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REVIEW ARTICLE

Implications of Untreated Hypertension on Chronic Kidney Disease: A Literature Review

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ABSTRACT

The untreated progression of hypertension holds significant implications for the development and progression of chronic kidney disease (CKD). Therefore, necessitating the implementation of strategic hypertension management measures to mitigate its impact on chronic kidney disease. This review highlights the necessity of precise diagnostic methodologies that employ oscillometric equipment and advocates for pharmacological interventions, the incorporation of combination therapies such as the "Polypill" to effectively control hypertension, and lifestyle adjustments. The pivotal role of the renin-angiotensin-aldosterone system (RAAS) in hypertension is acknowledged, noting the importance of stringent blood pressure regulation and the utilization of RAAS-blocking agents to attenuate its association with chronic kidney disease. A comprehensive analysis is provided on the effects of various classes of antihypertensive medications on renal function, encompassing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and nonsteroidal mineralocorticoid receptor antagonists. Additionally, both non-invasive and invasive therapeutic modalities for managing resistant hypertension in CKD patients are examined, alongside discussions on prognostic indicators and outcomes across different stages of chronic kidney disease. Lifestyle modifications such as sodium restriction, weight management, and moderation of alcohol intake are assessed for their influence on chronic kidney disease prognosis. The review also extensively delves into the impact of ethnicity on the prevalence and outcomes of hypertension-induced CKD, highlighting disparities and distinctive trends among diverse ethnic cohorts including Indian, African American, Middle Eastern, Chinese, Pacific Islander, Native American, and Hispanic populations. Additionally, this study addresses the intricate relationship between cardiovascular abnormalities and CKD, the significance of gastrointestinal disorders, and the importance of multidisciplinary approaches in CKD management. Furthermore, insights are provided into the significance of neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for identifying renal injury and chronic kidney disease progression alongside factors influencing adverse prognosis and life expectancy in CKD patients. This study accentuates the importance of tailored treatment assessments and interventions to address varied patterns and obstacles within ethnic groups, aiming to optimize chronic kidney disease management strategies and reduce health disparities.

Keywords: Hypertension, high blood pressure, chronic kidney disease, atherosclerosis, renal failure, renin-angiotensin-aldosterone system, kidney disease markers, proteinuria, end-stage renal disease.

1. Introduction

Millions of individuals worldwide suffer from hypertension, a serious public health issue. Hypertension is the most prevalent cardiovascular risk factor and carries the highest population-based risk for cardiovascular disease (CVD)[1]. Untreated hypertension significantly impacts chronic kidney disease (CKD). Therefore, blood pressure management is crucial, where combining non-pharmacological and pharmaceutical therapies can provide optimal control[2]. Additionally, accurate diagnosis, including oscillometric equipment, is essential. Addressing CKD-associated sympathetic hyperactivity with angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors is vital for the patient's life. Non-pharmaceutical interventions such as lifestyle changes like diet, exercise, and alcohol moderation can also aid management.

Hypertension was found to correlate with cognitive decline and stroke, emphasizing the importance of treatment. Combination drugs like the "Polypill" offer a comprehensive approach to hypertension management, especially in high-risk populations[3]. The renin-angiotensin-aldosterone system (RAAS) increases the amount of aldosterone secreted from the adrenal cortex, which helps to maintain the tonicity inside blood vessels and aids in blood volume regulation[4]. A surplus or insufficiency of RAAS in the body can result in various pathological manifestations associated with hypertension and kidney functions. While the RAAS system may be necessary for maintaining arterial pressure, excessive angiotensin II can cause hypertension by excessively constricting artery branches[4,5].

For people with CKD, managing hypertension is crucial because it can exacerbate renal impairment and increase the risk of cardiovascular events. Different antihypertensive drug classes have different effects on renal function, and the choice of these medications is often based on the stage of CKD and the individual characteristics of each patient[6]. One of the main signs and symptoms of chronic renal disease is resistant hypertension, which is treated with a variety of invasive procedures, including renal sympathetic denervation, baroreflex activation treatment, renal artery stenting, and arteriovenous coupling[8]. The prognosis of CKD can be attributed to multiple factors[9]. There is a hidden relationship between the prevalence of hypertension and ethnic backgrounds, and it is hypothesized that ethnicity plays a significant role in determining both survivability and the likelihood of hypertension-induced CKD[10]. Several lifestyle modifications have been shown to improve prognosis and outcomes in patients with CKD. Reducing dietary salt intake is one of the most common recommendations for such patients and It has been shown to significantly decrease blood pressure plasma renin, serum aldosterone, and proteinuria[11]. To optimize CKD management techniques and reduce health disparities, this study highlights the significance of untreated hypertension on CKD and how customized treatment assessments are needed to address various patterns and challenges within ethnic groups.

2. The Effects of Untreated Hypertension on Chronic Kidney Disease

Blood pressure management is crucial because it is not only easily controlled but

may have catastrophic consequences if left untreated. Ideally, for the best blood pressure control and lowest risk of cardiovascular disease, nonpharmacological and pharmaceutical therapies must be calibrated to maximum acceptable effectiveness with long-term adherence[2]. However, to provide adequate management, the first step would be accurate diagnosis. In the interest of effective management, the initial and critical step is to establish an accurate diagnosis. To do this, the American College of Cardiology Blood Pressure Guideline encourages the use of oscillometric equipment to collect automated office blood pressure readings and suggests taking blood pressure readings outside of the office to identify masked hypertension and white coat hypertension as well as to confirm elevated blood pressures within the office[2].

2.1 BLOOD PRESSURE MANAGEMENT

Given the correlation between chronic kidney disease and hypertension, it's important to understand that managing or treating one condition can mitigate the effects of the other[12]. Increased sympathetic nervous system activity is the primary cause of hypertension in patients with chronic kidney disease and this rise in activity is caused by impulses that arise from the damaged kidneys. Patients could benefit from lessening this sympathetic hyperactivity as it has been associated with detrimental cardiovascular effects. ARB and ACE inhibitors help reduce sympathetic hyperactivity in patients with chronic kidney disease, although they might not completely regulate it. One drug that can lower blood pressure is moxonidine and can additionally cause advantageous changes in lipid and glucose metabolism, which may reduce the overall risk of cardiovascular disease in chronic kidney disease patients. Blood pressure also has a significant impact on the renal prognosis of patients with and without diabetes mellitus, especially those who have proteinuric chronic kidney disease. Consequently, for the protection of the kidneys and heart, "goal blood pressure-oriented management" is fundamental. Moreover, because RAAS-blocking medications have a renoprotective effect that is enhanced by appropriate blood pressure control, their usage is also highly advised[12]. Furthermore, various environmental factors, specifically those which are related to one's diet such as exercise, and consumption of alcohol, play a very impactful role in managing blood pressure. To alleviate the repercussions of elevated blood pressure, the most effective therapies include eating a nutritious diet, cutting back on salt (sodium chloride), losing weight, increasing potassium intake, exercising, and abstaining from alcohol intake[2,3].

Recent studies and evidence have shown an association between cognitive dysfunction relating to stroke and hypertension. According to a mass study that was carried out on approximately 7.5 thousand patients, the study concluded that following a stroke, the likelihood of dementia increased two to five times[12,13]. This suggests that it plays a crucial role in this situation. Angiotensin 1 receptor activation is linked to a reduction in blood flow to the brain, inflammation, and disruption to the blood–brain barrier. In this case, blood-brain barrier-penetrating RAAS inhibitors may be effective in preventing cognitive decline by inhibiting the RAAS in the hippocampus, which is important for

cognition. The administration of ARBs and ACE Inhibitors, specifically brain-penetrating medicines like telmisartan, perindopril, and captopril, seems to enhance the function of the blood–brain barrier, augment cerebral blood flow, and prevent inflammation[13]. The epidemiology of blood pressure has advanced significantly since it was first discovered more than a century ago, where high blood pressure is linked to an increased risk of death. The burden associated with nonoptimal blood pressure is largely borne by high-risk individuals who would not typically be classified as hypertensive and, therefore, not be considered for antihypertensive treatment. It is now widely acknowledged that high blood pressure is a significant risk factor for a variety of cardiovascular and renal events (both fatal and nonfatal)[14]. Lastly, the concept of a combination drug, commonly referred to as the "Polypill" has also been regarded as an effective strategy in the management of hypertension[2]. The Polypill includes a multitude of active components, each of which has been extensively used in the medical field for over a decade. The concept underlying the development of the polypill is to abandon the notion that relevant risk factors require individual evaluation and treatment. It should be recognized that in the West, everyone is at risk due to the high prevalence of risk factors that cause fatal outcomes. Therefore, the widespread use of these medications in the form of a polypill can be deemed more advantageous than detrimental.

2.2 RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM FEEDBACK

The RAAS system helps with the regulation of blood volume by maintaining the tonicity inside blood vessels by increasing the secretion of aldosterone from the adrenal cortex[4]. Mineralocorticoid hormones like aldosterone act to restore blood volume by reabsorbing more sodium though channels like NCC (renal thiazide-sensitive NaCl cotransporter) and ENaC (epithelial sodium channels) within the kidney, while secretion of potassium occurs.

2.2.1 Function and Process of the Renin-Angiotensin-Aldosterone System

Additionally, an increase in antidiuretic hormone/vasopressin is upregulated, causing an increase in water retention and a reduction in urinary secretion. Due to this, the blood pressure increases as a consequence[15]. Initially, the kidney will produce renin which will convert angiotensinogen to angiotensin I; then, angiotensin I will be activated into Angiotensin II by the ACE enzyme produced by the lungs[4,16]. While ACE1, being more prominent in pulmonary blood vessels, causes an increase in sympathetic tone and helps constrict the blood vessels, ACE2 is an enzyme which can be found more in the kidney and helps to dilate blood vessels. As such, this indicates that these two enzymes act as antagonists to each other[17].

2.2.2 Renin-Angiotensin-Aldosterone System Feedback Related to Hypertension

An overproduction or deficiency in the RAAS system can lead to many pathological symptoms relating to hypertension and kidney problems. Although the RAAS system may be essential for maintaining arterial pressure, excessive amounts of angiotensin II can lead to hypertension by excessively constricting branches of arteries, leading to an increased risk of having hypertension-related complications like heart attacks, arterial

aneurysms, atherosclerosis, and brain hemorrhage[4]. Moreover, considering the rate limiting enzyme for the typical RAAS hormonal cascade is renin, which the kidney produces, it follows that one of the most frequent adverse consequences of RAAS is on the kidney[18]. One example of the effect of inadequate RAAS is that the ACE2 enzyme helps the kidney to maintain homeostasis, therefore a shortage in this enzyme can lead to albuminuria and glomerulosclerosis, a frequent kidney disease[4]. Additionally, some viruses like COVID-19 are likely to bind to ACE2 receptors; therefore, increasing ACE2 receptors may also increase the risk of COVID-19 infection. Therefore, medications that upregulate ACE2 production like ACE Inhibitors and ARBs were initially recommended against in patients with a combination of hypertension and COVID-19[17].

2.2.3 Renin-Angiotensin-Aldosterone System Feedback in Hypertension and its Correlation to Chronic Kidney Disease

The RAAS system is the major contributor to the feedback systems that control both cardiovascular and renal physiology. As such, any fluctuations of the RAAS system can contribute to the development of pathophysiologies associated with the cardiovascular and renal systems. These pathophysiologies can be grouped into cardiorenal systems, where cardiac function leads to renal dysfunction, or reno-cardio systems, where renal dysfunction leads to cardiac dysfunction[16]. In many scenarios, the kidney can play as both cause and effect: patients with CKD have an elevated risk of developing CVD, but patients with cardiovascular disorders are also at an increased risk for CKD itself. This encourages a cycle of failure of both the cardiovascular and renal systems together. An example of this is when CKD is secondary to hypertension, where reports indicate that in regions of renal injury or ischemia, the production of local and intra-renal angiotensin II rises which further worsens the systemic hypertension that was present in the first place[19].

Hypertension is considered a risk factor for CKD. This is due to the fact that intracapillary hypertension can lead to increased ultrafiltration of plasma proteins, which can lead to proteinuria. Proteinuria has many adverse effects on the kidney, including inflammation and fibrosis, which contribute to the onset of CKD or further exacerbate any pre-existing CKD[5]. Furthermore, abnormally high blood pressure can lead to the loss of nephrons. This loss of nephrons leads to the remaining nephrons developing glomerular capillary hypertension, and the single-nephron glomerular filtration rate (GFR) increases. This change initially aids in the maintenance of the overall GFR. However, it eventually leads to renal insufficiency, CKD, and End-stage renal disease (ESRD)[5,18].

2.3 CLASS DIFFERENCES BETWEEN ANTIHYPERTENSIVES

Hypertension leads to exacerbated renal damage and raises concerns with regards to cardiovascular health. Thus, it is crucial for one suffering from CKD to control their blood pressure levels to lower the possibility of a hypertensive crisis. The effects of antihypertensive drugs on renal function vary on their class, and the selection of these drugs is frequently contingent upon the stage of CKD, unique symptoms and underlying diseases of the patient. According to research, diuretics is the base of treatment for

hypertension associated with CKD[6]. This study highlights the effectiveness of diuretics in CKD while discussing their role in controlling volume expansion in the body, and thus, lowering blood pressure. Furthermore, another study examined the impact of a loop diuretic, "furosemide" on the left ventricular mass in CKD patients exempting dialysis[20]. Evidently, this emphasizes the possible advantages of diuretic therapy and its benefits in improving cardiovascular health. Following its renoprotective properties. Nonsteroidal mineralocorticoid receptor antagonists have been proven to be promising in controlling hypertension and thereby, reducing kidney damage. Furthermore, the study highlights the possible renoprotective benefits of nonsteroidal mineralocorticoid receptor antagonists with regards to diabetes underlying CKD, thus emphasizing the benefits in improving renal health beyond blood pressure regulation[24]. Moreover, β-adrenoceptor antagonists also lower blood pressure levels in patients with CKD by improving the functioning of the dysregulated sympathetic nervous system. Thus, these classes of drugs are known to possess well-established cardioprotective properties. One of the main groups of polyphenols, flavonoids, are known to enhance cardiovascular health and exhibit antioxidant properties via an inflammatory cascade and oxidative disruption , affecting many bodily pathways propulsing its anti-inflammatory properties against the various nephropathies[25]. Moreover, flavonoids possess strong antiapoptotic and antifibrotic characteristics and inhibit EMT and disrupt TGF-β1/Smad signaling, which may be crucial for its renoprotective effects in CKD.

ACE inhibitors and ARBs are two types of inhibitors of the RAS that are frequently prescribed for patients with CKD. A systematic review and meta-analysis assessing the renal outcomes associated with the use of these drugs emphasize its ability in lowering proteinuria and maintaining adequate functioning of the kidneys[21]. RAS inhibitors are of significant importance in treating CKD[22]. Additionally, patients with CKD are frequently prescribed calcium channel blockers (CCBs) that belong to the antihypertensive drug class. A study addressed the effectiveness and safety of using CCBs in reducing hypertension in patients with CKD[23]. Thereby, highlighting that further research is required to understand the precise effects of CCBs on renal outcomes and its long-term implications on kidney function. β-blockers have also shown renoprotective effects in animal studies, by decreasing the progression of interstitial fibrosis after renal damage. Regardless of the pharmacological class, antihypertensives provide a monotherapy in patients with early-stage CKD and dramatically slow the progression of estimated GFR (eGFR) over time.

For eGFR maintenance, RAS inhibitors like ACE inhibitors or ARBs do not pose a superiority to other antihypertensive medication classes[26]. Evidently, this may influence clinical decisions when prescribing antihypertensive therapy for an individual with CKD. While RAS inhibitors greatly improve kidney functioning, other classes such as diuretics and CCBs require further research to determine its efficacy in renal functioning. In order to maximize positive renal outcomes for patients with CKD, clinicians should take into account the unique characteristics of each patient as well as any comorbidities.

2.4 NON-INVASIVE THERAPEUTIC IMPLICATIONS

Non-invasive therapies allow for early detection and treatment of patients with Chronic Kidney Disease. The development of early detection technology allows for an effective prognosis for patients with CKD. For example, innovative technologies such as Raman spectroscopy, have emerged as promising assets for the diagnosis of kidney diseases. Delrue et al. highlight the potential of this non-invasive technique in early CKD detection and monitoring[30].

2.4.1 Early Detection and Diagnosis Through Non-invasive Implications

Furthermore, there are risk factors associated with CKD patients and the increase in the prevalence of Chronic Kidney Disease is partly explained by this increase in the number of CKD risk factors[31]. As a result, there is a need to identify these risk factors before treating CKD patients. One such tool used to do that is retinal photography. It is a non-invasive and widely utilized diagnostic test that provides information on not only the eye but also the systemic vasculature of the patient as the kidney and eye are both highly vascularized organs that share common developmental, physiological, and pathogenic pathways. Damage of one organ often indicates damage to the other which is typically noticeable in hypertensive and diabetic conditions[32]. As such, retinal photography can be used to identify any hidden risk factors associated with Chronic Kidney Disease. Other non-invasive therapies include the use of biomarkers to identify CKD. Identifying specific exosomal biomarkers or small RNA clusters within intact human urinary exosomes holds the potential to complement traditional renal function tests, advancing CKD research toward earlier detection and thus more effective management[30].This further clarifies the importance of the use of non-invasive therapeutics in diagnosing patients with Chronic Kidney Disease effectively. Overall, non-invasive therapies demonstrate various benefits that can allow for a better quality of diagnosis and treatment for CKD patients.

2.4.2 Pharmacological Therapies

Medications such as ACE inhibitors, ARBs and Beta-blockers are an effective form of non-invasive first-line therapy for CVDs in CKD. 2,410 patients with CKD were studied by the Swedish Cardiac Insufficiency Registry where they used propensity score matching to compare the mortality rates of patients who used ACE inhibitors and patients who did not use ACE inhibitors. After 1 year, results indicated that the mortality rate was lower in patients who took ACE inhibitors[7]. Subsequently, a large sample of individuals was studied, and a control group was formed which was used to enhance the accuracy of this study. The study demonstrates the effectiveness of ACE inhibitors in reducing the rate of mortality for patients with CKD (who also have cardiovascular complications). Therefore, ACE inhibitors are considered a satisfactory non-invasive treatment option to be used for untreated hypertension in CKD and can help reduce mortality rates. Furthermore, the panel members of the Eighth Joint National Committee (JNC8) along with the guidelines published by the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend the use of both ACE inhibitors and ARBs for hypertension in patients with CKD[27]. A study done on 141,413 U.S. veterans

with CKD showed that treatment with a combination of ACE inhibitors and ARBs showed a reduction in mortality rates amongst patients (hazard ratio of 0.81)[28]. Although there are several studies that lead to the widespread usage of ACE inhibitors and ARBs for treatment, the U.S. veteran study is a specific example where this kind of therapy reduces mortality rates and has a positive effect on patients by improving the prognosis.

Additionally, beta-blockers can be used to effectively reduce blood pressure in patients with CKD. In the African American Study of Kidney Disease (AASK), it was shown that the use of Metoprolol, a beta-blocker, resulted in lower rates of ESRD and mortality in patients who have CKD29. This non-invasive therapy has several benefits for patients as it helps improve both hypertension and the renal symptoms of CKD. There are several viable pharmaceutical therapies for untreated hypertension in CKD such as ACE inhibitors, ARBs, and Beta-blockers. All three treatments have yielded positive results in several studies by reducing mortality rates and improving symptoms.

2.5 INVASIVE THERAPEUTIC IMPLICATIONS

Resistant hypertension is one of the major symptoms of CKD. Many invasive techniques, such as arteriovenous coupling, renal sympathetic denervation, baroreflex activation therapy, and renal artery stenting, are used to treat it[8]. In arteriovenous coupling, creating a peripheral arteriovenous fistula to use for hemodialysis is shown to reduce vascular resistance. An example of this would be the ROX coupler, which is placed between the distal iliac vein and artery to establish an anastomosis. However, although this resulted in a slight reduction in blood pressure in patients undergoing dialysis, it also caused significant right ventricular dilation and a decrease in right ventricular function[8,33]. Hence, more research is needed to fully understand the exact effects of arteriovenous shunting. Another possible treatment method is renal artery stenting, which involves a balloon angioplasty of renal artery stenosis. Thus resulting in a relief of hypertension. Additionally, the use of vascular stents could lead to revascularization to overcome renal artery stenosis due to hypertension in kidney disease[8]. A study conducted with a sample size of 9 patients (an average age of 71 years) showed that renal artery stenting was effective in controlling their systolic and diastolic blood pressure and stabilizing their renal functions for an average of 21 months. A contradictory study was conducted to compare the effects of renal artery stenting with medications, and the results showed that both treatment methods are equally effective. Hence, in certain situations, it may be preferred to continue with medications instead of using invasive treatments, which could have further adverse effects[34]. This could indicate that there might be other unstudied factors involved in determining the implications of invasive compared to non-invasive methods. Overall, in terms of both renal artery stenting and arteriovenous coupling, there are results from both ends of the spectrum. Although some research shows that both treatment methods can have positive outcomes, the risk that they are invasive treatments and may not work for certain people given their medical history should be considered while deciding between administering medicines or proceeding with invasive treatments. Resistant hypertension is thought to be

maintained by sympathetic nervous system hyperactivity.

One possible treatment for resistant hypertension could be to reduce this hyperactivity to better control blood pressure. Renal sympathetic denervation is a method based around ablating the renal sympathetic efferent and afferent in the walls of the renal artery by using ultrasound energy through a catheter-based system or by applying neurotoxin in the wall of neurovascular space[34]. In SPYRAL HTN-ON MED, trials resulted in a 7.0 mm drop in the mean 24-hour systolic blood pressure, which was both statistically significant and clinically meaningful after six months[35]. Another study investigated blood pressure and muscular sympathetic nerve activity in response to renal denervation in uncontrolled hypertension. The study results demonstrated a substantial drop-in muscular sympathetic nerve activity, accompanied by a reduction in systolic and diastolic blood pressures[36]. In a longer observational trial of 46 individuals with CKD, there was an improvement in eGFR in three months[35,36]. The aortic arch and carotid sinuses contain baroreceptors that regulate the sympathetic nervous system and the cardiovascular system. Electric stimulation of the carotid sinus baroreceptors is another way to reduce sympathetic tone and assist manage blood pressure in patients with resistant hypertension in CKD[37]. The mean arterial blood pressure of 23 patients with CKD and resistant hypertension treated with the Neo system, a second-generation device, was significantly decreased. However, a larger randomized controlled study is needed to demonstrate the long-term effectiveness and safety of second-generation baroreflex activation devices in patients with resistant hypertension and CKD[8]. A study of ten patients found that bilateral nephrectomy was the most effective treatment for resistant hypertension in ESRD. It successfully reduced systolic and diastolic blood pressure more than other invasive treatments because it shuts down renin-angiotensin levels by removing the affected kidney[38]. Nevertheless, further research is needed to confirm it as one of the therapies, as it is frequently neglected in favor of antihypertensive medicine.

2.6 PROGNOSIS OF DIFFERENT STAGES OF CHRONIC KIDNEY DISEASE

There are several factors that can be attributed to the prognosis of CKD. A systematic review concluded that the most common prognosis factors used were age, GFR and diabetes[39]. For instance, the participants who were older were less likely to develop ESRD but more likely to die and end up in long term care (LTC)[9]. Thus, this suggests that ESRD should not be a major concern for older patients but rather for younger patients. While the opposite would be true for death and LTC. A cohort study found that the increased number of comorbidities a patient has would increase the likelihood of death and LTC.

2.6.1 Defining Prognosis of Chronic Kidney Disease

As those with 0-2 comorbidities have a 31.1% of death and 9.0% of LTC, while those with 3-5 have a 45.3% of death and 13.5% of LTC. Suggesting that the chances of death and LTC are linked to the number of comorbidities one has and increase as the comorbidities increase. However, it was also noted that those who reach ESRD decrease with the increase of comorbidities. Those with 0-2

comorbidities have a 8.7% of developing ESRD, while those with 3-5 have a 6.3% chance[9,40]. This shows that ESRD is inversely proportional to the number of comorbidities. Furthermore, in a study using only Chinese patients, it was found that ESRD is more likely to happen than cardiovascular events and death. It also highlighted that age; history of CVD and other factors have a nonuniform link to CKD[41]. Therefore, this suggests that prognosis can also differ based on ethnicity and is not limited to age and comorbidities but requires considering other factors too.

2.6.2 Life Expectancy of Chronic Kidney Disease

Similar to other chronic disorders, CKD has various prognostic factors that determine the life expectancy and reaching ESRD. To determine life expectancy of the patient is renal dysplasia falling under congenital anomalies of the kidney and urinary tract (CAKUT) or other congenital diseases are considered. If investigation shows none, a biopsy is required to further investigate[42].To measure one's life expectancy, the root cause of CKD should be considered. A population-based registry in Alberta, Canada, provided life expectancy tables for CKD that were stratified for varying eGFR values. The participants were grouped according to their eGFRs, sex and age. In accordance, life expectancy decreases gradually as renal function deteriorates with age. Additionally, life expectancy is reduced for all levels of renal function below an eGFR of 60 ml/min/1.73 m2[42]. Therefore, studies show that eGFR and age are two main determining factors in measuring life expectancy of an individual suffering from CKD. Furthermore, with age CKD renal function rapidly deteriorates.

The authors of an alternate review investigated the impact of lower eGFR and albuminuria on cardiovascular mortality discovered that both higher albumin/ creatinine ratio (ACR ≥10 mg/g) and lower eGFR (<60 ml/min/1.73 m2) were independent predictors of mortality risk in the general population. The rapidly declining state of renal failure often worsens in proportion to proteinuria[42,43]. Reviews explain that apart from eGFR, proteinuria is also an indicator of CKD, and the increasing levels of proteinuria represents the stage of ESRD and thus will be able to determine life expectancy of the patient. The higher risk of CVD is the main cause of the further mortality associated with renal failure. The leading cause of mortality in Alberta related to CKD was found to be cardiovascular[42]. Apart from the factors mentioned above cardiovascular episodes play a major role in reducing life expectancy of an individual with CKD and are fatal. Therefore, eGFR, proteinuria, age, sex, and cardiovascular health are key determining factors of life expectancy of an individual with CKD.

2.6.3 Neutrophil Gelatinase-Associated Lipocalin (NGAL)

The elevation in NGAL level in acute kidney injury (AKI) has long been known. An elevated NGAL level can predict the progression of CKD[44] .Thus, NGAL is a protein biomarker that indicates renal damage, Acute Kidney Infection (AKI) and thus the progression of CKD can be identified, monitored and suitable treatment can be provided to prevent further damage. Patients with Stage 2 CKD had substantially greater plasma NGAL levels, creatinine levels, and eGFRs than those with Stage 1 CKD[44]. Evidently, NGAL can be used as a marker to monitor the progression of the

stages of CKD by physicians in identifying the right course of treatment and providing an accurate prognosis for the patient.

2.6.4 Factors of Poor Prognosis

There are several factors that indicate a poor prognosis with regards to the progression of CKD in patients. In a study, it was found that those with stage 1 CKD tend to be younger than those with 3-5 by almost a decade. Around 6% reported a family history of CKD, and 69% were in advanced stages (3b-5). The most common comorbidities were Type 2 Diabetes mellitus and hypertension (each around 50%), overweight, and obesity were prevalent (60%), with a slight decrease in stage 5 (43%). Type 2 Diabetes mellitus was the primary cause of CKD, followed by hypertension[45]. The most concerning factors of prognosis that accelerate CKD were patients with Type 2 Diabetes mellitus and hypertension followed by overweight and obesity. The presence of Hyperuricemia worsens CKD and lowering serum uric acid through medication has been shown to reduce cardiovascular risk and slow kidney disease progression[45]. High levels of Uric acid are another cause to increase renal damage, where reducing it can alleviate cardiovascular risk, thus, positively impacting CKD prognosis. Hyperkalemia poses a significant risk for cardiac arrhythmias, especially when compounded by other conditions like Type 2 Diabetes mellitus, high blood pressure, and heart failure. Additionally, anemia is associated with increased cardiovascular mortality in CKD patients[43,45]. High levels of potassium and anemia in prognosis show accelerated CKD-associated CVD, leading to a poor prognosis. Thereby, poor prognosis of CKD due to renal damage can also deteriorate cardiovascular health.

2.6.5 Cardiovascular Disease

Abnormalities in the cardiovascular system act as biomarkers for identification and prognosis of CKD. Disorders of the heart and kidneys known as "cardiorenal syndrome" involve circumstances in which abnormalities with one organ can lead to complications with the other[43]. Therefore, cardiovascular and renal systems comply with each other, damage the other and present as biomarkers facilitating prognosis. Due to elevated blood pressure and fluid overload, individuals with CKD frequently experience structural and functional abnormalities of the heart. Outcomes were estimated using echocardiographic measures, such as increased left ventricular wall thickness and diameter, left atrial dimension and decreased left ventricular function[43]. This explains that the same pathology exists behind the heart abnormalities and effects of CKD. Vascular calcification is more common in ESRD patients than in the general population. This highlights another cardiovascular marker for the prognosis of CKD and ESRD. The NEFRONA study, which monitored subclinical atherosclerosis through vascular ultrasound, found a higher prevalence of atherosclerosis in moderate CKD patients. As CKD stage increased, the adjusted odds ratio for subclinical atherosclerosis also rose, indicating CKD's direct involvement in its development. Atherosclerosis progression correlated with both CKD advancement and the initial presence of atheroma plaque[46]. This study indicates a strong association between CKD and subclinical atherosclerosis by highlighting a heightened prevalence of atherosclerosis in moderate CKD patients, with CKD stage directly correlating with increased odds of atherosclerosis. Thus, there is a strong

interconnection amongst cardiovascular and renal health and damage.

2.6.6 Gastrointestinal Tract & Influence of Multidisciplinary Team

Those with CKD tend to have digestive problems as well. A common manifestation of hemodynamic disturbances is digestive disorders. It was found that gastrointestinal diseases are present in 80% of those on dialysis and the number increases as the CKD progresses. This also expands on patients who are not in dialysis as symptoms of nausea and vomiting have been linked to a high GFR[47]. This suggests that digestive diseases are very common in patients with kidney disease, thus, it also requires medical attention. A study confirmed that those with CKD need a multidisciplinary approach to manage the disorder, as it disrupts the quality of life[47]. Another study that compared traditional clinical treatment with multidisciplinary team (MDT) treatment, found that the MDT approach improved the prognosis of the patients. Specifically, the MDT approach maintained the GFR and creatinine levels and improved the quality of life, while the traditional approach had lower GFR and quality of life and increased creatinine levels[40]. Thus, proving that MDT approach should be more considered in treating those with CKD than traditional treatments.

2.7 LIFESTYLE CHANGES

Several lifestyle modifications have been shown to improve prognosis and outcomes in patients with CKD. Reduced intake of dietary salt is one of the most common recommendations for such patients. It has been shown to significantly decrease blood pressure, plasma renin, serum aldosterone, and proteinuria[11]. In a randomized control trial, the reduction in blood pressure and proteinuria were shown to be more effective than dual blockade medication[48]. Further studies have shown that combined therapy of RAAS blockers and sodium restriction have an additive effect in reducing blood pressure and proteinuria[49]. Such effects are likely explained due to increased angiotensin II production resulting from high intake of dietary salt, leading to increased renal sympathetic activity[50].

Weight control is also used as a treatment strategy in CKD. Reduction of body weight through dieting and non-surgical interventions in CKD patients with high BMI has been shown to decrease proteinuria as well as maintaining stable renal function[51]. Surgical intervention for body weight reduction in morbidly obese individuals has also shown a reduction of GFR, albuminuria, and hypertension[52]. There are multiple mechanisms linking diabetes and increased BMI as both causative agents of CKD and as indicators of poor prognosis[53]. Alleviating these conditions through lifestyle changes such as dieting, and exercise can help patients with CKD better manage their condition. It should be noted that exercise alone was not shown to influence GFR, hypertension, or proteinuria, but it significantly decreased insulin resistance, suggesting it could have preventative effects for CVD typically associated with CKD[54].

Limiting alcohol intake is also recommended to patients with CKD, as heavy alcohol intake has been shown to significantly reduce eGFR and increase proteinuria[55]. Tobacco and illicit drug usage are also implicated in poor outcomes in CKD patients, with tobacco increasing all-cause mortality with no

significant impact on CKD prognosis and hard illicit drugs resulting in poorer CKD prognosis and increased all cause mortality[56,57]. As such recommendations are given to CKD patients to limit the intake of such substances to control their symptoms and to improve their quality of life. Significant evidence is present to indicate weight loss and limiting salt intake for improving CKD prognosis. Illicit drugs and alcohol intake have also been shown to negatively impact CKD prognosis, but more research is needed as there are conflicting findings in their roles in CKD.

2.8 COMPARING SURVIVAL OUTCOMES IN DIFFERENT ETHNICITIES

There is an underlying connection between ethnic backgrounds and the incidence of hypertension. Ethnicity is suggested to be a strong determinant of survivability and the risk of developing CKD through hypertension. It is critical to consider ethnic backgrounds, as they can be the basis for therapies and medications. About 25% of adult Indians living in rural areas and 33% of those living in cities suffer from hypertension[10]. The frequency of hypertension across India is significant and raises the risk of developing CKD. 25% of rural Indians with hypertension are cognizant of their condition and receive treatment for it, and for Indian patients who are living in cities, only 42% are aware and receive treatment for the condition[10]. Additionally, certain regions of India, such as South India, are at higher risk of mortality due to untreated hypertension[10,58].

A study also shows African Americans are three times more likely to require renal replacement therapy in contrast to other ethnic groups[59]. African American groups within the population who cannot afford to visit clean healthcare facilities have untreated hypertension, which can lead to CKD. Furthermore, these groups are exposed to prejudice and unjust stereotypes, which cause them to have a lack of faith in the healthcare system. African Americans have a higher rate of hypertension (43.3%)[59]. Additionally, increased albuminuria is a significant component in the advancement of CKD. Lab testing for African Americans revealed increased albumin in urine, which confirms the higher risk for hypertension and CKD and an examination was conducted by the Kidney Early Evaluation Programme (KEEP), a screening programme for people with or at risk for CKD run by the National Kidney Foundation[59]. Participants who took part in the study revealed that those without insurance had an 82% higher chance of mortality and a 72% higher chance of developing ESRD than those with private insurance[59,60]. Another indication of increased blood pressure in African Americans is the extensive use of calcitriol and the limited use of statins[60]. This explains the increased mortality of African Americans who develop CKD. Additionally, African Americans are faced with an increased risk of non-diabetic ESRD due to a gene encoding a non-muscle myosin heavy chain type II isoform A[61]. This may indicate that hypertension is a leading cause for the development of CKD rather than diabetes mellitus.

A cohort study in the United States found that Native Americans are at higher risk of mortality from CKD, however, the factors were unclear. In the US, 27.8% of Hispanic people suffer from hypertension, while Hispanics suffer from a higher frequency of hypertension, they are at a lower risk of

mortality in comparison to Caucasians[63]. The effects of pharmacologic antihypertensive treatments on individuals of Hispanic descent have not been extensively studied.

The Middle East has a lower prevalence of hypertension in contrast to the global average, with 24.36% of people having hypertension, respectively, however, there is variety among Middle Eastern countries due to variations in socioeconomic status[58]. On the other hand, the Chinese population faces the lowest rates of hypertension in comparison to African Americans and Hispanics[62]. Additionally, the Chinese population presents with exceptional lab values with improvements in GFR, albuminuria, and CKD[62]. Suggesting a strong correlation between hypertension and CKD. The course of CKD in Pacific Islanders was unknown or poorly studied[60]. Suggesting the need for further exploration and study. Subgroup evaluations of clinical trials including racial minorities have indicated that racial/ethnic differences may exist in the impact of antihypertensive medications[63,64]. Treatment plans for different ethnicities need to be further evaluated, as discrepancies among ethnicities are common.

3. Conclusion

Ethnicity emerges as a pivotal factor influencing the prevalence and outcomes of hypertension in CKD. In Indian populations, awareness and treatment disparities underscore the need for targeted interventions to address hypertension and reduce the risk of CKD development. African Americans face an elevated risk of CKD, with hypertension playing a substantial role in its progression. Disparities in awareness, treatment, and healthcare system trust contribute to the intricate relationship between ethnicity, hypertension, and CKD outcomes in this population. In the Middle East and China, unique patterns of hypertension prevalence correlate with variations in socioeconomic status. The distinct lab values among the Chinese population, including improvements in GFR and albuminuria, suggest a noteworthy correlation between hypertension and CKD. The course of CKD in Pacific Islanders remains poorly studied, indicating a critical need for further exploration and comprehensive research efforts. Similarly, Native Americans exhibit higher CKD mortality risks, emphasizing the imperative for in-depth investigations into contributing factors and tailored interventions. Among U.S. Hispanics, while hypertension prevalence is higher, the lower risk of mortality compared to Caucasians raises questions about the impact of pharmacologic antihypertensive treatments. Substantial ethnic differences in treatment responses highlight the necessity for nuanced, ethnicity-specific approaches in CKD management. The intricate relationship between cardiovascular abnormalities and CKD serves as vital biomarkers, highlighting the interplay between these systems and their implications for prognosis. Gastrointestinal disorders further emphasize the multidisciplinary approach essential in managing CKD, as hemodynamic disturbances manifest as digestive issues. Lifestyle modifications, such as sodium reduction and weight control, prove significant in improving CKD prognosis. These interventions, supported by evidence, offer tangible strategies for patients to actively manage their condition, with potential impacts on blood pressure and proteinuria. Ultimately, the intersection of ethnicity,

hypertension, and CKD outcomes emphasizes the imperative for tailored treatment evaluations and interventions. Recognizing the unique patterns and challenges within ethnic groups is crucial for optimizing CKD management strategies and mitigating health disparities.

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