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Chronic kidney disease in the elderly

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ABSTRACT

The incidence of Chronic Kidney Disease (CKD) increases with age. Decreased Glomerular Filtration Rate (GFR) and increased albuminuria are the main characteristics of CKD in elderly patients. In the elderly, aging of the kidneys causes structural and functional changes in the kidneys, making them susceptible to the development of CKD. Frequent comorbidities in elderly patients such as hypertension and diabetes mellitus and the use of non-steroidal anti-inflammatory drugs and antibiotics also contribute to worsening renal function and increasing the development of CKD in the elderly. Decreased renal reserve in the elderly also leads to susceptibility to kidney damage from infection, dehydration and surgery. Mechanisms related to the development of CKD in the elderly can be explained by premature aging, decreased autophagy in podocytes, mitochondrial dysfunction, epigenetic regulation and inflammation and immunosenescence.

Keywords: etiology, pathogenesis, chronic kidney disease, advanced age

Abbreviations:

CKD	Chronic Kidney Disease
GFR	Glomerular Filtration Rate

ECM	extracellular matrix
AGEs	Advanced Glycation end Products
RPF	Renal Plasma Flow
FF	Filtration Fraction
RFR	Renal Functional Reserve
AKI	Acute Kidney Injury
RAS	Renin-Angiotensin-Aldosterone System
PI 3-kinase	Phosphatidylinositol 3-Kinase
SASPs	Senescence and Its Associated Secretory Phenotypes

INTRODUCTION

Chronic kidney disease (CKD) is a decrease in kidney function that lasts >3 months with a Glomerular Filtration Rate (GFR) <60 ml/min/1.73 m^2. According to American Society of Nephrology research, GFR indicators are employed according to age: 75 ml/min per 1.73 m^2 is used for people under 40, 60 ml/min per 1.73 m^2 is used for people between 40 and 65, and 45 ml/min per 1.73 m^2 is used for people over 65 [1]. Although it can strike at any age, chronic kidney disease primarily affects the elderly [2]. The prevalence of CKD among people 65 and older was 33.2% in 2017–2020 [3].

Chronic kidney disease in the elderly due to changes in the anatomical structure of the kidneys, such as progressive nephrosclerosis (glomerulosclerosis, tubular atrophy and atherosclerosis) with supporting examinations performed such as urine albumin excretion and creatinine can help confirm the diagnosis of CKD in the elderly [4]. In the population age 18-29 years the number of nephrons is 1,000,000 while in the population age >65 years there is a decrease in nephrons to 500,000, meaning that with increasing age the number of nephrons decreases. In the elderly, kidney function decreases so that prevention and therapeutic measures can be started early [1,5].

Recent estimates indicate that the number of elderly people is rising in every nation in the world [6]. The elderly population, those at high risk of developing CKD, are expected to double by 2050 with one in six people in the world aged 65 years or older [2]. Understanding the pathogenesis and risk factors of CKD in the elderly can inform the prevention of CKD in the elderly. The aim of this paper to present the etiology and pathogenesis of CKD in the elderly.

Structural and functional changes of the kidney in old age

The primary organs in charge of eliminating excess fluid and waste products from metabolism are the kidneys. About 20–25% of cardiac output is received by the kidneys, which also filter 200 L of blood per day and generate 1.5 L of waste-containing urine. In physiological conditions, the

kidney is a highly metabolic organ, which is able to withstand considerable oxidative stress and is susceptible to the aging process. During normal aging, the kidney is one of the organs that undergoes the most noticeable alterations [7].

Systemic comorbidities including diabetes mellitus and hypertension, as well as underlying or pre-existing renal illness, exacerbate the kidney's steady functional decline and macroscopic and microscopic histologic alterations that occur with aging. Although renal injury is not a direct result of aging, the physiological changes brought on by normal aging tend to reduce the kidney's ability for repair, making older people more vulnerable to acute, chronic, and other renal illnesses [7].

Kidney mass declines by roughly 10% every ten years between the ages of 30 and 80. Each decade of aging is linked to a 10% loss in renal cortex thickness, which is accompanied by a decline in the number of functioning nephrons. GFR declines at the same rate after age 40, and renal blood flow declines by roughly 10% every ten years. Nonetheless, glomerular volume and single nephron GFR stay mostly unchanged with age [8].

The glomerular basement membrane thickens, tubulointerstitial alterations occur, glomerulosclerosis increases, and the size and number of nephrons decreases with age. As people age, their GFR falls. At a rate as low as 0.4 ml/min per year per 1.73 m^2, renal function deteriorates at a rate of 3.8 ml/min per year per 1.73 m^2. The decline in GFR increases with age. Aging is characterized by progressive tubular dysfunction, decreased sodium reabsorption, potassium excretion, and urine concentration capacity potentially contributing to increased susceptibility to acute renal failure. In reaction to fludrocortisone or when hyperkalemic, elderly people fail to enhance distal tubular potassium excretion and have reduced trans tubular potassium gradients. Reduced potassium excretion may be a result of a slower rate of sodium and chloride transport to the distal cortical tubule, and it is correlated with decreased GFR. The aging kidney also exhibits changes in vascular anatomy and function. The cortex is mainly affected by increased intrarenal shunts and capillary bypass, increased intimal cell proliferation in preglomerular arterioles, and increased extracellular matrix (ECM) deposition. While aortic baroreceptors' attenuation to sympathetic tone diminishes with age, elevated renal sympathetic tone encourages vasoconstriction [9].

Structural and functional changes of the aging kidney are described as follows [8]:

1. changes
    a. Glomerulus
        1) Decreased glomerular number
        2) Increased glomerulosclerosis (focal and global, but not segmental)
        3) Progressive decline followed by increase in glomerular size

4) Shunt formation between afferent and efferent arterioles
5) Thickening of the glomerular basement membrane
6) Increased mesangial volume and matrix

b. Tubules
1) The number, volume, and length of tubules decrease
2) Atrophy of tubules with simplification of tubule epithelium and thickening of tubule basement membrane
3) Increased number of tubular diverticula
4) Acquired cyst

c. Interstitial and blood vessels
1) Interstitial fibrosis and increased interstitial volume
2) Fibrosis pericapsular
3) Arteriosclerosis

2. Functional changes
a. Decline of GFR
b. Stabilized GFR of a single nephron
c. Stabilized urinary and minimal albumin excretion
d. Impairment of renal blood flow
e. Reduced sodium resorption
f. Reduced potassium excretion
g. Impairment of urinary concentrating capacity
h. Increase in renal sympathetic tone
i. Reduced nitric oxide production
j. Reduced hemodynamic response to vasodilatory stimuli

Characteristics of chronic kidney disease in the elderly

Chronic kidney disease has various etiologies that can also occur in conjunction with physiological changes in the kidneys caused by normal aging. In contrast to CKD patients, healthy people experience distinct aging-related alterations in their kidneys. Apoptosis or senescence, which is characterized by modifications in morphology and transcriptional profile, secretory phenotype, and resistance to apoptosis, can occur in cells in response to stress and/or damage. Normal aging causes a gradual loss of the balance between cellular dysfunction and repair since the body's capacity to produce new cells and tissues decreases with age. Cell and organ damage can be further exacerbated by the accumulation of several detrimental elements, such as mitochondrial injury and oxidative stress (oxygen radicals and profibrogenic mediators) on intrinsic age-related alterations,

as happens in illnesses. Such alterations might be made worse by additional disease-specific damage mechanisms as ischemia and inflammation. Therefore, physiological aging and harm from illness typically coexist [10].

The structure and regulatory function of the kidney can be altered by aging in a variety of ways, which can raise the risk of acute renal damage and chronic kidney disease. Overall, the extremely slow alterations seen in the aging kidney vary from CKD in that they entail increasing genetic, immunological, or toxic processes of harm, even if renal aging and renal failure share some pathophysiology and clinical aspects. According to available data, the activation of pathways frequently involved in the inflammation and renal fibrosis that define CKD may be caused by an imbalance between blunted protective factors (vascular density, antioxidant capacity, telomere shortening, PPARγ, and Klotho expression) and stress factors (hypoxia, overexpression of collagen I and III, TGF-β, and oxidative stress). This results in increased microvascular thinning and senescence, which causes damage and accelerates the process. The kidney's vascular alterations may also be influenced by Advanced Glycation end Products (AGEs). In both diabetics and non-diabetics, AGEs build up in plasma and tissues with aging, diabetes, and chronic kidney disease. AGEs buildup may also accelerate the aging of tubular epithelial cells and impair insulin sensitivity, which might contribute to the pathogenesis of type 2 diabetes. These processes alter the structure of the kidneys and alter their functionality [11].

Age-related decreases in GFR are gradual and have a somewhat normal distribution, suggesting that physiological processes are the main cause of the reduction. It's interesting to note that in around one-third of older people, renal function stays fairly constant: the average yearly loss in GFR falls between 0.4 and 2.6 ml/min. Under typical circumstances, the aging kidney can preserve fluid and electrolyte balance. On the other hand, vulnerability to acute kidney damage rises when renal reserve falls. Specifically, mildly decreased GFR and markedly decreased Renal Plasma Flow (RPF) in healthy older adults cause changes in renal hemodynamics. Filtration Fraction (FF) typically rises in the elderly when the latter declines more than GFR. The rise in FF is also a result of blood flow being redistributed from the brain to the medulla. Renal Functional Reserve (RFR) is also decreased as a result of the age-related rise in sclerotic glomerular fraction and the incapacity to raise RPF in response to maximum vasodilatory stimulation. Low GFR and decreased tubular salt and water reabsorption are the two main functional traits that the aging kidney has in common with the failing or injured kidney. However, in healthy older adults, blood levels of calcium, magnesium, and phosphorus are normal, erythropoietin and hemoglobin are normal, and proximal tubular function is maintained. Furthermore, as people age, their serum erythropoietin levels rise, perhaps making up for the diminished erythroid response [11].

The most significant characteristic of renal failure is a decreased GFR, whereas kidney injury is indicated by an increased albumin to creatinine ratio. Identification of the etiology of CKD may be aided by the presence of systemic illnesses other than CKD, such as diabetes, skeletal-muscular disorders, cardiovascular and respiratory diseases, and polypharmacy. Albuminuria is a defining feature of CKD in 19% of older people [11]. Other investigations have demonstrated the involvement of albuminuria in chronic kidney disease. Based on molecular research, there may be biological similarities between renal aging and several causes of chronic kidney disease. Age-related and kidney disease-related proteomic patterns have been identified using proteome analysis of the extracellular matrix composition in rat and human kidneys. Extracellular matrix proteins (collagen I, III, VI, and XV, fibrinogen, and nephronectin) are present in greater quantities than basic membrane components (laminin, collagen types IV, and VIII). Perhaps in an effort to support the basement membrane weakening that underpins the development of interstitial fibrosis/tubular atrophy, collagen VI is elevated early in aging and disease models. The absence of albuminuria in normal age-related GFR decline suggests that this functional decline is not closely and causally related to podocytopenia but in disease processes that cause glomerular hyperfiltration, the presence of albuminuria suggests a direct relationship with podocyte dysbiosis [10]. In addition, it is reported that higher albuminuria is associated with other abnormalities in the function and structure of the aging kidney, such as decreased renal plasma flow, decreased maximal urine concentration and acidification, glomerular and arterial sclerosis, and tubular atrophy, which are considered pathological if observed in younger people. The kidney is a highly vascular organ, and GFR and albuminuria levels are related to the severity of vascular disease risk factors and vascular disease, indicating that the abnormalities are a consequence of vascular disease in the kidney.[12] In addition, in healthy aging, there is stable and minimal urinary albumin excretion. In patients with advanced renal failure, 3.0% have proteinuria. Thus albuminuria/proteinuria is an indicator of worsening renal function in elderly patients [11].

Table1. Similarities and differences between renal aging and CKD based on renal function parameters [12]

	GFR	Urea FE[a]	Urea	Ca, Mg, P FE	K FE[a]	Eryth-ropoi-etin
Aging kidney	<60 ml/m	↑	=	=	↓	=
CKD	<60 ml/m	↑	↑	↑	↑	↓

FE: Fractional excretion

a Decreased GFR may prevent full compensation of CKD-related increases in urea and K FE

In the study of Aucella et al. stated that GFR < 60 ml/min/1.73 m^2 is characteristic of normal aging kidneys and CKD but in the study of Mallapallil stated that maintenance of renal hormonal function, electrolyte and acid-base balance and normal urinalysis in elderly patients with GFR < 60 ml/min/1.73 m^2 is indicative of normal aging kidneys and not kidneys with CKD [13]. According to renal disease criteria, a substantial percentage of older persons with CKD, particularly those 70 years of age or older, had albuminuria and a GFR of less than 45 ml/min/1.73 m^2 [14].

Chronic Kidney Disease causes biological aging through a number of mechanisms, including the accumulation of uremic toxins and altered homeostasis when GFR drops below 60 mL/min/1.73 m^2, the early loss of additional renal function not measured in routine clinical care, such as the production of the anti-aging protein Klotho, when CKD is already present (e.g., urinary albumin/creatinine ratio ≥30 mg/g but global renal function GFR is still normal. The urinary albumin/creatinine ratio and GFR thresholds for defining CKD were selected because they are linked to a higher risk of death, progression to renal failure requiring renal replacement therapy, and Acute Kidney Injury (AKI) when they last for three months or longer [15]. Due to changes in renal volume, including fewer nephrons, altered vasoactive responses, and altered renin-angiotensin system activity, which is linked to cellular oxidative stress, aging causes decreased GFR, a normal biological phenomenon associated with cell and organ aging. The glomerular basement membrane's increased permeability, which permits the excretion of significant quantities of proteins, including albumin, is another functional aberration of aging that contributes to the higher incidence of kidney damage in the elderly [14].

Etiology of chronic kidney disease in the elderly

Chronic kidney disease is more common among the elderly for a number of reasons. Reduced renal blood flow and fewer functional nephrons are two examples of the morphological and functional changes that aging may bring about in the kidneys. Atherosclerosis, cardiovascular disease, diabetes, and hypertension are among the illnesses that are more prevalent in older persons and may have a role in the onset and progression of CKD. Multimorbid older persons frequently use a variety of medications, some of which, like antibiotics and non-steroidal anti-inflammatory drugs, can harm the kidneys, particularly if taken in excess or for an extended length of time. Additionally, age-related changes in medication metabolism and excretion make older people more vulnerable

to drug-induced kidney injury. Older adults are more vulnerable to kidney injury from infections, dehydration, and surgery because of the age-related decrease in renal reserve [21].

Hypertension imposes an additional burden on the functional reserve of the kidneys, substantially accelerating the progression of CKD [20]. In addition, increased intraglomerular hypertension caused by glomerular loss results in hypertrophy and hyperfiltration of the remaining nephrons. The remaining nephrons continue to deteriorate forming a vicious cycle where additional nephron loss culminates in hypertrophy and hyperfiltration which further leads to nephron loss until the kidney fails. Additional insults are contributed by various hormones and cytokines such as angiotensin II, which causes vasoconstriction of efferent arterioles exacerbating intra-glomerular hypertension and TGF-β, which results in fibrosis [13].

In general, the rate of progression to CKD is slow, although there is a high prevalence of CKD in elderly patients. The annual rate of GFR decline is only 0.8 to 1.4 mL/min/1.73 m^2 in nondiabetic patients older than 65 years but eGFR declines 2.42 mL/min/1.73 m^2 per year in elderly patients with diabetes mellitus. Diabetes mellitus accelerates the development of CKD in elderly patients. The mechanism of progression to CKD in patients with diabetes remains controversial. Hyperactivity of the Renin-Angiotensin-Aldosterone System (RAS), osmotic sodium retention, endothelial dysfunction, dyslipidemia, extracellular signal-regulated RAS/RAF/kinase pathway, purinergic system modification, Phosphatidylinositol 3-Kinase (PI 3-kinase)-dependent signaling pathway, and inflammation are pathways that may explain it [14]. The processes behind renal lesions in diabetics lead to glomerular hyperfiltration, which often results in proteinuria, glomerulosclerosis, and decreased GFR [14].

Pathogenesis of chronic kidney disease in the elderly

The prevalence of CKD increases with age [14]. The kidney is a metabolically active organ that requires energy to carry out various processes such as tubular reabsorption and secretion, and shows a decline in function with age. Various molecular mechanisms, including genomic instability, telomere reduction, inflammation, autophagy, mitochondrial function, and changes in sirtuin and Klotho signaling pathways are important factors that regulate renal aging [16].

The aging kidney alters structurally and exhibits different hemodynamic, physiological, and transcriptome characteristics both at rest and in response to renal damage. These alterations make it more difficult for the kidneys to tolerate and heal from damage, which makes older people more vulnerable to AKI and more likely to develop progressive CKD in the future [9]. Numerous stresses, such as premature aging, autophagy, epigenetic and mitochondrial dysfunction, etc., are

shared by CKD and aging, which implies that the kidney may be controlled by comparable underlying processes. We will go into great detail on the common pathways that lead to CKD and kidney aging.

Premature aging

Oxidative stress, inflammation, abnormal gut microbiota, advanced glycation end products, and fructose consumption are factors that contribute to premature aging in kidney disease patients. Oxidative stress is an important mechanism to accelerate aging and muscle shrinkage in CKD. [17] Cells can age prematurely as a result of acute traumas such wounds, oxidative stress, and acute ischemia, which activate the p16Ink4a and/or p53-p21 pathways. In order to prevent unchecked mitosis and provide cells more time for DNA repair, premature aging momentarily stops the cell cycle. In the meantime, "immune surveillance"—the process by which activated immune cells get rid of cells that age too quickly—can help to further enhance tissue healing. The development of Senescence and Its Associated Secretory Phenotypes (SASPs) is the outcome of a shift from premature to complete aging brought on by prolonged exposure to stress-induced damage. Chronic injury, caused by repeated and persistent stress, leads to irreversible aging and cell cycle arrest. The increased number of aging cells accumulates and causes more severe aging through the secretion of SASP, which eventually leads to kidney aging and CKD. [18] After acute kidney damage, SASP may help with tissue regeneration; however, long-term exposure to SASP impairs tissue function and repair, ultimately resulting in CKD. Furthermore, by encouraging renal fibrosis, SASP results in sterile inflammation and aids in the development of CKD. [17]

Autophagy

One extremely conserved lysosomal mechanism that breaks down cytoplasmic components is autophagy. Renal homeostasis, shape, and function are all maintained in large part by basal autophagy in renal cells. The capacity of autophagy to prevent kidney aging. Along with tubule shrinkage and tubulointerstitial fibrosis, decreased autophagy in the kidney's proximal tubules causes a substantial deterioration in renal function, suggesting that reduced autophagy speeds up aging and tubule damage. Reduced podocyte autophagy linked to aging speeds up the development of SASPs, which ultimately cause renal aging and chronic kidney disease. [18]

Mitochondrial dysfunction

The inner and outer membranes of mitochondria, which are intracellular organelles, are separated by an intermembrane gap. Cellular homeostasis throughout aging and chronic kidney disease depends on the maintenance of normal mitochondrial structure and function. The development of CKD and aging can be accelerated by a variety of endogenous and external insults that cause

mitochondrial dysfunction, mitochondria-mediated inflammation, and reduced mitophagy. [18]

Epigenetic Regulation

Changes in epigenetic regulation, such as DNA methylation, histone modification, chromatin remodeling, non-coding RNA (ncRNA) regulation, and RNA modification, are associated with aging and CKD. There is a consistent trend toward genomic hypomethylation as people age. Ten-eleven translocation (TET) eliminates methyl groups from DNA, whereas DNA methyltransferase (DNMT) mediates DNA methylation. The occurrence and development of CKD are also influenced by DNA methylation. TGF-β and other profibrotic factors can cause DNMT1/3a/3b to be upregulated, which inhibits Klotho expression in CKD mice. On the other hand, TET activity restoration can reverse the Klotho promoter's methylation, slowing the course of CKD. [18] Histone alterations can also control kidney aging and CKD. These modifications include methylation, acetylation, phosphorylation, ubiquitination, and ADP ribosylation. Methylation and acetylation of lysine residues are two of these alterations that have been well investigated in relation to aging and chronic kidney disease. [18]

Inflammation and Immunosenescence

The immune system's malfunction and dysregulation, which are generally referred to as immunosenescence and inflammaging, can be linked to aging. Because immunosenescence is linked to low-grade sterile inflammation and diminished cellular responses to infections and vaccinations, it is seen as hazardous. Numerous variables, including genetics, diet, exercise, exposure to microbes, gender, and human cytomegalovirus status, affect the alterations associated with immunosenescence. High blood levels of proinflammatory cytokines in elderly people are indicative of inflammation. [17] Immunosensitivity is more prominent in patients with kidney disease than in healthy controls, characterized by the accumulation of immunological senescent cells (such as CD28- T cells, CD14CD16 monocytes) and the production of pro-inflammatory cytokines. When senescent cells accumulate in the kidney and cause chronic low-grade inflammation, aggravating renal damage, accelerating renal aging and further increasing the susceptibility of the elderly to kidney disease. [21]

High levels of innate immunity lead to inflammation, which is typified by proinflammatory cytokines including interleukin 6, interleukin 1, and tumor necrosis factor as well as activated macrophages. Adaptive immunity has also changed somewhat. Immunosensitivity in CKD is demonstrated by a decrease in the quantity and functionality of naïve T cells and an increase in memory T cells, especially proinflammatory CD4+CD28- T cells. In CKD, systemic inflammation results in muscular atrophy. Proteolytic processes are triggered by proinflammatory cytokines

generated by aged cells with SASP, which hinder muscle regeneration.[17]

CONCLUSION

The susceptibility of developing CKD in the elderly is related to the decline in renal function due to structural and functional changes in the kidney with age, comorbidities of chronic diseases such as hypertension and diabetes mellitus, medications in the elderly such as the use of nonsteroidal anti-inflammatory drugs and antibiotics that increase the susceptibility of damage to the kidney. Various stressors contribute to the development of CKD in the elderly including oxidative stress, inflammation, abnormal gut microbiota, advanced glycation end products, and fructose consumption leading to premature aging of the kidneys; decreased autophagy in podocytes; mitochondrial dysfunction disrupting cellular homeostasis; epigenetic regulation such as DNA, histone modifications, chromatin remodeling, non-coding RNA (ncRNA) regulation, and RNA modifications that can activate gene expression in CKD; inflammation and immunosenescence that activate proteolytic mechanisms, and impair muscle regeneration. Some of these mechanisms are mediated by SASPs where prolonged exposure to SASPs disrupts tissue function and repair leading to CKD.

Conflict of interest:

The authors declare no conflict of interest.

Author's contributions:

RS (Concept, Design, Sources, Materials, Literature Search, Manuscript Writing). HR (Concept, Design, Supervision, Literature Search). NM (Concept, Design, Literature Search). AS (Concept, Design, Supervisi, Literature Search). AA (Concept, Design, supervision, Literature Search).

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