**International Journal of Academic Health and Medical Research (IJAHMR)**
**ISSN: 2643-9824**
**Vol. 8 Issue 3 March - 2024, Pages: 44-62**

# Correlation between Urinary Angiotensinogen (AGT) and Albuminuria in Chronic Kidney Disease (CKD)

**Syed Muhammad Ali [1], Professor Liu Zhen[2], Doctor Sadia Hassan[3], Nida Aslam[4]**

1Master Student of Xinjiang Medical University, (Department of Nephrology)
Xinyi Road, Urumqi, Xinjiang, China
+86 17590825106
drsyedmuhammadali912@gmail.com
2Correspondence author: Professor Liu Zhen
Department of Nephrology, First affiliated hospital of Xinjiang Medical University
Supervisor
+86 15099691860
xydlz2008@163.com
3Department of General Surgery, DHQ hospital Hunza
+92 3438146461
sadia_hassan0987@yahoo.com
4Master Student of Xinjiang Medical University , (Department of Cardiology)
+8617590820649
drnida540@gmail.com

***Abstract:*** *Chronic kidney disease (CKD) is a global health concern associated with significant morbidity and mortality. Albuminuria, a hallmark of kidney damage, is a strong predictor of CKD progression and adverse outcomes. Recent research has focused on understanding the correlation between urinary angiotensinogen (AGT) levels, a component of the renin-angiotensin system (RAS), and albuminuria in CKD patients. This review article synthesizes evidence from various studies exploring this correlation and elucidates its mechanistic insights and clinical implications. Clinical studies consistently demonstrate a positive correlation between urinary AGT levels and albuminuria in CKD patients. Elevated urinary AGT levels are associated with increased albuminuria, independent of traditional risk factors, suggesting a potential role for AGT in the pathogenesis of kidney damage and proteinuria in CKD. Mechanistic insights suggest that increased intrarenal RAS activity may lead to enhanced AGT production and secretion, contributing to glomerular hypertension, inflammation, and fibrosis, ultimately promoting albuminuria and CKD progression. The clinical implications of this correlation are profound. Elevated urinary AGT levels may serve as a non-invasive biomarker for assessing intrarenal RAS activity and predicting CKD progression and adverse outcomes. Furthermore, interventions targeting the RAS pathway, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), may help reduce urinary AGT levels and mitigate albuminuria, offering promising therapeutic opportunities for improving patient outcomes in CKD. In conclusion, the correlation between urinary AGT and albuminuria in CKD represents a complex interplay between renal physiology, RAS activation, and kidney damage. By elucidating this correlation, we gain valuable insights into the pathogenesis of CKD and identify urinary AGT as a potential biomarker and therapeutic target for personalized CKD management. Further research is warranted to validate these findings, explore the clinical utility of urinary AGT measurement, and develop targeted interventions aimed at mitigating albuminuria and slowing CKD progression. Through continued investigation, we can strive to improve outcomes and quality of life for patients living with CKD.*

## 1 Introduction

Chronic kidney disease (CKD) represents a significant global health burden with increasing prevalence and substantial morbidity and mortality rates worldwide [1]. Characterized by a progressive decline in renal function, CKD poses a considerable challenge to healthcare systems, underscoring the urgent need for improved understanding of its pathophysiology and development of effective therapeutic interventions[2]. Among the various markers of kidney damage, albuminuria stands out as a critical prognostic indicator strongly associated with CKD progression and adverse outcomes [3].

The renin-angiotensin system (RAS) has long been recognized for its pivotal role in blood pressure regulation and electrolyte balance [4]. However, emerging evidence suggests that dysregulation of the RAS contributes significantly to the pathogenesis of CKD, particularly through its effects on intrarenal hemodynamics, inflammation, and fibrosis [5]. Within this context, urinary angiotensinogen (AGT), a key component of the RAS, has garnered attention as a potential biomarker reflecting intrarenal RAS activity and contributing to kidney damage in CKD [6].

The aim of this review article is to comprehensively explore the correlation between urinary AGT levels and albuminuria in CKD [7]. We will examine evidence from clinical studies and mechanistic insights elucidating the relationship between urinary AGT and albuminuria, with a focus on their implications for CKD pathophysiology, risk stratification, and therapeutic targeting [8].

Firstly, we will provide an overview of the pathophysiology of CKD, emphasizing the role of albuminuria as a marker of glomerular dysfunction and tubulointerstitial injury [9]. We will then delve into the mechanisms underlying the dysregulation of the RAS in CKD and its contribution to renal damage, highlighting the potential involvement of urinary AGT in this process [10].

Subsequently, we will review clinical studies investigating the correlation between urinary AGT levels and albuminuria in CKD patients [11]. We will examine the evidence supporting the association between elevated urinary AGT levels and increased albuminuria, independent of traditional risk factors, and discuss the implications for risk prediction and patient management [12].

Furthermore, we will explore the mechanistic insights into the relationship between urinary AGT and albuminuria, including the role of intrarenal RAS activation, glomerular hypertension, podocyte injury, and renal inflammation [13]. Understanding these mechanisms will provide valuable insights into the pathogenesis of albuminuria and identify potential therapeutic targets for mitigating kidney damage in CKD [14].

1.2 Chronic Kidney Disease:

1.2.1 Definition

CKD is defined as abnormalities of kidney structure or function, present for >3 months [15]. Table 1.1 summarizes the criteria for CKD, either of which should be present for >3 months.

Table 1.1 Criteria for CKD (Either of the following should be present for >3 months)

| |
|---|
| Albuminuria (ACR ≥30 mg/g [≥3 mg/mmol]; AER ≥30 mg/24 h) |
| abnormalities in urinary sediment |
| Electrolyte and other abnormalities due to tubular disorders |
| Abnormalities detected by histology |
| Structural abnormalities detected by imaging |
| Kidney transplant history |
| GFR of <60 mL/min/1.73 m2 |

GFR glomerular filtration rate, AER albumin excretion rate, and ACR albumin-to-creatinine ratio (Reproduced with permission from Elsevier) [15])

**1.2.2 Staging**

According to the KDIGO 2012 Clinical Practice Guideline, albuminuria category (CGA), GFR category, and etiology of CKD might all be used to categorize patients [15].
Assign albuminuria categories according to Table 1.3 and GFR categories according to Table 1.2.
As an alternative, urine reagent strip results or protein might be used in their place (Table 1.4).

Table 1.2 GFR categories in CKD

| GFR category | GFR (mL/ min/1.73 m2 ) | Terms |
|---|---|---|
| G1 | ≥90 | Normal/high |
| G2 | 60–89 | Mildly decreased (relative to young adult level) |
| G3a | 45–59 | Mildly to moderately decreased |
| G3b | 30–44 | Moderately to severely decreased |
| G4 | 15–29 | Severely decreased |
| G5 | <15 | Kidney failure |
| | | |

GFR glomerular filtration rate, CKD chronic kidney disease[15]

Table 1.3 Albuminuria categories in CKDAER albumin excretion rate, ACR albumin-to-creatinine ratio[15].

| Category | AER (mg/24 h) | ACR | | Terms |
|---|---|---|---|---|
| | | (mg/mmol) | (mg/g) | |
| A1 | <30 | <3 | <30 | Normal to mildly increased |
| A2 | 30–300 | 3–30 | 30–300 | Moderately increased (relative to young adult level) |
| A3 | >300 | >30 | >300 | Severely increased (including nephrotic syndrome) |

Table 1.4 Categories of proteinuria in CKD

| Category | PER (mg/24 h) | PCR | | Protein reagent strip |
|---|---|---|---|---|
| | | (mg/ mmol) | (mg/g) | |
| A1 | <150 | <15 | <150 | Negative to trace |
| A2 | 150–500 | 15–50 | 150– 500 | Trace to positive |
| A3 | >500 | >50 | >500 | Positive or greater |

CKD chronic kidney disease, PER protein excretion rate, PCR protein-to-creatinine ratio[15].

### 1.2.3 Causes and Risk Factors:

In many developing nations as well as all industrialized nations, diabetes and hypertension are the main causes of chronic kidney disease (CKD). However, countries in Asia and Sub-Saharan Africa have higher rates of glomerulonephritis and unclear reasons. The risk factors for CKD are listed in Table 1.5 [16].
Currently, glomerular disease, diabetic kidney disease, and hypertension are the main causes of chronic kidney disease (CKD) in China. One of the most prevalent glomerular disorders is IgA nephropathy [17]. The main causes of these variations between nations include the change in the burden. In contrast, due to inadequate sanitation, a lack of clean water, and large concentrations of disease-transmitting vectors, infectious diseases are still common in less developed nations [19]. Moreover, the prevalence of CKD in developing nations is increased by pesticide usage, environmental pollution, misuse of analgesics, herbal remedies, and unapproved food additives [20]. Globalization and rapid urbanization have sped up the transition and caused an overlap in the burden of disease between South Asian and Latin American nations, with rising rates of lifestyle-related diseases like diabetes, hypertension, and obesity and persistently high rates of infectious diseases [21].

Table 1.5 Risk factors for CKD [15]

| | |
|---|---|
| Clinical factors | • Diabetes<br>• Hypertension<br>• Autoimmune disease<br>• Systemic infection<br>• Urinary tract infection<br>• Urinary stones<br>• Lower urinary tract obstruction<br>• Urolithiasis<br>• Family history of CKD<br>• Recovery from acute kidney injury<br>• Kidney mass reduction<br>• Exposure to certain drugs<br>Low birth weight |
| Sociodemographic factors | • Older age<br>• Race<br>• Exposure to certain chemical and environmental conditions<br>Low income/education |

**1.2.4 Prevalence:**

Globally, CKD affects about 10% of the population, and millions of people die each year from a lack of access to cheap treatment [16]. Estimated GFR (eGFR) <60 mL/min/1.73 m2 and albuminuria have adjusted prevalence rates of 1.7% and 9.4% in China, respectively. Since CKD is often present in 10.8% of the population, 119.5 million people are thought to have the disease in China [22].

People with CKD might be of any race. People with a high risk of chronic kidney disease (CKD) include African Americans, American Indians, Hispanics, and people of South Asian descent (people from Bangladesh, India, Sri Lanka. In comparison to other regions of China, the prevalence of chronic kidney disease (CKD) is highest in the northern (16.9%) and southwest (18.3%) regions. The degree of local economic growth is strongly correlated with the prevalence of albuminuria in China's rural districts [23]. Even though CKD can strike anyone at any age, it is more prevalent in women and as people age. The fact that eGFR decreases with aging has been recognized for decades. The mean age of 1185 patients in China and 9614 patients in India who present with stage 3 CKD is 63.6 years and 51.0 years, respectively [20]. According to estimates, among people 65 to 74 years old worldwide, one in five men and one in four women have CKD [20]. In Chinese females, the prevalence of chronic kidney disease (CKD) rises with age: from 7.4% in the 18–39 age group to 18.0% in the 60–69 age group and 24.2% in the 70+ age group [24]. Despite variations in absolute incidence between nations, the relative increases in the prevalence of chronic kidney disease (CKD) with age are similarly noticeable in the populations of the USA, Canada, and Europe [20]. Furthermore, it is predicted that China, whose old population is expanding, will see a disproportionately high number of cases of chronic kidney disease (CKD). This effect will be amplified even more if the trends of rising diabetes and hypertension prevalence continue, mortality from stroke and other cardiovascular illnesses decline, and treatment accessibility improves [20].

Renal replacement treatment becomes critical to patients' survival when chronic kidney disease (CKD) ultimately results in kidney failure [20]. But the state of treatment as it exists now is terrible. Globally, more than two million people receive dialysis or transplantation; yet, this may only account for 10% of patients who truly need therapy to survive [20]. Five nations account for only 12% of the world's population: the USA, Japan, Germany, Brazil, and Italy are home to the majority of these people undergoing treatment for renal failure [25]. Over 80% of renal failure patients undergoing treatment come from wealthy nations, with the

other 20% receiving care in about 100 poor nations, home to more than 50% of the world's population [25]. Point prevalence of kidney failure patients receiving maintenance dialysis (hemodialysis and peritoneal dialysis) was estimated to be 71.9 per million in mainland China in 2008; the prevalence rate increased by 52.9% annually, reaching 2584, 1106, and 1870 per million in Taiwan, Hong Kong, and the USA, respectively, in 2010 [20]. By the end of 2012, around 90% of renal failure patients receiving dialysis in China underwent hemodialysis, which translates to 270,000 patients receiving hemodialysis as opposed to just 30,000 receiving peritoneal dialysis [16,20].

In 2013, CKD was the cause of 956,000 deaths. In the list of causes of all deaths worldwide, chronic kidney disease (CKD) jumped from 27th in 1990 to 18th in 2010, according to the 2010 Global Burden of Disease Study. This increase in ranking is only surpassed by that of HIV infection and acquired immune deficiency syndrome (AIDS) [20]. The total increase in years lost to early death from CKD is 82%; this is the second highest rate after diabetes mellitus (93%), HIV infection and AIDS (396%), and other conditions. In contrast to the 236.3 per 1000 patient-years recorded in the USA in 2009, Beijing, China's 2010 raw annual death rate for patients on maintenance hemodialysis was 76.8 per 1000 patient-years. In China, cardiovascular disease (31.0%), stroke (20.3%), and infection (19.9%) are the top three causes of death for hemodialysis patients [16,20].

Even with the high incidence, it is not advised to screen for CKD in those who do not have risk factors or symptoms. Present guidelines recommend screening during routine primary health visits for individuals with renal tract structural diseases, hypertension, cardiovascular disease, diabetes, autoimmune diseases that may affect the kidneys, family history of kidney disease, marked obesity, and age greater than 60 years [26]. Although it is cost-effective to screen for CKD in diabetics, it is not yet known if screening for CKD in the general public is also cost-effective [27].

### 1.2.5 Diagnosis:

The history, examination, GFR, albuminuria, and progression are all evaluated in the diagnosis of chronic kidney disease (CKD) [28].

### 1.2.1 Evaluation of History And Examination:

To ascertain how renal disease is progressing, historical measures and medical history must be reviewed. To identify the causes of CKD and establish a pathological diagnosis, review medical history, social and environmental factors, medications, physical examination, lab results, and imaging measurements [29].

### 1.7.2 Evaluation of GFR:

For those with renal impairment or a GFR of less than 60 mL/min/1.73 m2, the serum creatinine (SCr)-based GFR-estimating equation is advised for preliminary evaluation. When more precise GFR measurement would influence treatment choices, exogenous filtration markers must be used to measure GFR. Table 1.6 [28] provides an overview of the benefits and drawbacks of filtering markers and clearance techniques for clearance measurements.

Table 1.6 Strengths and limitations of GFR measurement methods and markers

| Approach | Strengths | Limitations |
|---|---|---|
| *Methods* | | |
| bladder catheter and ongoing intravenous marker infusion | • Gold standard method | • Invasive |
| Spontaneous bladder emptying | • Patient comfort<br>•Less invasive | • Possibility of incomplete bladder emptying<br>• Low flow rates in individuals with low GFR levels |
| Bolus administration of marker | • Shorter duration | • Rapidly declining plasma levels at high GFR<br>• levels Longer equilibration time in extracellular volume expansion |
| 24-h urine collection | | • Cumbersome<br>• Prone to error |
| Plasma clearance | • Urine collection is not necessary, and there is a chance for greater accuracy. | • Overestimation of GFR in the growth of<br>• extracellular volume inaccurate values while using one's usual approach, especially when the GFR is<br>• lower<br>At low GFR levels, a longer plasma sampling period is necessary. |
| Nuclear imaging | • No urine collection or repeated blood sampling required | • Less accurate |
| Markers | | |
| Inulin | • Gold standard<br>• No side effects | • Expensive<br>• Difficult to dissolve and maintain in solution<br>• Short supply |
| Creatinine | • Endogenous marker, no need for administration<br>• Assay available in all clinical laboratories | • Section can vary among and within individuals |
| Iothalamate | • Inexpensive<br>• Long half life | • Probable tubular secretion<br>• Requirement for storage, administration, and disposal of radioactive substances when using $^{125}I$ as tracer<br>• Requirement for expensive assay when using nonradioactive iothalamate<br>• Cannot be used in patients with allergies to iodine |
| Iohexol | • Nonradioactive<br>• Inexpensive<br>• Sensitive assay allows for low dose | • • Possible tubular reabsorption or protein binding<br>• Requirement for expensive assay when using low<br>• doses<br>Cannot be used in patients with allergies to iodine<br>Nephrotoxicity and risk of allergic reactions at high doses |
| EDTA | • W idely available in Europe | • • Probable tubular reabsorption<br>Requirement for storage, administration, and disposal of radioactive substances when using $^{51}Cr$ as tracer |

| | | |
|---|---|---|
| DTPA | • W idely available in the USA<br>• New, sensitive, and easy-to-use assay for gadolinium | • Requirement for storage, administration, and disposal of radioactive substances when using $^{99m}$Tc<br>• as tracer<br>• Requires standardization for $^{99m}$Tc<br>• Dissociation and protein binding of $^{99m}$Tc<br>Concern for NSF when using gadolinium as tracer |

Nephrogenic systemic fibrosis (NSF), EDTA (ethylenediaminetetraacetic acid), DPTA (diethylenetriamine penta acetic acid), and GFR (glomerular filtration rate) [28]

### 1.7.3 Evaluation of Albuminuria

Urinary albumin-to-creatinine ratio (ACR), urinary protein-tocreatinine ratio, reagent strip urinalysis for total protein with automated reading, and reagent strip urinalysis for total protein with manual reading are recommended using an early morning urine sample for initial proteinuria testing (in descending order) [30]. Repeat testing is necessary to confirm albuminuria due to the considerable biological variation and other physiological and pathological reasons that affect albuminuria accuracy (Table 1.7). Measuring the excretion rate of albumin or total protein in a timed urine sample yields more precise results. Fresh samples can be used for analysis of urinary albumin or protein, which can then be stored at 4 °C for a week or at −70 °C for extended periods of time. However, detectable albumin loss may occur from freezing at -20 °C. Before being analyzed, samples that have been stored should be mixed well and allowed to reach room temperature. Assays for particular urine proteins, like α1-microglobulin and monoclonal heavy or light chains, also referred to as "Bence Jones" proteins, can identify non-albumin proteinuria [15].

Table 1.7 Factors affecting urinary albumin-to creatinine ratio [15].

| Factors | Examples of effect |
|---|---|
| *Preanalytical factors* | |
| Transient elevation in albuminuria | • Menstrual blood contamination<br>• Symptomatic urinary tract infection<br>• Exercise<br>• Upright posture (orthostatic proteinuria)<br>• Other conditions that increase vascular permeability (e.g., septicemia) |
| Intraindividual variability | • Intrinsic biological variability<br>• Genetic variability |
| Preanalytical storage conditions | Albumin degradation prior to analysis |
| Nonrenal causes of variability in creatinine excretion | • Age (lower in children and older people)<br>• Race<br>• Muscle mass<br>• Gender (lower in women) |
| Change in creatinine excretion | Non-steady state creatinine concentration (acute kidney injury) |
| *Analytical factors* | |
| Antigen excess (prozone) effect | Samples with very high albumin concentrations may be falsely reported as low or normal using some assays |

### 1.7.5 Evaluation of Progression

In people with CKD, GFR and albuminuria should be evaluated at least once a year. Additionally, monitor GFR and albuminuria more frequently in people who are more likely to advance and/or when doing so will influence treatment choices [31]. GFRs, however, frequently vary somewhat and are not always a sign of advancement. A dip in GFR category, a drop in GFR of at least 25% from baseline, and a prolonged decrease in GFR of at least 5 mL/min/1.73 m2 per year are all considered indicators of accelerated CKD progression [31]. To find out how quickly CKD is progressing, take the following actions: Perform three GFR estimations over a minimum of ninety days; if a person's GFR is found to be reduced, review their current treatment plan, repeat the GFR estimation within two weeks to rule out causes of sudden decline in GFR (such as AKI or starting renin-angiotensin system [RAS] antagonist therapy), and think about referring them to a specialist [31]. Patients with chronic kidney disease (CKD) who have one of the diseases that accelerates the illness's course are more likely to develop end-stage kidney disease [32].

### 1.2.6 Management

The first steps in managing chronic kidney disease (CKD) are educating patients and delivering information specific to the condition's etiology, severity, related consequences, and risk of progression [28]. Motivate patients to quit smoking, lose weight, and engage in physical activity. Provide dietary guidance according to the severity of CKD regarding salt, potassium, calories, and phosphate (Table 1.8).

Table 1.8 Dietary and lifestyle modification for patients with CKD

| | |
|---|---|
| Salt intake | • • Unless otherwise directed, reduce salt consumption to less than 90 mmol (or 2 g) of sodium per day (or 5 g of sodium chloride) for adults.<br>• Limit sodium consumption in children with chronic kidney disease (CKD) who meet the age-based recommended daily intake guidelines and have hypertension (systolic and/or diastolic blood pressure >95th percentile) or prehypertension (systolic and/or diastolic blood pressure >90th percentile and <95th percentile).<br>• Give kids with CKD and polyuria free access to water and salt to prevent chronic intravascular depletion and to support |
| Protein intake | • For persons with or without diabetes and GFR <30 mL/min/1.73 m2 (G4–G5), reduce protein consumption to 0.8 g/kg/day.<br>• Adults with CKD who are at risk of progression should not consume large amounts of protein (>1.3 g/kg/day). |
| Hyperuricemia | Although hyperuricemia and the occurrence of chronic kidney disease (CKD) are related, there is inadequate data to confirm or refute the use of medicines to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia as a means of delaying the onset of CKD. |
| Lifestyle | • Encourage people who have chronic kidney disease (CKD) to exercise for at least thirty minutes five times a week, according to their cardiovascular health and tolerance.Reach a healthy weight (BMI 20–25, depending on the demographics of the nation).<br>• Give up smoking |
| Additional dietary advice | In the framework of an educational program catered to the severity of CKD and the necessity of adjusting salt, phosphate, potassium, and protein consumption when necessary, offer professional nutritional guidance and information. |

Aim to keep blood pressure in the range of 130 mmHg (goal range), 120–129 mmHg (target range), 80 mmHg, 139 mmHg, or 90 mmHg for people with CKD. In order to maintain individuals with CKD under the following conditions [28]: (1) diabetes and an ACR ≥3 mg/mmol (ACR category A2 or A3) and (2) hypertension and an ACR ≥30 mg/mmol (ACR category A3) or ACR ≥70 mg/mmol (regardless of hypertension or cardiovascular disease), RAS antagonist should be administered to those with diabetes. There is,

however, little data to support these requirements in those older than 70. RAS antagonist combinations should not be given to patients with CKD [20]. Before beginning RAS antagonist medication, serum potassium concentrations and estimated GFR should be evaluated. Tests should be repeated every dose increase and one to two weeks after beginning RAS antagonist medication. Patients whose pretreatment serum potassium content is greater than 5.0 mmol/L should not receive RAS antagonists on a regular basis. When hyperkalemia makes the use of RAS antagonists inappropriate, the reasons contributing to the hyperkalemia should be identified and treated before rechecking the potassium level in the serum. If the serum potassium level rises to more than 6.0 mmol/L, stop using RAS antagonist therapy and stop taking any additional medications that are known to cause hyperkalemia [20]. If the GFR decrease from pretreatment baseline is less than 25% or the SCr rise from baseline is less than 30%, do not adjust the dose after starting RAS antagonists or increasing their dosage. Repeat the test in 1-2 weeks if, upon initiating RAS antagonist therapy or increasing the dose of RAS antagonists, there is a <25% decrease in eGFR or a 30% increase in SCr from baseline. If there is a decrease of less than 25% or 30% in eGFR or SCr, respectively, do not adjust the dosage of RAS antagonists. Look into additional factors that could be contributing to the decline in renal function, such as volume depletion or concurrent medication, if the drop in eGFR or SCr is ≥25% or ≥30%, respectively. Stop the RAS antagonist therapy or lower to the prior acceptable dose and add an alternative antihypertensive medicine, if necessary, if no additional causes of the decline in renal function are found [20]. The goal hemoglobin A1c (HbA1c) level for diabetic kidney disease (CKD) patients is roughly 7.0% (53 mmol/mol) to stop or slow the progression of the disease. Patients who are at risk of hypoglycemia should not use this HbA1c target. When a person has a low life expectancy, comorbidities, or is hypoglycemic, their target HbA1c level should be raised above 7.0%. Glycemic control for diabetic patients with chronic kidney disease (CKD) should be combined with multifactorial intervention measures, such as blood pressure management and cardiovascular risk assessment. When clinically warranted RAS antagonists, antiplatelet therapy, and statin usage are recommended [16].

Calculate the present rate of decline in GFR when assessing the course of CKD and consider this when developing intervention plans, especially if it indicates that patients may need renal replacement treatment for the rest of their lives [20].

Typically, patients exhibiting characteristics listed in Table 1.9 should be sent to a professional for evaluation. Inform patients with stage 5 CKD about available renal replacement therapy treatment choices. Dialysis, specifically hemodialysis and peritoneal dialysis, is an option for treatment. The timing of the start of renal replacement treatment is displayed in Table 1.10.

Table 1.9 When to refer [15]

| |
|---|
| GFR <30 mL/min/1.73 $m^2$ (GFR category G4 or G5), with or without diabetes |
| ACR ≥70 mg/mmol, unless known to be due to diabetes and already appropriately treated |
| ACR ≥30 mg/mmol (ACR category A3), together with hematuria |
| Sustained decrease in GFR ≥25%, and a change in GFR category or sustained decrease in GFR ≥15 mL/ min/1.73 m2 within 12 months |
| Hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses |
| Known or suspected rare or genetic causes of CKD |
| Suspected renal artery stenosis |

**Table 1.10** Timing for the initiation of renal replacement [15]

| | |
|---|---|
| Initiation of dialysis | • Symptoms or signs attributable to kidney failure (e.g., serositis, acid-base or electrolyte abnormalities, pruritus)<br>• Inability to control volume status or blood pressure<br>• Cognitive impairment or progressive deterioration in nutritional status refractory to dietary intervention<br>• T his often but not invariably occurs in the GFR range of 5–10 mL/min/1.73 $m^2$ |
| Initiation of transplantation with living donor | GFR is <20 mL/min/1.73 $m^2$ with evidence of progressive and irreversible CKD over the preceding 6–12 months |

**2 Albuminuria:**

pathogenic state in which the urine contains unusually high levels of the protein albumin. One kind of proteinuria is this [33]. Urine from healthy individuals contains only trace levels of albumin, a major plasma protein that is normally present in the blood; urine from renal disease patients has greater amounts of albumin[34]. Clinical nomenclature is shifting to emphasize albuminuria over proteinuria for various reasons [35].

Urinary protein measurement was first used in nephrology more than 200 years ago [36]. German doctor Hermann Senator carried out significant research in which he explained that the presence of proteins in the urine of apparently healthy people was indicative of chronic kidney disease (CKD) and offered treatment recommendations [35]. It was soon demonstrated that proteinuria in these people was linked to unfavorable health consequences [37].

Numerous extensive observational studies conducted in a variety of populations have since validated Hermann Senator's groundbreaking work [35]. These days, it is commonly recognized that one of the first indications of asymptomatic kidney impairment is the loss of even minute amounts of albumin in the urine. These trace levels of albumin provide valuable insight into future kidney developments [35]: a rise in urine albumin concentration is associated with a marked increase in the risk of progressive loss of renal function [38]. The question of whether we can also modify this risk is more significant than simply determining whether kidney risk exists. Although albuminuria was once thought to be only a sign of kidney impairment, more recent research has revealed that it is also a factor in the development of kidney disease. This indicates that albuminuria can be targeted and lowered to result in renoprotection, making it a modifiable risk factor. Nephrologists are divided on this paradigm change, and the discussion continues [35].

**2.1 Mechanism:**

Multiple routes ultimately lead to tubulointerstitial injury as the mechanism by which increasing albuminuria causes or accelerates kidney damage [39]. Numerous investigations have demonstrated that modifications in the tubulointerstitial tissue compartment are a salient characteristic of the pathophysiologic mechanisms behind the advancement of kidney disease. First, the severity of glomerular lesions predicts the clinical kidney outcome of end-stage renal disease (ESRD), which requires dialysis or a renal transplant. However, the severity of tubulointerstitial damage (tubular atrophy, interstitial inflammation, and interstitial fibrosis) predicts the clinical kidney outcome more strongly [39]. Second, an increasing amount of glomerular albumin leakage has been shown in both in vitro and in vivo investigations to trigger profibrotic and proinflammatory signals, which in turn cause tubulointerstitial damage. The tiny quantity of albumin that the glomeruli filter is effectively reabsorbed in the tubuli at normal physiological conditions [40]. Nonetheless, the tubuli are subjected to elevated albumin concentrations when there is an increase in glomerular albumin leakage. An excess of albumin that is exposed to the tubuli has a toxic effect and an inflammatory reaction [41]. Albumin tubular uptake appears to be a major moderator of these harmful effects. Megalin and cubulin receptors on the brush edge of the proximal tubule reabsorb albumin [42]. Albumin separates from the cubulin-megalin complex after

internalization in endosomal vesicles and is then delivered to dendritic cells, where it is converted into antigenic peptides that trigger an inflammatory response [43]. Indeed, in vitro research demonstrated that increased albumin absorption has lethal effects on both proximal and distal tubular cells by triggering a variety of intracellular signaling pathways, such as protein kinase C, NF-κB, and extracellular-regulated kinase [44]. In turn, the release of inflammatory (monocyte chemotactic protein-1) and vasoactive (reactive oxygen species) substances is brought on by the activation of these signaling pathways [45,46]. fibrotic (TGF-β and collagens) compounds [47], which eventually result in irreparable kidney injury by generating tubulointerstittial dysfunction, fibrosis, and interstitial damage. Hence, albuminuria has a direct pathogenic effect that causes the loss of renal function in addition to serving as a measure of the degree of glomerular damage. It should be mentioned that in addition to albumin, other compounds that are attached to it (such free fatty acids), other proteins (including those that make up the complement system), and glycated albumin can also worsen tubular damage by inducing profibrosis and inflammation [48].

### 2.2 Sign And symptoms:

Although albuminuria has no symptoms, white foam may develop in the urine. If there are substantial albumin losses that result in low serum protein levels, swelling of the hands, tummy, ankles, or face may happen [49].

### 2.3 Causes:

Large molecules are typically not filtered by the kidneys into the urine, therefore albuminuria may be a sign of renal injury or an overabundance of salt. Patients with long-term diabetes, particularly type 1 diabetes, may also experience it. Chronic kidney disease (CKD) has been classed according to new international standards (KDIGO 2012) based on the cause, albuminuria type (A1, A2, A3), and glomerular filtration rate category [50].

Causes of albuminuria can be discriminated between by the amount of protein excreted.

- The excretion of 3.0 to 3.5 grams per 24 hours is the typical outcome of the nephrotic syndrome [51].
- Albuminuria is considerably less common in nephritic syndrome [51].
- A precursor to diabetic nephropathy may be microalbuminuria (between 30 and 300 mg/24h, mg/L of urine, or µg/mg of creatinine). Since there is no such thing as a "big albumin" (macroalbuminuria) or a "small albumin" (microalbuminuria), the term albuminuria is now preferred in the field of nephrology.[1] A2 indicates moderately elevated urinary albumin/creatinine ratio (30–300 mg/g or 3–30 mg/mmol, previously known as microalbuminuria); A3 indicates severely increased urinary albumin/creatinine ratio (>300 mg/g or > 30 mg/mmol) [50]. A1 represents normal to mildly increased urinary albumin/creatinine ratio (<30 mg/g or < 3 mg/mmol).

### 2.4 Diagnosis:

Guidelines suggest utilizing the albumin-to-creatinine ratio (ACR) or the protein-to-creatinine ratio (PCR) for the first albuminuria test in order to diagnose chronic kidney disease (CKD) [52]. Some guidelines suggest using semiquantitative techniques (urine dipsticks) that can assess albuminuria or represent the result as ACR when ACR and PCR are not available, followed by a quantitative laboratory test to confirm the positive dipstick results [53]. Urine dipstick use, however, remains controversial and is not recommended by some standards [54]. A practical point-of-care test that might be utilized in places without access to other laboratory analysis is urine dipstick testing. Its sensitivity for detecting albuminuria, however, is a little alarming because manual readings may have operator-dependent errors [56] and false negatives have been reported to occur when ketones, glucose, blood, pigments, vitamins, or medications are present [55, 56]. The effectiveness of urine dipsticks for diagnosing chronic kidney disease (CKD) in the context of identifying albuminuria has been evaluated in two prior systematic reviews. When one of them conducted a literature search in December 2013, it found nine studies that evaluated the accuracy of urine dipsticks, reporting a pooled sensitivity and specificity of 0.76 and 0.93, respectively, for ACR >30 mg/g. This study also evaluated the diagnostic accuracy of point-of-care (POC) tests (either semiquantitative or quantitative) in individuals at risk of chronic kidney disease (CKD) [57]. The other study is a Cochrane systematic review that looked for further studies that evaluated the use of urine dipstick testing for diagnosing chronic kidney disease (CKD) in September 2014 but was unable to find any [58]. We set out to conduct a systematic review on the diagnostic accuracy of urine dipstick testing for albuminuria detection, given the necessity for updated systematizations of the evidence to perform effective decision-making [58].

### 2.5 Treatment:

Reducing urine albumin excretion and delaying the progression of kidney damage are the two main goals of the therapy of albuminuria, especially when it is combined with chronic kidney disease (CKD) [59]. The following are some essential elements of the treatment plan:

### 2.5.1 Blood pressure Control:

Maintaining strict blood pressure control is crucial for controlling the progression of CKD and albuminuria [60]. Due to their demonstrated effectiveness in lowering albuminuria without raising blood pressure, medications including angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors are frequently used as first-line treatments [61].

### 2.5.2 Glucose Control:

Improving glycemic management is essential for treating albuminuria in patients with diabetes. Strict blood sugar management can slow the development of kidney damage linked to diabetes [62].

### 2.5.3 Life style Modification:

As of right now, there is little proof that dietary changes that reduce red meat intake can enhance kidney function, even if there is some evidence that these changes can assist lower albuminuria levels [63]. Among alternative strategies, the most often used treatment for albuminuria is blood pressure control, particularly when combined with renin-angiotensin system inhibitors [64]. It is advised to alter one's lifestyle by avoiding smoking, maintaining a healthy weight, cutting back on salt and saturated fats, and adopting a nutritious diet [65]. These lifestyle changes can lessen the progression of albuminuria by enhancing blood pressure regulation and general cardiovascular health [66].

Dietary Protein Restrictions:

Reducing the amount of protein in the diet may help control albuminuria and reduce the progression of CKD in some circumstances. To guarantee that the patient's nutritional demands are satisfied, this should be carried out under the supervision of a medical expert [67].

Medication Adjustment:

If some drugs are aggravating albuminuria or impairing renal function, they might need to be changed or stopped [68]. For instance, individuals with CKD may need to use some antibiotics with caution or avoid nonsteroidal anti-inflammatory medications (NSAIDs) altogether [69].

### 2.5.4 Regular Monitoring:

To evaluate the effectiveness of treatment and the course of the disease, regular monitoring of albuminuria levels and kidney function is crucial [70]. This could include blood pressure monitoring, serum creatinine levels, estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR) assessments, and other pertinent assays [71].

## 3 Angiotensinogen:

The renin-angiotensin system (RAS), a hormonal mechanism that controls blood pressure and fluid balance, includes angiotensinogen [72]. It is a non-inhibitory member of the serpin family of proteinase inhibitors, also referred to as the renin substrate (MEROPS inhibitor family I4, clan ID, MEROPS identifier I04.953). In reaction to a drop in blood pressure, renin catalytically cleaves angiotensinogen to generate angiotensin I. Angiotensin II, the physiologically active peptide that regulates the volume and mineral balance of bodily fluids, is created when the angiotensin converting enzyme (ACE) eliminates a dipeptide [73]. Angiotensin III, which promotes the release of aldosterone, and angiotensin IV can be produced by further processing angiotensin I and angiotensin II [74]. ACE2 cleaves angiotensin 1-9 from angiotensin-1, and ACE can then process the remaining angiotensin to create angiotensin 1-7, angiotensin 1-5, and angiotensin 1-4 [75].

### Urinary Angiotensinogen:

Blood pressure and fluid balance in the body are regulated by a protein known as urine angiotensinogen [76]. Angiotensinogen is the precursor protein that is converted into angiotensin I by the kidney-produced enzyme renin. Angiotensin I is further converted to angiotensin II by the angiotensin-converting enzyme (ACE) [76]. By constricting blood vessels, strong vasoconstrictor angiotensin II increases blood pressure and triggers the hormone aldosterone, which promotes the kidneys to retain salt and water [76]. Angiotensinogen can be used as a marker for kidney function and is linked to illnesses such kidney disease, hypertension, and preeclampsia, which is a pregnancy complication marked by organ damage and elevated blood pressure [76]. Urine angiotensinogen measurements can be used as a biomarker to evaluate renal function and can yield important data for

these disorders' diagnosis and treatment. Furthermore, studies on urine angiotensinogen are still being conducted, which may have an impact on the creation of fresh approaches to kidney illness and hypertension diagnosis and treatment [75].

**Urinary Angiotensinogen:**

A protein called urinary angiotensinogen is important for controlling blood pressure and maintaining the body's fluid balance. Renin, an enzyme generated by the kidneys, transforms the precursor protein angiotensinogen into angiotensin I [77]. The angiotensin-converting enzyme (ACE) further transforms angiotensin I into angiotensin II [78]. Strong vasoconstrictor angiotensin II raises blood pressure by narrowing blood vessels and induces the production of aldosterone, a hormone that encourages the kidneys to retain water and salt [79]. Angiotensinogen can be used as a marker for kidney function and is linked to illnesses such kidney disease, hypertension, and preeclampsia, which is a pregnancy problem marked by organ damage and elevated blood pressure [80]. Urinary angiotensinogen measurement is a biomarker that can be used to evaluate renal function and may yield useful data for these disorders' diagnosis and treatment [81]. Furthermore, studies on urine angiotensinogen are still being conducted, which may have an impact on the creation of fresh approaches to renal illness and hypertension diagnosis and treatment [82].

### 3.1 Conversion of Angiotensinogen to Angiotensin:

#### 3.1.1Conversion of Angiotensinogen to Angiotensin I:

The liver is the primary organ that produces and releases angiotensinogen into the bloodstream [83].
Specialized kidney cells known as juxtaglomerular cells produce renin in response to dips in blood pressure or in the kidney's salt content [84].
Angiotensinogen is bound by renin and is cleaved to produce angiotensin I.

#### 3.1.2Conversion of Angiotensin I to Angiotensin II:

The peptide angiotensin I is comparatively inactive [85].
Angiotensin-converting enzyme (ACE) operates on angiotensin I to convert it into angiotensin II. ACE is mostly present in endothelial cells that line blood arteries [85].
Although it can happen in other tissues as well, this conversion mostly happens in the lungs.

### 3.2 Physiological Effects of Angiotensin II:

**3.2.1 Vasoconstriction:** Being a strong vasoconstrictor, angiotensin II narrows blood vessels. Blood pressure rises as a result of this vasoconstrictive effect's increase in systemic vascular resistance [86].

#### 3.2.2 Stimulation of Aldosterone Release:

The adrenal glands are stimulated to secrete aldosterone by angiotensin II [87].Aldosterone increases the reabsorption of sodium ions and water from the urine back into the bloodstream via acting on the kidneys, more especially the collecting ducts and distal convoluted tubules [87].
Blood volume rises as a result of this retention of water and sodium, which also raises blood pressure [87].

#### 3.2.3Stimulation of Antidiuretic Hormone (ADH) Release:

Additionally, the posterior pituitary gland releases ADH, also referred to as vasopressin, in response to angiotensin II stimulation [88]. By raising blood volume, ADH operates on the kidneys to enhance water reabsorption, which further helps to regulate blood pressure [88].

#### 3.2.4 Sympathetic Nervous System Activation:

Angiotensin II helps to maintain blood pressure by stimulating the sympathetic nervous system's production of neurotransmitters, which raises heart rate and cardiac output [89].

### 3.4 Regulation of Angiotensin II Levels:

Renin, aldosterone, and other hormones are involved in feedback systems that tightly regulate the levels of angiotensin II [90].In order to avoid excessive vasoconstriction and salt retention, high doses of angiotensin II block the production of renin and encourage the release of other molecules that balance its effects [90].

### 3.5 Indicator of Kidney Function:

Renin-angiotensin system (RAS) changes can result from kidney impairment, which is important for controlling blood pressure and fluid balance [91].
The activity of the RAS in the kidneys is reflected in urinary angiotensinogen levels, which offer important information on renal function [91]. Urinary angiotensinogen levels are generally modest in healthy people, but they may rise in response to renal damage or dysfunction, which is indicative of an intrarenal RAS upregulation [82].

### 3.6 Association with Hypertension:

Dysregulation of the RAS is frequently associated with hypertension, and raised blood pressure is partly caused by elevated angiotensin II levels [82].Research has demonstrated that those with hypertension had higher urine angiotensinogen levels, which may indicate a possible function for this protein in the etiology of high blood pressure [92]. Urine angiotensinogen levels can be used to monitor the efficacy of antihypertensive medications or identify those who may be at risk of developing hypertension [92].

### 3.6 Implications in Kidney Disease:

Changes in renal function and RAS activity are hallmarks of several kidney illnesses, such as glomerulonephritis, diabetic nephropathy, and chronic kidney disease (CKD) [93].
Patients with these disorders have been shown to have elevated urine angiotensinogen levels, which suggests renal damage and dysfunction [82].
Urinary angiotensinogen levels can be measured to provide information on kidney disease development and therapy response, as well as to help with early kidney disease detection, diagnosis, and monitoring [82].

### 3.7 Role in Preeclampsia:

Preeclampsia is a dangerous pregnancy complication that is typified by elevated blood pressure and damage to the organs, especially the kidneys [94].
Preeclampsia has been linked to dysregulation of the RAS, which includes elevated levels of urine angiotensinogen [95].
Pregnant women who are at risk of developing preeclampsia may benefit from monitoring their urine angiotensinogen levels, which can also assist guide care options to minimize problems [96].**3.8 Diagnostic and Therapeutic Implications:**

Urinary angiotensinogen level measurement is a promising non-invasive biomarker for kidney damage or dysfunction assessment and early detection [97].
Urinary angiotensinogen evaluation may enable more individualized approaches to renal disease, preeclampsia, and hypertension diagnosis and treatment in clinical practice [97].
With the potential to improve outcomes for patients with renal and cardiovascular diseases, ongoing study into urinary angiotensinogen may lead to the creation of novel diagnostic tools and treatment strategies targeting the RAS [98].

## 4 Discussion:

A major worldwide health concern, chronic kidney disease (CKD) is linked to considerable morbidity and mortality [99]. An known indicator of kidney impairment, albuminuria (the presence of albumin in the urine) is highly correlated with unfavorable outcomes in individuals with chronic renal disease [101]. Determining the causes behind albuminuria is essential to creating therapies that effectively limit the disease's course and enhance patient outcomes. Urinary angiotensinogen (AGT) has garnered increasing attention as a possible cause of albuminuria in chronic kidney disease (CKD) in recent years [101]. The findings from review articles examining the relationship between urine AGT and albuminuria in chronic kidney disease are summarized in this discussion.

### 4.1 Renin-Angiotensin System (RAS) and CKD Pathophysiology:

The role of the renin-angiotensin system (RAS) in the pathogenesis of chronic kidney disease (CKD) is regularly emphasized in review papers [92]. In addition to being essential for controlling blood pressure and electrolyte balance, the RAS is linked to the onset and advancement of renal illness. Increased intrarenal angiotensin II activity, a sign of RAS dysregulation, is linked to glomerular hypertension, inflammation, and fibrosis, which can ultimately result in albuminuria and renal injury [92].

### 4.2 Urinary AGT as a Biomarker of Intrarenal RAS Activity:

One intriguing indicator of intrarenal RAS activity is urinary AGT [92]. When intrarenal RAS activity is elevated, AGT, which is predominantly generated in the kidney's proximal tubules, can be released into the urine. Urinary AGT levels and RAS activation in chronic kidney disease (CKD) have been linked to several review studies [92]. These articles emphasize the potential use of urine AGT as a non-invasive biomarker for monitoring kidney injury and disease progression.

**4.3 Correlation between Urinary AGT and Albuminuria**:

Comprehensive evidence is included in review articles [92] showing a favorable connection between urine AGT levels and albuminuria in patients with chronic kidney disease. Research has repeatedly demonstrated that, even in the absence of other conventional risk factors, elevated urine AGT levels are linked to increased albuminuria. Based on this link, AGT may have a function in the pathophysiology of albuminuria and kidney damage in patients with chronic kidney disease (CKD) [92].**4.4Mechanisms Underlying the Correlation**:

The discussion delves into the mechanistic insights underlying the correlation between urinary AGT and albuminuria [85]. Elevated urinary AGT levels may reflect increased intrarenal RAS activity, leading to glomerular hypertension, podocyte injury, and proteinuria [92]. AGT may also directly contribute to renal inflammation and fibrosis, exacerbating albuminuria and CKD progression [92].

**4.5 Clinical Implications and Therapeutic Opportunities**:

The review papers go into the clinical ramifications of the association between albuminuria in CKD and urine AGT [92]. AGT levels in the urine that are elevated may be used as a prognostic indicator to identify patients who are more likely to experience negative outcomes and disease progression [101]. Modulating AGT has therapeutic potential in the management of chronic kidney disease (CKD) as it can assist reduce urine AGT levels and attenuate albuminuria. ARBs and ACE inhibitors are two strategies that target the RAS pathway [91].

**5 Conclusion:**

In summary, the relationship between urine angiotensinogen (AGT) and albuminuria in chronic kidney disease (CKD) is an important field of study with broad implications for our knowledge of the pathophysiology of CKD and the creation of new treatment approaches. In order to provide readers with important insights into the underlying mechanisms and clinical consequences of the link between urine AGT levels and albuminuria in patients with chronic kidney disease, we have consolidated findings from a variety of research in this review article. Results from clinical trials show that urine AGT levels and albuminuria in patients with chronic kidney disease are positively correlated. Independent of other established risk factors, elevated urine AGT levels are linked to higher albuminuria, pointing to a possible function for AGT in the pathophysiology of kidney damage and proteinuria in chronic kidney disease. The correlation's mechanistic explanations include that elevated intrarenal renin-angiotensin system (RAS) activity could result in increased AGT secretion and synthesis, which would then exacerbate glomerular hypertension, inflammation, and fibrosis, ultimately accelerating the course of chronic kidney disease (CKD) and albuminuria. The link between urine AGT and albuminuria has significant clinical consequences. Increased urine AGT levels could be used as a non-invasive biomarker to measure intrarenal RAS activity and forecast the course of CKD and unfavorable consequences. Additionally, medications that block the RAS pathway, such as angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, may help lower urine AGT levels and lessen albuminuria, providing promising new treatment options for bettering CKD patient outcomes..

**References:**

[1] Lv, J. C., & Zhang, L. X. (2019). Prevalence and disease burden of chronic kidney disease. *Renal fibrosis: mechanisms and therapies*, 3-15.

[2] Kumar M, Dev S, Khalid MU, Siddenthi SM, Noman M, John C, Akubuiro C, Haider A, Rani R, Kashif M, Varrassi G, Khatri M, Kumar S, Mohamad T. The Bidirectional Link Between Diabetes and Kidney Disease: Mechanisms and Management. Cureus. 2023 Sep 20;15(9):e45615.

[3] Mihai, S., Codrici, E., Popescu, I. D., Enciu, A. M., Albulescu, L., Necula, L. G., ... & Tanase, C. (2018). Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. *Journal of immunology research*, *2018*.

[4] Nehme, A., Zouein, F. A., Deris Zayeri, Z., & Zibara, K. (2019). An update on the tissue renin angiotensin system and its role in physiology and pathology. *Journal of cardiovascular development and disease*, *6*(2), 14.

[5] Balakumar, P., Sambathkumar, R., Mahadevan, N., Muhsinah, A. B., Alsayari, A., Venkateswaramurthy, N., & Jagadeesh, G. (2019). A potential role of the renin-angiotensin-aldosterone system in epithelial-to-mesenchymal transition-induced renal abnormalities: Mechanisms and therapeutic implications. *Pharmacological Research*, *146*, 104314.

[6] Lourenço, B. N., Coleman, A. E., Berghaus, R. D., Tarigo, J. L., Schmiedt, C. W., & Brown, S. A. (2022). Characterization of the intrarenal renin-angiotensin system in cats with naturally occurring chronic kidney disease. *Journal of Veterinary Internal Medicine*, *36*(2), 647-655.

[7] Jiang, C., Wang, B., Li, Y., Xie, L., Zhang, X., Wang, J., ... & Qin, X. (2020). U-shaped association between serum albumin and development of chronic kidney disease in general hypertensive patients. *Clinical nutrition*, *39*(1), 258-264.

[8] Barrera-Chimal, J., & Jaisser, F. (2020). Pathophysiologic mechanisms in diabetic kidney disease: A focus on current and future therapeutic targets. *Diabetes, Obesity and Metabolism*, *22*, 16-31.

[9] Sharma, S., & Smyth, B. (2021). From proteinuria to fibrosis: An update on pathophysiology and treatment options. *Kidney and Blood Pressure Research*, *46*(4), 411-420.

[10] Salmenkari, H. (2019). *Renin-angiotensin system in intestinal inflammation–experimental studies with therapeutic interventions* (Doctoral dissertation, Dissertation. University of Helsinki).

[11] Smyth, L. J., Cañadas-Garre, M., Cappa, R. C., Maxwell, A. P., & McKnight, A. J. (2019). Genetic associations between genes in the renin-angiotensin-aldosterone system and renal disease: a systematic review and meta-analysis. *BMJ open*, *9*(4), e026777.

[12] Qin, Z., Li, H., Wang, L., Geng, J., Su, B., & Liao, R. (2022). Systemic immune-inflammation index is associated with increased urinary albumin excretion: a population-based study. *Frontiers in immunology*, *13*, 863640.

[13] Ohashi, N., Aoki, T., Matsuyama, T., Ishigaki, S., Isobe, S., Katahashi, N., ... & Yasuda, H. (2020). The urinary angiotensinogen to urinary albumin ratio reflects whether the renin-angiotensin system in the kidney is activated due to filtration of plasma angiotensinogen through the damaged glomeruli or the production of angiotensinogen in the proximal tubules. *Internal Medicine*, *59*(3), 357-364.

[14] Shabaka, A., Cases-Corona, C., & Fernandez-Juarez, G. (2021). Therapeutic insights in chronic kidney disease progression. *Frontiers in medicine*, *8*, 645187.

[15] Breyer MD, Susztak K. The next generation of therapeutics for chronic kidney disease. Nat Rev Drug Discov. 2016;15(8):568–88.

[16] Levin A, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline
for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1–150.

[17] Hou, J. H., Zhu, H. X., Zhou, M. L., Le, W. B., Zeng, C. H., Liang, S. S., ... & Liu, Z. H. (2018). Changes in the spectrum of kidney diseases: an analysis of 40,759 biopsy-proven cases from 2003 to 2014 in China. *Kidney Diseases*, *4*(1), 10-19.

[18] Stuckler D. Population causes and consequences of leading chronic diseases:a comparative analysis of prevailing explanations. Milbank Q. 2008 Jun;86(2):273 326.

[19] Khan, M. D., Thi Vu, H. H., Lai, Q. T., & Ahn, J. W. (2019). Aggravation of human diseases and climate change nexus. *International journal of environmental research and public health*, *16*(15), 2799.

[20] Zhou, Y., & Yang, J. (2020). Chronic kidney disease: Overview. *Chronic kidney disease: diagnosis and treatment*, 3-12.

*[21]* Koye, D. N., Magliano, D. J., Nelson, R. G., & Pavkov, M. E. (2018). The global epidemiology of diabetes and kidney disease. *Advances in chronic kidney disease*, *25*(2), 121-132.

[22] D'Agati VD, Kaskel FJ, Falk RJ. Focal seg-mental glomerulosclerosis. N Engl J Med. 2011;365(25):2398–411.

[23] Wang, A. Y. M., An, Y., Cai, G. Y., Chen, J. H., Chen, W., Chen, X. M., ... & Yu, X. Q. (2021). Nephrology in China. *Nephrology Worldwide*, 251-290.
[24] Zhang, L., Wang, Z., Chen, Y., Wang, X., Chen, Z., Feng, B., ... & Zhu, M. (2018). Prevalence and risk factors associated with chronic kidney disease in adults living in 3 different altitude regions in the Tibetan Plateau. *Clinica Chimica Acta*, *481*, 212-217.
[25] Robinson, B. M., Akizawa, T., Jager, K. J., Kerr, P. G., Saran, R., & Pisoni, R. L. (2016). Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *The Lancet*, *388*(10041), 294-306.
[26] Kakitapalli Y, Ampolu J, Madasu SD, Sai Kumar MLS. Detailed Review of Chronic Kidney Disease. Kidney Dis (Basel). 2020 Mar;6(2):85-91.
[27] Yeo, S. C., Wang, H., Ang, Y. G., Lim, C. K., & Ooi, X. Y. (2023). Cost-effectiveness of screening for chronic kidney disease in the general adult population: a systematic review. *Clinical Kidney Journal*, sfad137.
[28] Liu Y. New insights into epithelial-mesenchymal transition in kidney fibrosis. J Am Soc Nephrol. 2010;21(2):212–22.
[29] Levey, A. S., Eckardt, K. U., Tsukamoto, Y., Levin, A., Coresh, J., Rossert, J., ... & Eknoyan, G. (2005). Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney international*, *67*(6), 2089-2100.
[30] Arici, M. (2014). Clinical assessment of a patient with chronic kidney disease. In *Management of Chronic Kidney Disease: A Clinician's Guide* (pp. 15-28). Berlin, Heidelberg: Springer Berlin Heidelberg.
[31] Johnson, D. W., Jones, G. R., Mathew, T. H., Ludlow, M. J., Chadban, S. J., Usherwood, T., ... & Martin, H.(2012). Chronic kidney disease and measurement of albuminuria or proteinuria: a position statement. *Medical Journal of Australia*, *197*(4), 224-225.
[32] Sumida, K., & Kovesdy, C. P. (2017, March). Disease trajectories before ESRD: implications for clinical management. In *Seminars in Nephrology* (Vol. 37, No. 2, pp. 132-143). WB Saunders.
[33] Buch, A. C., Dharmadhikari, M., Panicker, N. K., Chandanwale, S. S., & Kumar, H. (2012). Microalbuminuria: an early detector of diabetic and hypertensive nephropathy. *International Journal of Basic and Applied Medical Sciences*, *2*(2), 218-225.
[34] Miller, W. G., Bruns, D. E., Hortin, G. L., Sandberg, S., Aakre, K. M., McQueen, M. J., ... & National Kidney Disease Education Program-IFCC Working Group on Standardization of Albumin in Urine. (2009). Current issues in measurement and reporting of urinary albumin excretion. *Clinical chemistry*, *55*(1), 24-38.
[35] Jerums, G., Panagiotopoulos, S., Isalamandris, C., Allen, T. J., Gilbert, R. E., & Comper, W. D. (1997). Why is proteinuria such an important risk factor for progression in clinical trials?. *Kidney International Supplement*, (63).
[36] Gansevoort RT, Ritz E: Hermann Senator and albuminuria—forgotten pioneering work in the 19th century. Nephrol Dial Transplant 24: 1057–1062, 2009
[37] Williams PS, Fass G, Bone JM: Renal pathology and proteinuria determine progression in untreated mild/moderate chronic renal failure. Q J Med 67: 343–354, 1988
[38] Johnson KR: Strengths and weaknesses of renal markers as risk factors and surrogate markers. Kidney Int 79: 1272–1274, 2011
[39] Okada T, Nagao T, Matsumoto H, Nagaoka Y, Wada T, Nakao T: Histological predictors for renal prognosis in diabetic nephropathy in diabetes mellitus type 2 patients with overt proteinuria. Nephrology (Carlton) 17: 68–75, 2012
[40] Ichimura K, Kurihara H, Sakai T. Actin filament organization of foot processes in rat podocytes. J Histochem Cytochem. 2003;51(12):1589–600.
[41] Gekle M: Renal tubule albumin transport. Annu Rev Physiol 67: 573–594, 2005
[42] Amsellem S, Gburek J, Hamard G, Nielsen R, Willnow TE, Devuyst O, Nexo E, Verroust PJ, Christensen EI, Kozyraki R: Cubilin is essential for albumin reabsorption in the renal proximal tubule. J Am Soc Nephrol 21: 1859–1867, 2010
[43] Macconi D, Chiabrando C, Schiarea S, Aiello S, Cassis L, Gagliardini E, Noris M, Buelli S, Zoja C, Corna D, Mele C, Fanelli R, Remuzzi G, Benigni A: Proteasomal processing of albumin by renal dendritic cells generates antigenic peptides. J Am Soc Nephrol 20: 123–130, 2009
[44] Morigi M, Macconi D, Zoja C, Donadelli R, Buelli S, Zanchi C, Ghilardi M, Remuzzi G: Protein overload-induced NF-kappaB activation in proximal tubular cells requires H(2)O(2) through a PKC-dependent pathway. J Am Soc Nephrol 13: 1179–1189, 2002
[45] Vlachojannis JG, Tsakas S, Petropoulou C, Goumenos DS, Alexandri S: Endothelin-1 in the kidney and urine of patients with glomerular disease and proteinuria. Clin Nephrol 58: 337–343,
[46] Whaley-Connell AT, Morris EM, Rehmer N, Yaghoubian JC, Wei Y, Hayden MR, Habibi J, Stump CS, Sowers JR: Albumin activation of NAD(P)H oxidase activity is mediated via Rac1 in proximal tubule cells. Am J Nephrol 27: 15–23, 2007
[47] Diwakar R, Pearson AL, Colville-Nash P, Brunskill NJ, Dockrell ME: The role played by endocytosis in albumin-induced secretion of TGF-beta1 by proximal tubular epithelial cells. Am J Physiol Renal Physiol 292: F1464–F1470, 2007
[48] Zoja C, Abbate M, Remuzzi G: Progression of renal injury toward interstitial inflammation and glomerular sclerosis is dependent on abnormal protein filtration [published online ahead of print August 2, 2014]. Nephrol Dial Transplant doi:gfu261
[49] Woo, K. T. (2011). *Clinical nephrology*. World Scientific Publishing Company.

[50] Eknoyan G, Lameire N, Eckardt K, Kasiske B, Wheeler D, Levin A, et al. (January 2013). "KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease" (PDF). *Kidney International Supplements*. **3** (1): 136–150. Archived from the original (PDF) on 4 March 2016.
[51] Politano, S. A., Colbert, G. B., & Hamiduzzaman, N. (2020). Nephrotic syndrome. *Primary Care: Clinics in Office Practice*, *47*(4), 597-613.
[52] Sumida, K., Nadkarni, G. N., Grams, M. E., Sang, Y., Ballew, S. H., Coresh, J., ... & Chronic Kidney Disease Prognosis Consortium‡. (2020). Conversion of urine protein–creatinine ratio or urine dipstick protein to urine albumin–creatinine ratio for use in chronic kidney disease screening and prognosis: an individual participant–based meta-analysis. *Annals of internal medicine*, *173*(6), 426-435.
[53] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney inter S.* 2013;3:1–150.
[54] Scottish Intercollegiate Guidelines Network . 2008. Guideline 103. Diagnosis and Management of Chronic Kidney Disease.
[55] Lee W., Kim Y., Chang S., Lee A.J., Jeon C.H. The influence of vitamin C on the urine dipstick tests in the clinical specimens: a multicenter study. *J. Clin. Lab. Anal.* 2017;31(5)
[56] Rumley A. Urine dipstick testing: comparison of results obtained by visual reading and with the Bayer CLINITEK 50. *Ann. Clin. Biochem.* 2000;37(Pt 2):220–221.
[57] McTaggart M.P., Newall R.G., Hirst J.A., Bankhead C.R., Lamb E.J., Roberts N.W. Diagnostic accuracy of point-of-care tests for detecting albuminuria: a systematic review and meta-analysis. *Ann. Intern. Med.* 2014;160(8):550–557.
[58] Krogsbøll L.T., Jørgensen K.J., Gøtzsche P.C. Screening with urinary dipsticks for reducing morbidity and mortality. *Coch. Database Syst. Rev.* 2015;(1)
[59] Yan, M. T., Chao, C. T., & Lin, S. H. (2021). Chronic kidney disease: strategies to retard progression. *International journal of molecular sciences*, *22*(18), 10084.
[60] Wühl, E., & Schaefer, F. (2011). Managing kidney disease with blood-pressure control. *Nature Reviews Nephrology*, *7*(8), 434-444.
[61] Casas, J. P., Chua, W., Loukogeorgakis, S., Vallance, P., Smeeth, L., Hingorani, A. D., & MacAllister, R. J. (2005). Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *The lancet*, *366*(9502), 2026-2033.
[62] Slinin, Y., Ishani, A., Rector, T., Fitzgerald, P., MacDonald, R., Tacklind, J., ... & Wilt, T. J. (2012). Management of hyperglycemia, dyslipidemia, and albuminuria in patients with diabetes and CKD: a systematic review for a KDOQI clinical practice guideline. *American Journal of Kidney Diseases*, *60*(5), 747-769.
[63] Kramer, H. (2019). Diet and chronic kidney disease. *Advances in Nutrition*, *10*, S367-S379.
[64] Mercier, K., Smith, H., & Biederman, J. (2014). Renin-angiotensin-aldosterone system inhibition: overview of the therapeutic use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and direct renin inhibitors. *Primary Care: Clinics in Office Practice*, *41*(4), 765-778.
[65] Rippe, J. M., & Angelopoulos, T. J. (2019). Lifestyle strategies for risk factor reduction, prevention and treatment of cardiovascular disease. *Lifestyle Medicine, Third Edition*, 19-36.
[66] Verma, P., Mahajan, J., Kumar, S., & Acharya, S. (2022). Lifestyle Modification and Nutrition: Halt the Progression to End-Stage Renal Disease. *International Journal of Nutrition, Pharmacology, Neurological Diseases*, *12*(3), 105-111.
[67] Cupisti, A., Gallieni, M., Avesani, C. M., D'Alessandro, C., Carrero, J. J., & Piccoli, G. B. (2020). Medical nutritional therapy for patients with chronic kidney disease not on dialysis: the low protein diet as a medication. *Journal of Clinical Medicine*, *9*(11), 3644.
[68] Alhassani, R. Y., Bagadood, R. M., Balubaid, R. N., Barno, H. I., Alahmadi, M. O., Ayoub, N. A., ... & Ayoub, N. (2021). Drug therapies affecting renal function: an overview. *Cureus*, *13*(11).
[69] Zhang, X., Donnan, P. T., Bell, S., & Guthrie, B. (2017). Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. *BMC nephrology*, *18*, 1-12.
[70] Levey, A. S., Gansevoort, R. T., Coresh, J., Inker, L. A., Heerspink, H. L., Grams, M. E., ... & Willis, K. (2020). Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. *American journal of kidney diseases*, *75*(1), 84-104.
[71] Levey, A. S., Becker, C., & Inker, L. A. (2015). Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *Jama*, *313*(8), 837-846.
[72] Fountain, J. H., Kaur, J., & Lappin, S. L. (2017). Physiology, renin angiotensin system.
[73] Ma, K., Wang, Y., Wang, M., Wang, Z., Wang, X., Ju, X., & He, R. (2021). Antihypertensive activity of the ACE–renin inhibitory peptide derived from Moringa oleifera protein. *Food & Function*, *12*(19), 8994-9006.

[74] Te Riet, L., van Esch, J. H., Roks, A. J., van den Meiracker, A. H., & Danser, A. J. (2015). Hypertension: renin–angiotensin–aldosterone system alterations. *Circulation research*, *116*(6), 960-975.
[75] Santos, R. A. S., Sampaio, W. O., Alzamora, A. C., Motta-Santos, D., Alenina, N., Bader, M., & Campagnole-Santos, M. J. (2017). The ACE2/angiotensin-(1–7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1–7). *Physiological reviews*.
[76] Li, X. C., Zhu, D., Zheng, X., Zhang, J., & Zhuo, J. L. (2018). Intratubular and intracellular renin–angiotensin system in the kidney: a unifying perspective in blood pressure control. *Clinical Science*, *132*(13), 1383-1401.
[77] Gelen, V., Kükürt, A., & Şengül, E. (2021). Role of the renin-angiotensin-aldosterone system in various disease processes: An overview. *Renin-Angiotensin Aldosterone System*, *55*.
[78] Khurana, V., & Goswami, B. (2022). Angiotensin converting enzyme (ACE). *Clinica Chimica Acta*, *524*, 113-122.
[79] Forrester, S. J., Booz, G. W., Sigmund, C. D., Coffman, T. M., Kawai, T., Rizzo, V., ... & Eguchi, S. (2018). Angiotensin II signal transduction: an update on mechanisms of physiology and pathophysiology. *Physiological reviews*, *98*(3), 1627-1738.
[80] Salih, M., Bovée, D. M., Roksnoer, L. C., Casteleijn, N. F., Bakker, S. J., Gansevoort, R. T., ... & Hoorn, E. J. (2017). Urinary renin-angiotensin markers in polycystic kidney disease. *American journal of physiology-Renal physiology*, *313*(4), F874-F881.
[81] Satirapoj, B., Siritaweesuk, N., & Supasyndh, O. (2014). Urinary angiotensinogen as a potential biomarker of diabetic nephropathy. *Clinical kidney journal*, *7*(4), 354-360.
[82] Ba Aqeel, S. H., Sanchez, A., & Batlle, D. (2017). Angiotensinogen as a biomarker of acute kidney injury. *Clinical Kidney Journal*, *10*(6), 759-768.
[83] Paul, M., Poyan Mehr, A., & Kreutz, R. (2006). Physiology of local renin-angiotensin systems. *Physiological reviews*, *86*(3), 747-803.
[84] Almeida, L. F., Tofteng, S. S., Madsen, K., & Jensen, B. L. (2020). Role of the renin–angiotensin system in kidney development and programming of adult blood pressure. *Clinical Science*, *134*(6), 641-656.
[85] Ferrario, C. M., & Iyer, S. N. (1998). Angiotensin-(1–7): a bioactive fragment of the renin–angiotensin system. *Regulatory peptides*, *78*(1-3), 13-18.
[86] Ayada, C., Toru, Ü., & Korkut, Y. (2015). The relationship of stress and blood pressure effectors. *Hippokratia*, *19*(2), 99.
[87] Yatabe, J., Yoneda, M., Yatabe, M. S., Watanabe, T., Felder, R. A., Jose, P. A., & Sanada, H. (2011). Angiotensin III stimulates aldosterone secretion from adrenal gland partially via angiotensin II type 2 receptor but not angiotensin II type 1 receptor. *Endocrinology*, *152*(4), 1582-1588.
[88] Carmona-Calero, E. M., González-Toledo, J. M., Castañeyra-Ruiz, L., González-Marrero, I., Castañeyra-Ruiz, M., de Paz-Carmona, H., ... & Castañeyra-Perdomo, A. (2014). Angiotensin II, vasopressin, and collagen-IV expression in the subfornical organ in a case of syndrome of inappropriate ADH. *Advances in Endocrinology*, *2014*.
[89] Navar, L. G. (2014). Physiology: hemodynamics, endothelial function, renin–angiotensin–aldosterone system, sympathetic nervous system. *Journal of the American Society of Hypertension*, *8*(7), 519-524.
[90] Te Riet, L., van Esch, J. H., Roks, A. J., van den Meiracker, A. H., & Danser, A. J. (2015). Hypertension: renin–angiotensin–aldosterone system alterations. *Circulation research*, *116*(6), 960-975.
[91] Hsu, C. N., & Tain, Y. L. (2021). Targeting the renin–angiotensin–aldosterone system to prevent hypertension and kidney disease of developmental origins. *International Journal of Molecular Sciences*, *22*(5), 2298.
[92] Kobori, H., Alper Jr, A. B., Shenava, R., Katsurada, A., Saito, T., Ohashi, N., ... & Navar, L. G. (2009). Urinary angiotensinogen as a novel biomarker of the intrarenal renin-angiotensin system status in hypertensive patients. *Hypertension*, *53*(2), 344-350.
[93] Gajjala, P. R., Sanati, M., & Jankowski, J. (2015). Cellular and molecular mechanisms of chronic kidney disease with diabetes mellitus and cardiovascular diseases as its comorbidities. *Frontiers in immunology*, *6*, 150995.
[94] Al-Jameil, N., Khan, F. A., Khan, M. F., & Tabassum, H. (2014). A brief overview of preeclampsia. *Journal of clinical medicine research*, *6*(1), 1.
[95] Lumbers, E. R., Delforce, S. J., Arthurs, A. L., & Pringle, K. G. (2019). Causes and consequences of the dysregulated maternal renin-angiotensin system in preeclampsia. *Frontiers in endocrinology*, *10*, 469943.
[96] Stepan, H., Hund, M., & Andraczek, T. (2020). Combining biomarkers to predict pregnancy complications and redefine preeclampsia: the angiogenic-placental syndrome. *Hypertension*, *75*(4), 918-926.
[97] Obert, L. A., Elmore, S. A., Ennulat, D., & Frazier, K. S. (2021). A review of specific biomarkers of chronic renal injury and their potential application in nonclinical safety assessment studies. *Toxicologic pathology*, *49*(5), 996-1023.
[98] Cruz-López, E. O., Ye, D., Wu, C., Lu, H. S., Uijl, E., Mirabito Colafella, K. M., & Danser, A. J. (2022). Angiotensinogen suppression: a new tool to treat cardiovascular and renal disease. *Hypertension*, *79*(10), 2115-2126.
[99] Couser, W. G., Remuzzi, G., Mendis, S., & Tonelli, M. (2011). The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney international*, *80*(12), 1258-1270.
[100] Heerspink, H. J. L., & Gansevoort, R. T. (2015). Albuminuria is an appropriate therapeutic target in patients with CKD: the pro view. *Clinical Journal of the American Society of Nephrology*, *10*(6), 1079-1088.
[101] Takemura, K., Board, P. G., & Koga, F. (2021). A systematic review of serum γ-glutamyltransferase as a prognostic biomarker in patients with genitourinary cancer. *Antioxidants*, *10*(4), 549.