardiovascular protection is. The important thing to remember is that choosing between ACEIs and ARBs can be significant for the course of the disease. [3] Research shows that while both groups of RAS inhibitors lower the hazard of kidney failure and cardiovascular events, ACE inhibitors may be more effective than ARBs in preventing overall mortality in patients with CKD. This suggests that ACE inhibitors could be the preferred treatment option for this group. However, using only RAS inhibitors in patients with hypertension may not be sufficient. [16] As a study shows, adding an aldosterone antagonist to treatment can help reduce proteinuria, eGFR, and systolic blood pressure in adults with mild to moderate CKD. However, when combined with ACE inhibitors or ARBs, they may raise the risk of hyperkalemia, acute kidney injury, and gynecomastia. Therefore, incorporating them into treatment must be preceded by an individual profit and loss analysis. We should not forget about a special case of patients suffering from COVID-19. [2] A conducted research states that patients with hypertension treated with the RAS inhibitors while being infected with SARS-CoV-2 experienced a significantly lower mortality rate. Therefore, therapy with ACE inhibitors or ARBs should not be discontinued during COVID-19 due to their beneficial effects on blood pressure control and potentially on mortality rates.

Sodium-glucose cotransporter-2 inhibitors

SGLT-2 inhibitors play a significant role in the treatment of patients with T2DM and HF while also having a nephroprotective role. [13] Recent evidence indicates that they have beneficial effects in slowing the onset and progression of renal complications in both diabetic and non-diabetic individuals. These effects are also seen in non-diabetic, lean, and normotensive individuals, indicating that the benefits of SGLT2 inhibitors are much more than just their glucose-lowering, weight-reducing, and blood pressure-lowering properties associated with their glucosuric action in diabetic patients. A primary mechanism is to increase sodium delivery along the nephron. This sodium is detected by macula cells, which use adenosine to constrict the afferent glomerular arterioles, thus lowering intraglomerular pressure and protecting the glomeruli. Additionally, SGLT2 inhibitors enhance tubular oxygenation and

metabolism while reducing renal inflammation and fibrosis. While SGLT2 is responsible for over 90% of glucose reabsorption in tubules, there also exists SGLT1, which mediates the process for the remaining glucose molecules. However, SGLT1 is primarily found in the apical membranes of enterocytes, where it facilitates the absorption of glucose from the intestinal lumen. This is why the more selective the inhibition of SGLT2 is, the more a given medicine is preferred. [14] There are drugs that inhibit both transporters. Sotagliflozin and canagliflozin are linked to some degree of SGLT1 inhibition in the intestines, but neither is thought to significantly inhibit SGLT1 in the kidneys. Therefore, the effectiveness and safety of a dual inhibitor that also targets renal SGLT1 remains unknown. [16] Nevertheless, a trial showed that patients with T2DM and kidney disease treated with canagliflozin had a lower risk of kidney failure and cardiovascular events compared to those who received a placebo. Flozines are a particularly important element of treatment for patients with diabetes, regardless of its type, as they are a group at high risk of developing diabetic kidney disease (DKD). Fortunately, a growing body of evidence now indicates that SGLT2 inhibitors can prevent the onset of DKD and slow its progression, both independently and in addition to the effects of blocking the RAS. [15] What is more, a trial demonstrates that the kidney-protective benefits of SGLT2 inhibitors also apply to a wider population of individuals with chronic kidney disease who do not have type 2 diabetes. Individuals with chronic kidney disease who were treated with dapagliflozin had a significantly lower risk of experiencing a combination of outcomes, including a sustained decline in eGFR of 50% or more, progression to end-stage kidney disease, or death from renal or cardiovascular causes, compared to those who received a placebo, regardless of whether they had type 2 diabetes. Additionally, patients on dapagliflozin had a reduced risk of death from cardiovascular causes or hospitalization for heart failure and showed improved overall survival. [12] Another trial was run with a subgroup of patients with eGFR<30 ml/min per 1.73 m2, and the outcome was similar to a previous one, which proved that dapagliflozin is safe for individuals with CKD in stage 4. [18] Furthermore, in a trial enrolled on a group of patients with CKD who had an eGFR of at least 20 but less than 45 ml/min per 1.73 m2 and the ones who had an eGFR of at least 45 but less than 90 ml/min per 1.73 m2, empagliflozin was studied. In this case, therapy also resulted in decreasing the risk of acceleration of kidney disease or death from cardiovascular causes compared to placebo.

Glucagon-like peptide-1 receptor agonists

GLP-1 analogs in another drug group mainly used in T2DM treatment. [19] However, GLP-1 RAs are now mentioned in international treatment guidelines for T2DM with CKD as second-line therapy due to their glycemic control and cardiovascular-reducing properties. GLP-1 is a hormone of the incretin system secreted as a response to food intake. It causes lowering of blood glucose levels by enhancing insulin secretion and reducing glucagon release. Additionally, since GLP-1 increases feelings of fullness through its actions in the brain, it is really helpful with weight management in individuals with obesity or overweight. Notwithstanding, the half-life of endogenous GLP-1 is brief (1–2 minutes), primarily because it is quickly broken down by the enzyme dipeptidyl peptidase IV (DPP-IV). This is why GLP-1 analogs had to be modified in various ways to extend the duration of action. [17] Due to the strong link between CKD and cardiovascular disease (CVD), clinical trials that examine the cardiovascular effects of GLP-1 RAs often include many participants who are also at high risk for kidney disease. As a result, the most reliable evidence regarding the kidney-protective effects of GLP-1 RAs comes from these cardiovascular outcomes trials (CVOTs). Generally, data from these CVOTs suggests that GLP-1 RAs may have benefits for kidney health. Nevertheless, it is important to note that kidney-related outcomes were assessed as secondary endpoints, and the trials were not specifically designed or powered to confirm the impact of GLP-1 RAs on kidney-related clinical outcomes. [20,21] Both semaglutide and liraglutide have been shown to decrease the risk of developing new or worsening nephropathy in studies, although renal outcomes were secondary endpoints in each of these studies. For patients with stage 3 CKD and T2DM, liraglutide is the GLP-1 RA with the most robust evidence supporting its use. In cases where atherosclerotic cardiovascular disease (ASCVD) is the primary concern, it is recommended to use a GLP-1 RA with proven cardiovascular benefits, provided the eGFR is adequate. Among GLP-1 RAs, liraglutide, followed by semaglutide, has the strongest evidence. [22] There is a currently running, first specifically focused on kidney outcomes trial called FLOW, which evaluates kidney-protective effects of semaglutide in patients suffering from CKD and T2DM and is about to be completed by the end of 2024.

Finerenone

Finerenone is a nonsteroidal selective mineralocorticoid receptor (MR) antagonist (MRA). [23] Overactivation of MRs leads to inflammation and fibrosis, which contribute to a

faster decline in kidney function. This is why finerenone plays an important role as a nephroprotective drug. Although there exist also well-known steroidal MRAs like spironolactone or eplerenone, their mechanisms vary from finerenone. [24] Finerenone is recognized as a highly selective, third-generation nonsteroidal MRA with stronger anti-inflammatory and antifibrotic effects compared to spironolactone and eplerenone. [23] Furthermore, finerenone was found to have an even distribution between the kidney and the heart, whereas spironolactone and eplerenone tend to accumulate more in the kidney, which raises the risk of hyperkalemia. [28] In a trial run in patients with treatment-resistant hypertension (TRH) and CKD, it was shown that individuals receiving finerone had lower systolic blood pressure (SBP) reduction but, on the other hand, also reduced the occurrence of hyperkalemia and a decreased risk of kidney function deterioration while compared to those patients who received spironolactone. [25] Finerenone has also been shown to reduce the urinary albumin to creatinine ratio while maintaining significantly lower potassium levels than spironolactone. Additionally, finerenone was well-tolerated in patients with CKD and T2DM. [26] The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial reported that finerenone treatment leads to better cardiovascular outcomes compared to a placebo in patients with T2DM and stage 2 to 4 CKD. [27] What is more, the trial also proved that finerenone reduces the risk of the first hospitalization for heart failure (HHF) by 29% and decreased the risk of cardiovascular death or first HHF by 18% compared to placebo, regardless of a prior history of HF. Additionally, developing new-onset HF itself was also lower by 32% with finerenone than with placebo. This is the first study to demonstrate that selective, nonsteroidal MRAs may prevent HF in patients with chronic kidney disease (CKD) and T2DM.

Nutrition in chronic kidney disease

Despite pharmacological treatment, patients with CKD have to face strict dietary rules. The most important ones are about protein and phosphorus intake, which in both cases should be limited. In case of phosphorus, there is a problem of its accumulation in patients with eGFR<45 ml/min per 1.73 m2. Therefore, additional intake is undesirable. Protein, on the other hand, is being lost due to the nephrons' destruction. However, it is not a loss that could be supplemented dietarily, as higher protein intake causes even more severe kidney injury. That is why low-protein and very low-protein diets are eligible for pre-dialysis patients. [31] According to the KDOQI 2020 Guidelines, the recommended dietary protein supply per kg of body weight

per day in pre-dialysis patients varies depending on stage of CKD and occurrence of diabetes. Therefore, patients with 3-5 stage CKD who do not suffer from diabetes mellitus (DM) shall follow a low-protein diet (LPD) providing 0.55–0.60 g of protein/kg body weight/day or a very low-protein (VLPD) providing 0.28–0.43 g dietary protein/kg body weight/day with additional keto acid or amino acid analogs. On the other hand, individuals suffering from 3-5 stage CKD without DM are recommended with a higher protein intake of 0.6-0.8 g/kg body weight per day. [35] A randomized trial indicates that among randomly selected patients with advanced CKD receiving regular nephrology care, a long-term strict VLPD does not provide extra advantages over a standard LPD in terms of kidney function and patient survival. Additionally, it is not linked to any deterioration in nutritional status. [36] On the other hand, a meta-analysis of adults with non-diabetic CKD stages 3 to 5 concluded that very low-protein diets likely decrease the number of individuals with CKD stages 4 or 5 who advance to ESKD. Conversely, low-protein diets may have minimal impact on the progression to ESKD. When it comes to the type of protein, KDOQI claims that there is no sufficient evidence to favor plant or animal protein. Nevertheless, there is an expanding pool of research showing that a plant-based diet may be more favorable. [30] According to KDIGO, a diet consisting primarily of whole plant foods while minimizing consumption of animal products and ultraprocessed foods could be beneficial in slowing the progression of CKD and postponing the need for dialysis. This benefit is achieved by lowering cardiometabolic risk factors, including hypertension, cardiovascular disease, diabetes, and obesity. [32] What is more, the probiotic properties of plant-based foods may help maintain a healthy microbiome, lower inflammation, and decrease the intestinal production of uremic toxins. [33] According to research, replacing one serving of red meat with soy or legumes is linked to a 50.4% lower risk of kidney failure. [34] In an observational study, plant-based diets were linked to a 12% reduced risk of a decline in eGFR compared to diets based on meat.

Impact on physical activity

[37] Customarily, patients with CKD are not recommended to engage in physical exercise as it can be a factor in increased proteinuria and, consequently, further kidney injury. There are trials showing that the increased sympathetic nerve activity that occurs during physical exertion diminishes renal blood flow, potentially disrupting the delicate structures of the kidneys and impairing their function. However, it also enhances aerobic and functional capacity, helps optimize blood pressure control, and improves hemoglobin levels. [38] In

another trial, patients with moderate to severe CKD were engaged. The trial explored 4 groups: dietary restriction of 10%−15% reduction in caloric intake, exercise three times per week, combined diet and exercise, and control. Then adipocytokines levels were measured at both the start and conclusion of the study. The study revealed that adiponectin levels significantly increased in participants assigned to the dietary intervention alone, but not in those who followed the combined diet and exercise intervention. It may show that physical exertion does not have as strong a positive impact on patients' health as dietary restriction itself. Nevertheless, there is a wide range of research proving a beneficial effect of exercise for individuals suffering from T2DM or hypertension, both of which are serious risk factors in CKD. Therefore, it could be beneficial or at least neutral for kidney function to prescribe moderate physical activity to patients in stable condition.

Author's Contribution

Conceptualization: Olga Wieczorek; Methodology: , Olga Wieczorek, Daria Aleksandrowicz; Software: Marta Głąbień, Paweł Miłkowski; Check: Anna Kuśnierz, Zofia Jakubczak; Formal analysis: Olga Wieczorek, Daria Aleksandrowicz, Investigation: Olga Wieczorek, Patryk Śliwiak; Resources: Aneta Kondratowicz, Maria Weronika Zimniak; Data curation: Marta Głąbień, Paweł Miłkowski; Writing - rough preparation: Olga Wieczorek; Writing- review and editing: , Olga Wieczorek, Daria Aleksandrowicz; Visualisation: Olga Wieczorek, Daria Aleksandrowicz, Karolina Kusiak; Supervision: Zofia Jakubczak, Maria Weronika Zimniak; Project administration: Olga Wieczorek, Agata Kondratowicz, Patryk Śliwiak

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

Funding Statement

Study did not receive special funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgments

Not applicable.

Conflict of Interest Statement

The authors of the paper report no conflicts of interests.

Bibliography:

1. Filev R, Rostaing L, Lyubomirova M, Bogov B, Kalinov K, Svinarov D. Renin-angiotensin-aldosterone system blockers in Bulgarian COVID-19 patients with or without chronic kidney disease. Medicine (Baltimore). 2022 Dec 2;101(48):e31988. doi: 10.1097/MD.0000000000031988. PMID: 36482641; PMCID: PMC9726321.
2. Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, Zhao N, Liu L, Lv J, Zhang H, Wang H. Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. Am J Kidney Dis. 2016 May;67(5):728-41. doi: 10.1053/j.ajkd.2015.10.011. Epub 2015 Nov 18. PMID: 26597926.
3. Evans M, Lewis RD, Morgan AR, Whyte MB, Hanif W, Bain SC, Davies S, Dashora U, Yousef Z, Patel DC, Strain WD. A Narrative Review of Chronic Kidney Disease in Clinical Practice: Current Challenges and Future Perspectives. Adv Ther. 2022 Jan;39(1):33-43. doi: 10.1007/s12325-021-01927-z. Epub 2021 Nov 5. PMID: 34739697; PMCID: PMC8569052.
4. Tuegel C, Bansal N. Heart failure in patients with kidney disease. Heart. 2017 Dec;103(23):1848-1853. doi: 10.1136/heartjnl-2016-310794. Epub 2017 Jul 17. PMID: 28716974.
5. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, Chambless LE, Coresh J. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. J Am Soc Nephrol. 2007 Apr;18(4):1307-15. doi: 10.1681/ASN.2006101159. Epub 2007 Mar 7. PMID: 17344421.
6. Singhania N, Bansal S, Mohandas S, Nimmatoori DP, Ejaz AA, Singhania G. Role of renin-angiotensin-aldosterone system inhibitors in heart failure and chronic kidney

disease. Drugs Context. 2020 Nov 11;9:2020-7-3. doi: 10.7573/dic.2020-7-3. PMID: 33240389; PMCID: PMC7673621.

7. Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. N Engl J Med. 1996 Jun 20;334(25):1649-54. doi: 10.1056/NEJM199606203342507. PMID: 8628362.
8. Stoll M, Steckelings UM, Paul M, Bottari SP, Metzger R, Unger T. The angiotensin AT2-receptor mediates inhibition of cell proliferation in coronary endothelial cells. J Clin Invest. 1995 Feb;95(2):651-7. doi: 10.1172/JCI117710. PMID: 7860748; PMCID: PMC295531.
9. Hornig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. Circulation. 1997 Mar 4;95(5):1115-8. doi: 10.1161/01.cir.95.5.1115. PMID: 9054837.
10. Tomiyama H, Kushiro T, Abeta H, Ishii T, Takahashi A, Furukawa L, Asagami T, Hino T, Saito F, Otsuka Y, et al. Kinins contribute to the improvement of insulin sensitivity during treatment with angiotensin converting enzyme inhibitor. Hypertension. 1994 Apr;23(4):450-5. doi: 10.1161/01.hyp.23.4.450. PMID: 8144214.
11. Chung EY, Ruospo M, Natale P, Bolignano D, Navaneethan SD, Palmer SC, Strippoli GF. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2020 Oct 27;10(10):CD007004. doi: 10.1002/14651858.CD007004.pub4. PMID: 33107592; PMCID: PMC8094274.
12. Chertow GM, Vart P, Jongs N, Toto RD, Gorriz JL, Hou FF, McMurray JJV, Correa-Rotter R, Rossing P, Sjöström CD, Stefánsson BV, Langkilde AM, Wheeler DC, Heerspink HJL; DAPA-CKD Trial Committees and Investigators. Effects of Dapagliflozin in Stage 4 Chronic Kidney Disease. J Am Soc Nephrol. 2021 Sep;32(9):2352-2361. doi: 10.1681/ASN.2021020167. Epub 2021 Jul 16. PMID: 34272327; PMCID: PMC8729835.
13. Bailey CJ, Day C, Bellary S. Renal Protection with SGLT2 Inhibitors: Effects in Acute and Chronic Kidney Disease. Curr Diab Rep. 2022 Jan;22(1):39-52. doi: 10.1007/s11892-021-01442-z. Epub 2022 Feb 3. PMID: 35113333; PMCID: PMC8888485.
14. Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium-Glucose Cotransporter Inhibitors: Effects on Renal and Intestinal Glucose Transport: From Bench to Bedside. Diabetes Care. 2015 Dec;38(12):2344-53. doi: 10.2337/dc15-0642. PMID: 26604280.

15. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446. doi: 10.1056/NEJMoa2024816. Epub 2020 Sep 24. PMID: 32970396.
16. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306. doi: 10.1056/NEJMoa1811744. Epub 2019 Apr 14. PMID: 30990260.
17. Aldrich S, Ashjian E. Use of GLP-1 receptor agonists in patients with T2DM and chronic kidney disease. Nurse Pract. 2019 Mar;44(3):20-28. doi: 10.1097/01.NPR.0000553396.65976.bb. PMID: 30695005.
18. The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, Preiss D, Judge P, Mayne KJ, Ng SYA, Sammons E, Zhu D, Hill M, Stevens W, Wallendszus K, Brenner S, Cheung AK, Liu ZH, Li J, Hooi LS, Liu W, Kadowaki T, Nangaku M, Levin A, Cherney D, Maggioni AP, Pontremoli R, Deo R, Goto S, Rossello X, Tuttle KR, Steubl D, Petrini M, Massey D, Eilbracht J, Brueckmann M, Landray MJ, Baigent C, Haynes R. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023 Jan 12;388(2):117-127. doi: 10.1056/NEJMoa2204233. Epub 2022 Nov 4. PMID: 36331190; PMCID: PMC7614055.
19. von Scholten BJ, Kreiner FF, Rasmussen S, Rossing P, Idorn T. The potential of GLP-1 receptor agonists in type 2 diabetes and chronic kidney disease: from randomised trials to clinical practice. Ther Adv Endocrinol Metab. 2022 Jul 19;13:20420188221112490. doi: 10.1177/20420188221112490. PMID: 35874312; PMCID: PMC9301118.
20. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844. doi: 10.1056/NEJMoa1607141. Epub 2016 Sep 15. PMID: 27633186.

21. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13. PMID: 27295427; PMCID: PMC4985288.
22. Rossing P, Baeres FMM, Bakris G, Bosch-Traberg H, Gislum M, Gough SCL, Idorn T, Lawson J, Mahaffey KW, Mann JFE, Mersebach H, Perkovic V, Tuttle K, Pratley R. The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. Nephrol Dial Transplant. 2023 Aug 31;38(9):2041-2051. doi: 10.1093/ndt/gfad009. Erratum in: Nephrol Dial Transplant. 2024 Mar 27;39(4):724. doi: 10.1093/ndt/gfad252. PMID: 36651820; PMCID: PMC10469096.
23. González-Juanatey JR, Górriz JL, Ortiz A, Valle A, Soler MJ, Facila L. Cardiorenal benefits of finerenone: protecting kidney and heart. Ann Med. 2023 Dec;55(1):502-513. doi: 10.1080/07853890.2023.2171110. PMID: 36719097; PMCID: PMC9891162.
24. Yasmin F, Aamir M, Najeeb H, Atif AR, Siddiqui AH, Ahsan MN, Moeed A, Ali SH, Tahir HM, Asghar MS. Efficacy and safety of finerenone in chronic kidney disease and type 2 diabetes patients: a systematic review and meta-analysis. Ann Med Surg (Lond). 2023 Aug 16;85(10):4973-4980. doi: 10.1097/MS9.0000000000001180. PMID: 37811017; PMCID: PMC10553111.
25. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, Nowack C, Kolkhof P, Kim SY, Zannad F. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur Heart J. 2013 Aug;34(31):2453-63. doi: 10.1093/eurheartj/eht187. Epub 2013 May 27. PMID: 23713082; PMCID: PMC3743070.
26. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, Joseph A, Kolkhof P, Nowack C, Schloemer P, Ruilope LM; FIGARO-DKD Investigators. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med. 2021 Dec 9;385(24):2252-2263. doi: 10.1056/NEJMoa2110956. Epub 2021 Aug 28. PMID: 34449181.
27. Filippatos G, Anker SD, Agarwal R, Ruilope LM, Rossing P, Bakris GL, Tasto C, Joseph A, Kolkhof P, Lage A, Pitt B; FIGARO-DKD Investigators. Finerenone Reduces

Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial. Circulation. 2022 Feb 8;145(6):437-447. doi: 10.1161/CIRCULATIONAHA.121.057983. Epub 2021 Nov 13. PMID: 34775784; PMCID: PMC8812430.

28. Agarwal R, Pitt B, Palmer BF, Kovesdy CP, Burgess E, Filippatos G, Małyszko J, Ruilope LM, Rossignol P, Rossing P, Pecoits-Filho R, Anker SD, Joseph A, Lawatscheck R, Wilson D, Gebel M, Bakris GL. A comparative post hoc analysis of finerenone and spironolactone in resistant hypertension in moderate-to-advanced chronic kidney disease. Clin Kidney J. 2022 Oct 30;16(2):293-302. doi: 10.1093/ckj/sfac234. PMID: 36864892; PMCID: PMC9972517.
29. Wei H, Ren J, Li R, Qi X, Yang F, Li Q. Global, regional, and national burden of chronic kidney disease attributable to high fasting plasma glucose from 1990 to 2019: a systematic analysis from the global burden of disease study 2019. Front Endocrinol (Lausanne). 2024 Mar 27;15:1379634. doi: 10.3389/fendo.2024.1379634. PMID: 38601204; PMCID: PMC11004380.
30. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314. doi: 10.1016/j.kint.2023.10.018. PMID: 38490803.
31. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, Fouque D, Friedman AN, Ghaddar S, Goldstein-Fuchs DJ, Kaysen GA, Kopple JD, Teta D, Yee-Moon Wang A, Cuppari L. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. Am J Kidney Dis. 2020 Sep;76(3 Suppl 1):S1-S107. doi: 10.1053/j.ajkd.2020.05.006. Erratum in: Am J Kidney Dis. 2021 Feb;77(2):308. doi: 10.1053/j.ajkd.2020.11.004. PMID: 32829751.
32. Cosola C, Rocchetti MT, Sabatino A, Fiaccadori E, Di Iorio BR, Gesualdo L. Microbiota issue in CKD: how promising are gut-targeted approaches? J Nephrol. 2019 Feb;32(1):27-37. doi: 10.1007/s40620-018-0516-0. Epub 2018 Aug 1. PMID: 30069677.
33. Lew QJ, Jafar TH, Koh HW, Jin A, Chow KY, Yuan JM, Koh WP. Red Meat Intake and Risk of ESRD. J Am Soc Nephrol. 2017 Jan;28(1):304-312. doi: 10.1681/ASN.2016030248. Epub 2016 Jul 14. PMID: 27416946; PMCID: PMC5198288.

34. Khatri M, Moon YP, Scarmeas N, Gu Y, Gardener H, Cheung K, Wright CB, Sacco RL, Nickolas TL, Elkind MS. The association between a Mediterranean-style diet and kidney function in the Northern Manhattan Study cohort. Clin J Am Soc Nephrol. 2014 Nov 7;9(11):1868-75. doi: 10.2215/CJN.01080114. Epub 2014 Oct 30. PMID: 25359387; PMCID: PMC4220748.
35. Bellizzi V, Signoriello S, Minutolo R, Di Iorio B, Nazzaro P, Garofalo C, Calella P, Chiodini P, De Nicola L; ERIKA Study Group Investigators of the Italian Society of Nephrology-Conservative Therapy of CKD Work Group. No additional benefit of prescribing a very low-protein diet in patients with advanced chronic kidney disease under regular nephrology care: a pragmatic, randomized, controlled trial. Am J Clin Nutr. 2022 May 1;115(5):1404-1417. doi: 10.1093/ajcn/nqab417. PMID: 34967847.
36. Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with chronic kidney disease. Cochrane Database Syst Rev. 2020 Oct 29;10(10):CD001892. doi: 10.1002/14651858.CD001892.pub5. PMID: 33118160; PMCID: PMC8095031.
37. Villanego F, Naranjo J, Vigara LA, Cazorla JM, Montero ME, García T, Torrado J, Mazuecos A. Impact of physical exercise in patients with chronic kidney disease: Sistematic review and meta-analysis. Nefrologia (Engl Ed). 2020 May-Jun;40(3):237-252. English, Spanish. doi: 10.1016/j.nefro.2020.01.002. Epub 2020 Apr 15. PMID: 32305232.
38. Aydemir N, Pike MM, Alsouqi A, Headley SAE, Tuttle K, Evans EE, Milch CM, Moody KA, Germain M, Lipworth L, Himmelfarb J, Ikizler TA, Robinson-Cohen C. Effects of diet and exercise on adipocytokine levels in patients with moderate to severe chronic kidney disease. Nutr Metab Cardiovasc Dis. 2020 Jul 24;30(8):1375-1381. doi: 10.1016/j.numecd.2020.04.012. Epub 2020 Apr 21. PMID: 32571614; PMCID: PMC7659879.